Report of The External Review Committee for The Institute of Medical Science The University of Tokyo March 2021

The Institute of Medical Science
The University of Tokyo

Contents

Prologue

(1) Goals and aim for External Review of IMSUT

The Institute of Medical Science, the University of Tokyo (hereafter IMSUT) is one of Japan's largest national institutes in the life science field with its own affiliated hospital. The missions of IMSUT are to implement translational research promoting basic and clinical research to apply its findings in medical practice, and to integrate a genome-based precision medicine into clinical practice. Furthermore, IMSUT enhances postgraduate education in association with many graduate schools of the University of Tokyo. We believe that it is important to create the environment in which researchers and students can focus on their studies, so as to deliver world-leading, high quality research along with an education system fit for the next generation of researchers.

With these in mind, aiming to improve research and education standards in accordance with the emerging trend, IMSUT formed the IMSUT Self-Inspection and Evaluation Committee (hereafter "Self-Inspection and Evaluation Committee") and scrutinized the vision of our research and education evaluation. In this context, the Committee played the central role in making an evaluation of IMSUT research and education activities as well as its administrative performance. Following this, IMSUT raised its sights to advancing research and education activities by developing our strengths and clarifying areas for improvement. In addition, IMSUT commissioned researchers who are active in Japan and overseas to objectively re-evaluate the self-inspection and evaluation results from a professional perspective, and IMSUT will reflect their evaluation in its future activity policies.

(2) Period of Review

April 1, 2016 – June 30, 2020

(3) External Review Method

External Review of IMSUT is to be conducted according to the following procedure.

(1) Implementation of the self-inspection and evaluation
(2) Compilation of Materials for External Review of IMSUT based on the self-inspection and evaluation results
(3) Prior review in writing by the external review committee members
(4) Holding an external review meeting
(5) Summary of external review results
(6) Publication of Report of External Review of IMSUT

(4) List of External Review of IMSUT Committee Members

(alphabetically)

Mary Collins (Okinawa Institute of Science and Technology Graduate University)

Rudolf Jaenisch (Whitehead Institute, Massachusetts Institute of Technology)

Aikichi Iwamoto (Japan Agency for Medical Research and Development)

Minoru Kanehisa (Institute for Chemical Research, Kyoto University)

Thirumala-Devi Kanneganti (Immunology Department, St. Jude Children's Research Hospital)

Hiroaki Mitsuya (National Cancer Institute, National Institute of Health)

Takuro Nakamura (The Cancer Institute of JFCR)

Masato Okada (Research Institute for Microbial Diseases, Osaka University)

Emmanuelle Passegué (Columbia Stem Cell Initiative, Colombia University Irving Medical Center)

Toshio Suda (International Research Center for Medical Sciences, Kumamoto University)

Takaji Wakita (National Institute of Infectious Diseases)

Limsoon Wong (School of Computing, National University of Singapore)

I. General Statement: Current Status of IMSUT

(1) Mission and Features

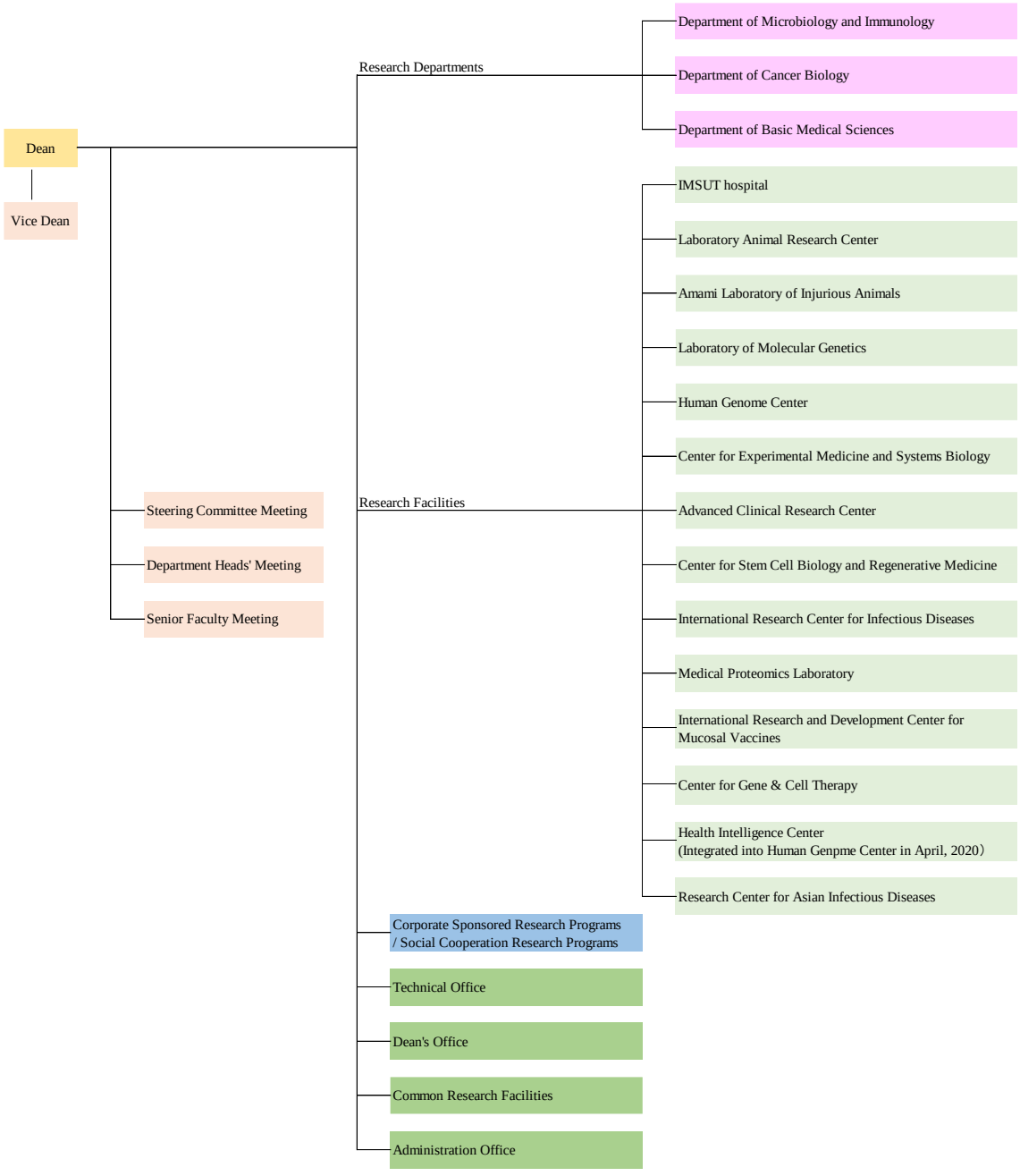
IMSUT is the only national university-affiliated research institute of Japan with its own hospital. IMSUT explores the universal truth of biological phenomena and the principles underlying diseases through basic research, with the results gained promptly applied for medical practice. Our clinical information is then to be reflected forthwith on basic research, which leads to the establishment of our leading medical research system. Under this virtuous-cycle system, we set our minds to making a contribution to society through advanced medical treatment, drug discovery and translational research such as vaccine development. In addition to diseases research including emerging and re-emerging infections, immune disorders, and cancer, IMSUT has been advancing basic medical research focusing on stem cells, regenerative medicine, and clinical genome sequencing. Along with this, with the aim of applying research results to medical practice, we are conducting advanced medical treatment by promoting next generation vaccine development, gene and cell therapy, and translational research such as personalized medicine with AI (Artificial Intelligence). Following our university's third mid-term goal, "pursuing excellence and diversity in every academic area, and based on which, vigorously creating new academic fields", IMSUT continuously implements its organizational reformation to create project-oriented research centers which satisfy the needs of the present generation as bases for leading research open to Japan and the rest of the world (Material 1).

Furthermore, in FY2010, IMSUT was authorized as a Joint Usage/Research Center by the Ministry of Education, Culture, Sports, Science and Technology, Japan (hereafter MEXT). On top of that, when re-authorized in FY2018, IMSUT became the only International Joint Usage/Research Center among the national university-affiliated research institutes of Japan serving the field of medical science and biology. While widely calling upon expertise of researchers from Japan and abroad, we have been providing the public with research materials, technology platforms, and medical information, such as a supercomputer supporting research in the life science field across the nation; banks of DNA, serum, and tissue essential for the personalized medicine; a disease-specific iPS cell bank supporting regenerative medicine research; and a pathogenic microbes repository indispensable to infectious disease research. Through developing and offering these research resources and environment which an individual university cannot provide on its own, IMSUT executes its commitment to efficient promotion of medical research throughout Japan.

Yuji Yamanashi, Ph.D.
Dean
The Institute of Medical Science, The University of Tokyo

(2) Organization

【Material 1】Organization chart of IMSUT



(3) Status of Current Research Activities

1) Implementation System and Support/Promotion System for Research

In the MEXT Budget Request, our new five proposed programs satisfying societal needs have been approved since FY2013, which led to the reinforcement of IMSUT organizational structures, during the third mid-term target period (hereafter “the third period”) (Material 2). Among these five programs, **“**Global Promotion of Strategic Research and Development for Mucosal Vaccines” and “Establishment of a Collaborative Platform for Research and Human Resources for the Control of Infectious Diseases” were approved in FY2016 or later, each of which is currently being implemented principally by the International Research and Development Center for Mucosal Vaccines, and the International Research Center for Infectious Diseases, respectively. Meanwhile, “Core Research for Creating New Dimension Genomic Medicine by Integrating Human Intelligence and AI” launched in FY2020, and we plan to open up a new dimension of genomic medical treatment (in line with society 5.0, our new society in which cyberspace and our real space are fused by AI) with the Health Intelligence Center’s effective integration into the Human Genome Center (Material 2). Along with this, the Center for Antibody and Vaccine Therapy, the Center for Gene & Cell Therapy, and the Center for Translational Research play the central roles in our system promoting the development of advanced medical treatment and translational research.

【Material 2】MEXT Budget request within the third mid-term target period

Projects	Period	Project outline and its related centers
Cultivation of Human Resources for Global Leaders and Coordinators Conducting Clinical Trials of Innovative Antibody and Vaccine Therapy at First in Man (FIM)	FY2013 ～ FY2017 （for 5 years）	●Center for Antibody and Vaccine Therapy The aim of this project is to build a medical/educational system to enable systematic and continuous clinical practice of exploratory advanced medicine. Through On-the-Job Training (OJT), the center develops leading professionals who can conduct the world's first "clinical trial" using antibodies/vaccines developed by IMSUT.
Organization of International Genomic Medicine Research Initiative for Innovative Therapies and Prevention	FY2015 ～ FY2019 （for 5 years）	●Health Intelligence Center With the view that the development of genomic medical science is an urgent issue in health care, this project works to establish an International Genomic Medicine Research Initiative by gathering all efforts of the University of Tokyo aiming to enhance its capabilities. Also, it seeks to create and promote an academic field called “medical informatics” that integrates genomic information and clinical/health information so that patients will be able to receive personalized medicine and disease prevention.

Global Promotion of Strategic Research and Development for Mucosal Vaccines	FY2016 ～ FY2020 （for 5 years）	●International Research and Development Center for Mucosal Vaccines This project aims to establish a collaborative research system with university research institutions both in Japan and overseas based around IMSUT. The center forms an international joint research center and accumulates academic fundamental research seeds to develop a safe and effective "prospective mucosal vaccine" against infectious diseases, allergies, cancers, etc. from the perspective of mucosal immunology. By doing this, it is expected to create a new academic area, "mucosal vaccinology", to develop a "prospective mucosal vaccine that does not require syringes and needles" to contribute to global medical care, and to nurture global human resources in related fields. The center works to contribute to enhancement of university functions and globalization through leading/international research and human resource development based on "mucosal vaccinology", and "next generation mucosal vaccines".
Establishment of a Collaborative Platform for Research and Human Resources for the Control of Infectious Diseases	FY2016 ～ FY2021 （for 6 years）	●International Research Center for Infectious Diseases Hokkaido University, The University of Tokyo, Osaka University, and Nagasaki University form the Alliance in Research and Education for the Control of Infectious Diseases, and by utilizing the characteristics that each center has built to date, establish an organic collaboration base for research and human resource development between each base. By doing this, the center aims to establish an all-Japan system for control of infectious diseases.
Core Research for Creating New Dimension Genomic Medicine by Integrating Human Intelligence and AI	FY2020 ～ FY2024 （for 5 years）	●Progressive integration of a Health Intelligence Center into the Human Genome Center Based on the integrated genome information of "the human genome" (20,000 genes) and "the symbiotic and virus plexus genome" (20 million genes), and vast literature information, this project focuses on advancing genome research that generates medical value with a uniquely developed AI and on creating a new dimension of genomic medicine for Society 5.0 that fuses human intelligence and AI.

More than 11 of our large-scale research projects have been adopted during this third period, which includes the four approved or renewed in FY2016 or later. IMSUT has taken a lead role in promoting each project (Material 3). Through the National Bioresource Project, the Tailor-made Medical Treatment Program, and the BioBank Japan Project for Genomic and Clinical Research, one of the world's largest sets of data and samples acquired from 267,000 patients with 51 diseases including DNA, serum, and medical records has been stored and offered to researchers at home and abroad.

【Material 3】Leading research projects implemented within the third mid-term target period

Projects	Period
Translational Research Network Program (AMED) "Advanced Center for the Establishment and Coordination of Biomedical Innovation Development Assistance"	FY2012-FY2016
National Bioresource Project (NBRP) (AMED) "Collection, cryopreservation and distribution of human umbilical cord blood stem cells for basic researches"	FY2012-FY2016
Tailor-Made Medical Treatment with the BioBank Japan Project (BBJ) (AMED) "Establishment of a Biobank and Creation of a Database of Clinical Information"	FY2013-FY2017

Advanced Research and Development Programs for Medical Innovation, Leading Advanced Projects for medical innovation (LEAP)（AMED） "Research and development of innovative treatment and prevention methods aimed at controlling influenza"	FY2014-FY2018
Advanced Research and Development Programs for Medical Innovation, Leading Advanced Projects for medical innovation (LEAP) (AMED) "Generation of Functional Organs using Developmental Niche"	FY2015-FY2019
Japan Initiative for Global Research Network on Infectious Diseases (J-GRID) (AMED) "China-Japan Research Collaboration on Defense against Emerging and Reemerging Infections"	FY2015-FY2019
Post-K Supercomputer Development Project (Flagship2020) (MEXT) "Integrated computational life science to support personalized and preventive medicine"	FY2015-FY2019
The Translational Research Program; Strategic Promotion for Practical Application of Innovative Medical Technology (TR-SPRINT) "Strategic Promotion and Expansion of a Translational Research to Establish a Global Base for Knowledge Collaboration"	FY2017-FY2021
National Bioresource Project (NBRP) (AMED) "Collection, cryopreservation and distribution of human umbilical cord blood stem cells for basic researches"	FY2017-FY2021
BioBank Japan Project for Genomic and Clinical Research (AMED) "Management of BioBank Japan (BBJ) for utilization of the human materials and medical information"	FY2018-FY2022
Japan Program for Infectious Diseases Research and Infrastructure "Studies to control emerging, re-emerging and imported infectious diseases to be conducted in international collaboration sites in China"	FY2020-FY2024

With support from the program for promoting the enhancement of research universities and the World-leading Innovative Graduate Study Program for Life Science and Technology in FY2018, IMSUT has enhanced its research support system with the expansion of common research facilities and core laboratories. To cite a case, a high-speed confocal microscopy analysis system has been installed in the Imaging Core Laboratory and so have the most advanced cell metabolism measurement devices in our common facility spaces (Material 4).

【Material 4】Outline of common-use facilities and core laboratories

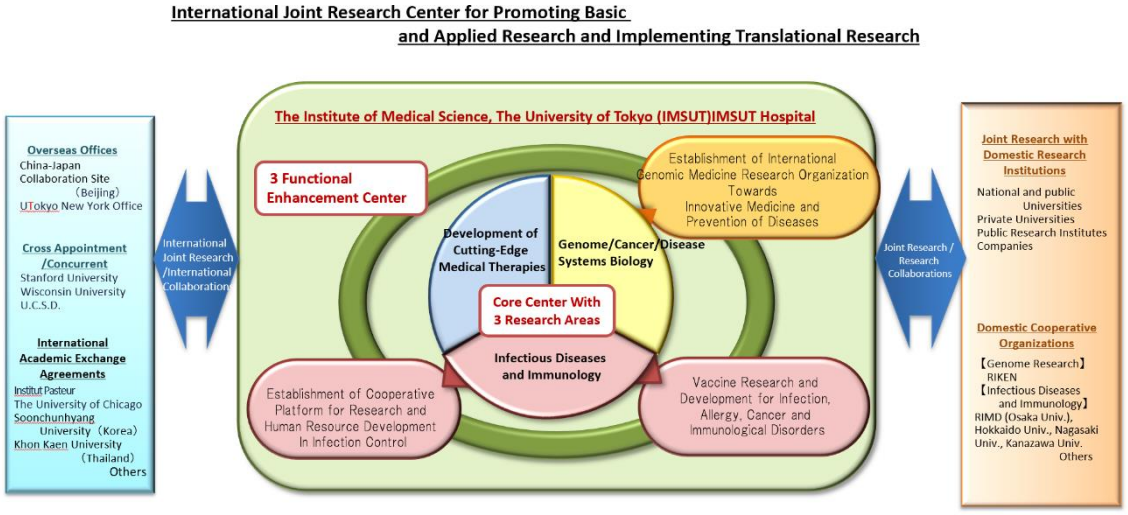
Name	Overview
Animal Center	Services offered by the Laboratory Animal Research Center include the provision of animal breeding spaces and a complete set of mouse-and-rat sterilization gauges. Support for embryo/sperm freezing/thawing. Storage and supply in embryo bank. Provision of an experimental laboratory for conducting animal infection experiments (P2A/P3A). Support for experimental animals with X-ray irradiator, biological imaging system, MRI, and irradiation system.
Medical Proteomics Laboratory	（Proteome Information Analysis） Comprehensive identification and analysis support for protein complexes using nanoLC-MS/MS-type mass spectrometer system. Precise identification analysis support for post-translational modification of proteins such as phosphorylation and ubiquitination. High-precision relative quantitative analysis support based on mass spectrometry spectrum data.

	（Micromorphological Analysis） Support for micromorphological analysis using transmission/scanning electron microscope.
	（Culture Media Section） Cleaning of laboratory glassware. Drying heat sterilization. Pure water supply.
Pathology Core Laboratory	Manufacture of histopathological specimens. Pathological consultations/morphologic diagnoses and analyses.
Gene Manipulated Mouse Section	Generating genetically modified mice.
FACS Core Laboratory	Supporting cell sorting and analysis using flowcytometry equipment.
Imaging Core Laboratory	Providing a basic research environment with state-of-the-art microscopes and imaging-related equipment. Instruction and support for imaging operation.
IMSUT Clinical Flow Cytometry Laboratory	Analysis of clinical samples using flowcytometry equipment and its result report, and cell sorting.
Photographic Laboratory	Printing figures for academic papers and posters for scientific meetings. Photography at various events within IMSUT such as symposiums and seminars.
IT Service Room	Maintenance and management of webserver and IMSUT website. Setting and registration of DNS/mail hosting. Maintenance and management of the institute's local area network. Handling security and information ethics issues. Technical consultation (network related).
Radioisotope Center	Facilities for radioisotope (RI) analysis and X-ray irradiation.
Office of Health and Safety	Planning and implementation regarding health and safety management. Safety education and notification.
Genetically Modified Microorganisms Support Office	Education on genetic recombination experiments and experiments using research microorganisms. Support with the application forms required for experiments. Implementation of preliminary examinations.
Office of Research Ethics	Management of the Research Ethics Committee (REC) at IMSUT. Research ethics support. Planning/conducting/management of research ethics seminar at IMSUT.

In IMSUT Joint Usage/Research projects, there are a "Core Center" with three research areas and a "Functional Enhancement Center" with three projects. We have been promoting core activities by close collaboration across the entire institute with each of three areas/projects as stated below. Namely, the Core Center is composed of three research areas: (1) Development of Cutting-Edge Medical Therapies, (2) Genome/Cancer/Disease Systems Biology, and (3) Infectious Diseases/Immunology. For its part, the Functional Enhancement Center is composed of three projects: (1) Establishment of an International Genomic Medicine Research Organization Towards Innovative Medicine and Prevention of Diseases, (2) Establishment of a Cooperative Platform for Research and Human Resource Development in Infection Control, and (3) Vaccine Research and Development for Infection, Allergy, Cancer and Immunological Disorders. On 13 November 2018, IMSUT was re-authorized as the only International Joint Usage/Research Center among the national university-affiliated research institutes of Japan in the fields of medical science and biology. Thus, we are making a new start by serving as a contact point for partnership/cooperation in Japan and the

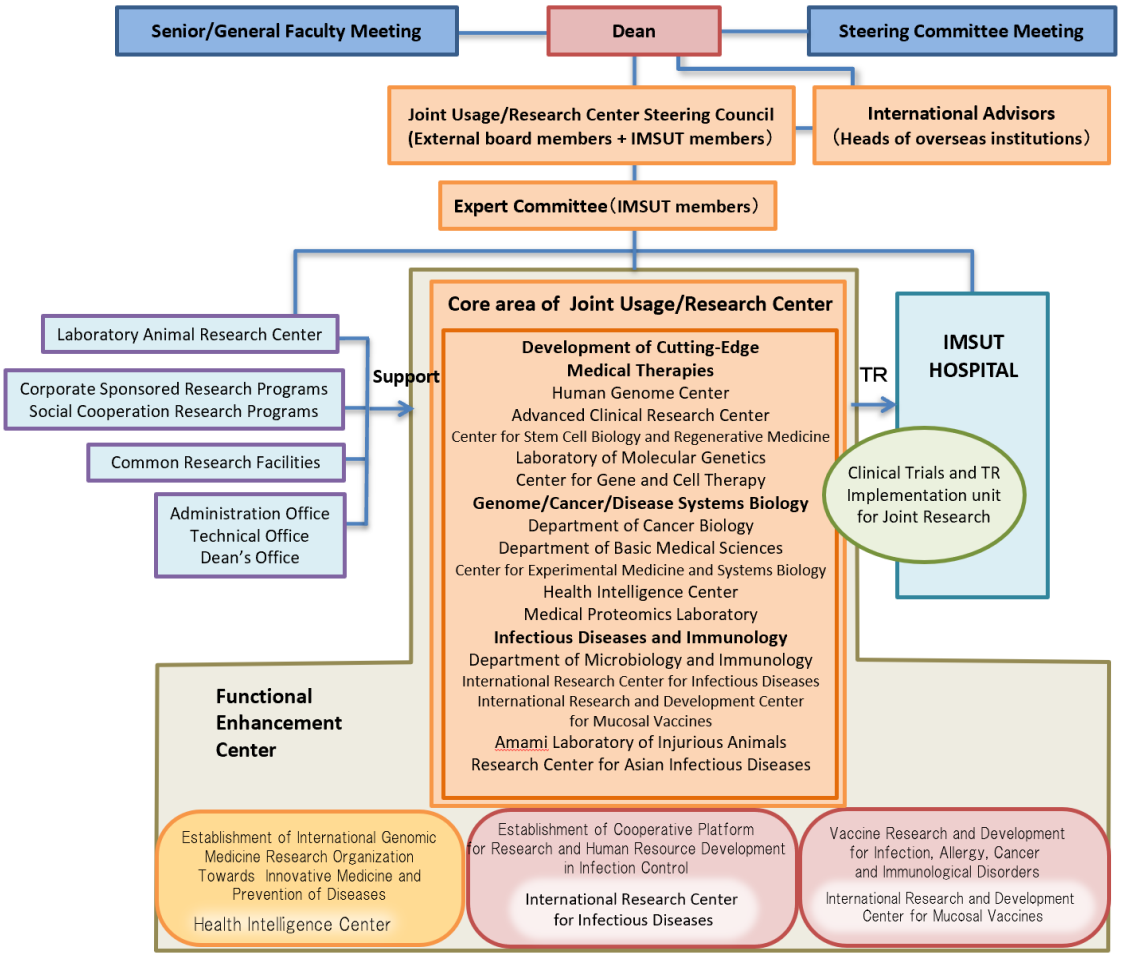
rest of the world, as well as by leading research development in the designated areas as Japan's foremost medical science institute (Material 5).

【Material 5】International Joint Usage/Research Center



Regarding the operation system of the Joint Usage/Research Center, a Steering Council is being set up to deliberate important items in response to the consultation from the Dean. Notable features are that more than half of the board members are from outside the institute, and that international advisors are assigned to provide advice from a global perspective at the request of the Dean. Furthermore, as its research support system, IMSUT boasts Common Research Facilities, Core Laboratories, the Technical Office, and the Administration Office, as well as the Clinical Trial/TR (translational research) Implementation Unit for Joint Research (Material 6).

【Material 6】Operation/support system for the International Joint Usage/Research Center

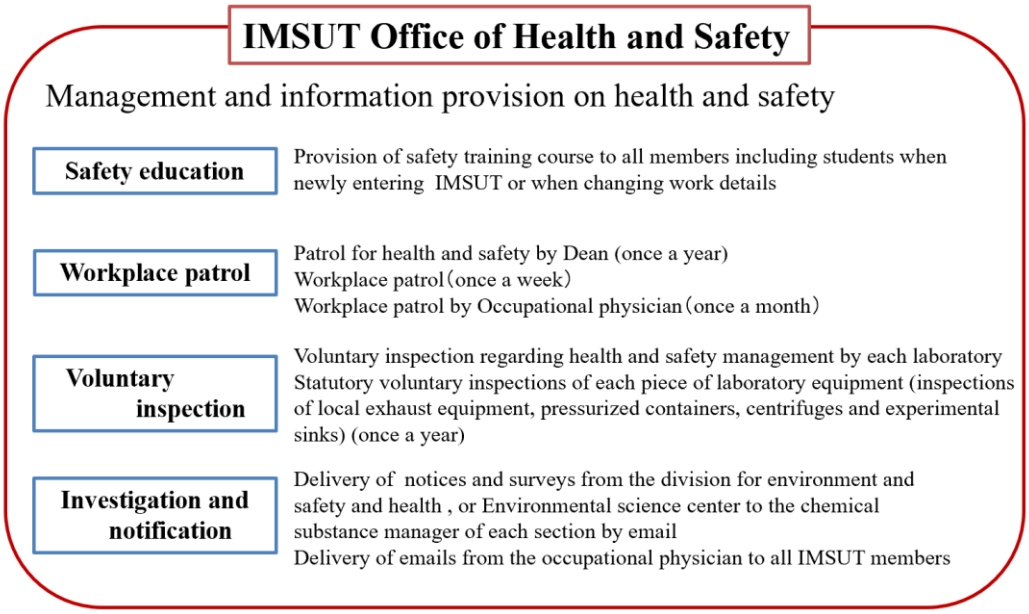


2) Initiatives and quality improvement in research activities

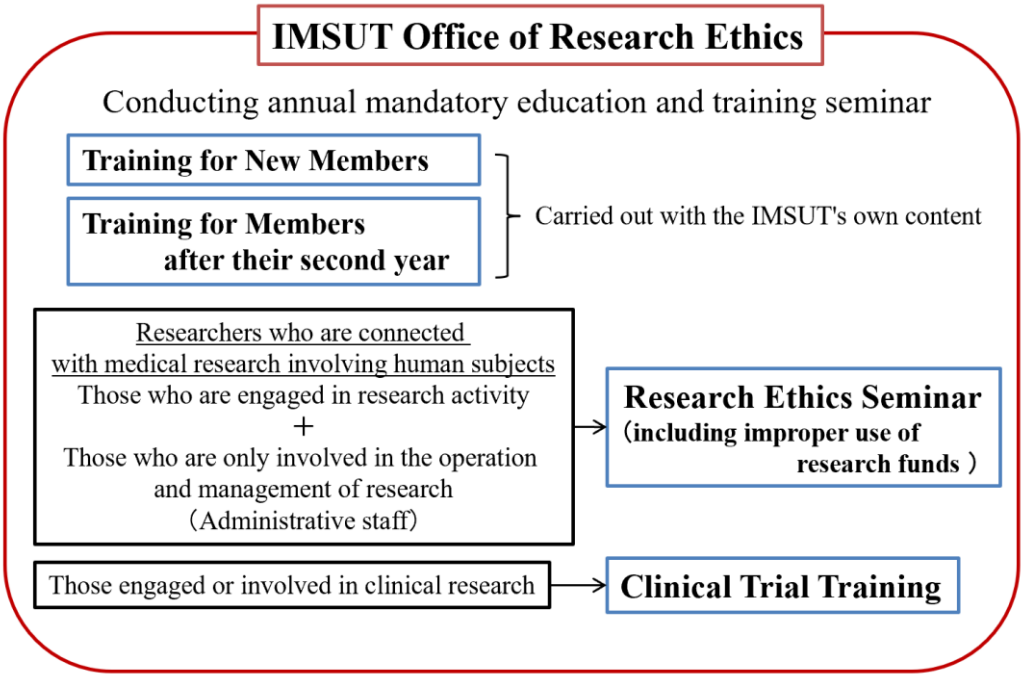
IMSUT boasts an Office of Health and Safety as the system to manage and provides information on its internal environment, health, and safety management. The office conducts activities such as safety education through safety training courses, workplace patrol, voluntary inspection of research equipment, and the control of chemical substances (Material 7-(a)).

【Material 7】 Efforts to address compliance and research ethics

(a) Environment, health and safety management



(b) Compliance, research ethics



(c) Number of research ethics seminars held and attendees in each fiscal year

	FY2010	FY2011	FY2012	FY2013	FY2014	FY2015	FY2016	FY2017	FY2018	FY2019
Number of seminars	8	4	4	6	3	10	10	4	5	7
Number of attendees	446	161	397	410	261	734	689	184	366	525
								※1	※2	※3

(For reference 1) Number of attendees for events not included above:
※1 Those who took e-learning as renewal training in fiscal 2017 / 451persons
※2 Those who took e-learning as renewal training in fiscal 2018 / 200 persons
※3 Those who took e-learning as renewal training in fiscal 2019 / 38 persons

(For reference 2) Regarding number of seminars held
Even if held on the same day, first and second sessions were counted separately.

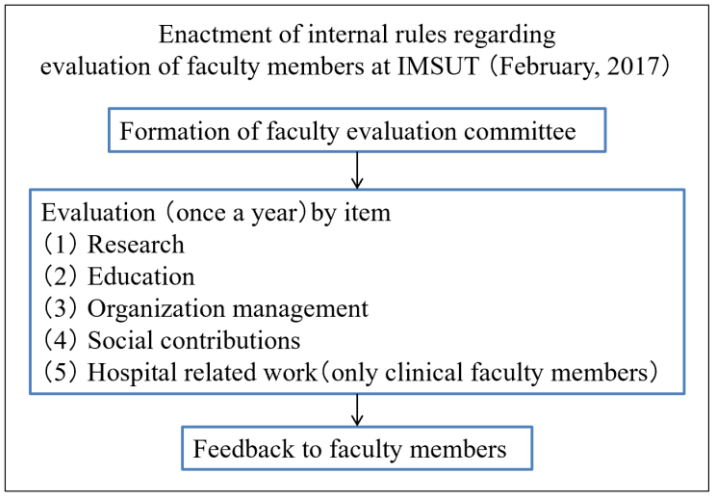
In 2008, IMSUT set up the Office of Research Ethics, which was a pioneering effort in Japan to maintain research ethics. The office conducts mandatory and unique ethics seminars for all members involved in medical research, and a total of 1,764 attended the seminars between FY2016 to FY2019. On top of this, the office appoints one research ethics leader to each laboratory and conducts an annual training workshop for the leaders, which enables them to share information with other laboratories.

Furthermore, 26 training sessions/workshops for new members on prevention of research fraud and conflicts of interest were conducted between FY2016 to FY2019, while the total number of participants in e-learning training sessions for the members after their second year amounted to 689 between FY2017 and FY2019 (Material 7-(b), 7-(c)).

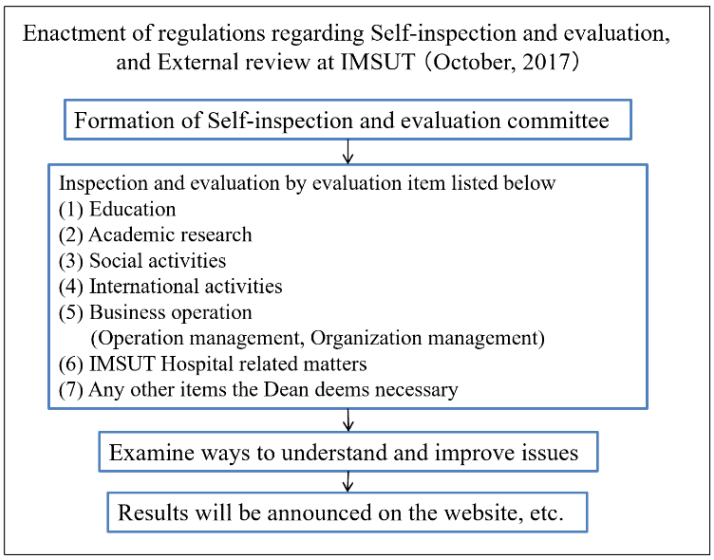
After the enactment of IMSUT internal rules in FY2016, evaluation of the full-time faculty members who have been employed for more than one year is implemented every fiscal year. In FY2017, rules on self-inspection and evaluation as well as on external review were enacted to form the system examining research/education activities, operation, social contributions, and other involvement. The results of self-inspection and evaluation implemented in FY2019 are available on the IMSUT website (Material 8-(a), 8-(b)).

【Material 8】Systematization of the verification of research activities, and method used

(a) Evaluation of faculty members



(b) Self-inspection and evaluation



Integrated Research Systems, the University of Tokyo enables multiple departments to carry out collaborative academic research within a specified period. Under this scheme, the Anti-infective Research Consortium, the University of Tokyo (ARC-UT) was launched in FY2017. By collaborating, a total of nine departments centered at IMSUT, ARC-UT commenced collaborative research aiming to control emerging and re-emerging infectious diseases. In FY2017, the Institute for Life Science Research Education and the One Health Collaboration Research Organization were launched. Subsequently, the Collaborative Research Institute for Innovative Microbiology (CRIIM) was launched in FY2018, where IMSUT faculty members are currently participating and promoting the creation of new academic fields and the development of highly skilled young scientists (Material 9).

【Material 9】Participation in Integrated Research Systems of the wider university

Outline of Integrated Research Systems	Participating Departments (◎: Responsible Dept.)
<Institute for Life Science Research and Education> **Establishment: April 1, 2017** Established for the purpose of setting up a global education and research base for bio-evolution research aiming to elucidate the principles of life systems developing over time. (1) Elucidation of the principle of bio-evolution. Clarification of the fundamental principles of evolution of life systems over time. (2) Bio-evolution analysis by new technology. Promotion of research by new dynamic system analysis technology. (3) Investigating the failure of bio-evolution and diseases. Social contribution based on creation of new disease concepts and development of preventive treatments. Through these three research issues, the institute works to develop professional human resources (high-level knowledge professionals) while forming a global research base that aims to elucidate the principle of life as a dynamic system and how it can fail.	◎Graduate School of Medicine ○Graduate School of Science ○Graduate School of Pharmaceutical Sciences ○IMSUT ○Institute for Quantitative Biosciences ※4 IMSUT faculty members are participating.
< Anti-infective Research Consortium, the University of Tokyo (ARC-UT) > **Establishment: October 1, 2017** Composed of altogether nine collaborating departments centered at IMSUT, ARC-UT carries out the development of innovative methods for prevention, diagnosis and treatment, and nurtures young scientists who will lead infectious disease research in the next-generation. ARC-UT also collects and analyzes data on the situation of infectious disease outbreaks in Japan and overseas and transmits accurate information to society. Furthermore, ARC-UT aims to control emerging and re-emerging infectious diseases by promoting collaborative research that integrates research resources, technological bases, and human resources.	◎IMSUT ○Graduate School of Medicine ○Graduate School of Agricultural and Life Sciences ○Institute of Industrial Science ○Graduate School of Engineering ○Graduate School of Frontier Sciences ○Graduate School of Pharmaceutical Sciences ○Graduate School of Science ○Graduate School of Arts and Sciences ※10 IMSUT faculty members are participating.
< One Health Collaboration Research Organization > **Establishment: October 1, 2017** One Health is an internationally recognized concept that human and animal health are similar and closely related to each other. Hence, there is a need to develop these two comprehensively and cooperatively as a single academic area, rather than to promote medicine, veterinary medicine, agriculture, and environmental studies individually as has been customary. By establishing an academic foundation, One Health aims to form the first academic base in Japan, to advance this academic field in cooperation with related universities and research institutes as a central base in Japan and Asia, and to play a role in leading this field internationally in cooperation with bases in other advanced nations.	◎Graduate School of Agricultural and Life Sciences ○IMSUT ○Graduate School of Medicine ○Graduate School of Frontier Sciences ※3 IMSUT faculty members are participating.

＜Collaborative Research Institute for Innovative Microbiology (CRIIM)＞ **Establishment: April 1, 2018** CRIIM is Japan's first integrated microbial research base consisting of researchers from various fields related to microbial science. It is working to develop cutting-edge innovative microbial science research in the four fields of "manufacturing", "environment/energy", "agricultural production/ecosystem" and "basic/fundamental technologies". "Basic/fundamental technologies" can support and connect the other three. Furthermore, it creates new academic value that transcends specific fields of study. Under industry-government-academia collaboration, CRIIM works to accelerate applied research for the social implementation of knowledge, to create new industries, and to train and produce internationally minded innovative young scientists who will be responsible for the next-generation of academic and industrial development in this field.	◎Graduate School of Agricultural and Life Sciences ○Graduate School of Engineering ○Graduate School of Science ○Graduate School of Pharmaceutical Sciences ○Graduate School of Frontier Sciences ○IMSUT ○Institute for Quantitative Biosciences ○Atmosphere and Ocean Research Institute ○Biotechnology Research Center ○Environmental Science Center ※2 IMSUT faculty members are participating.

Some IMSUT faculty members are currently participating in four of the research organizations which were set up by the Committee for Presidential Initiatives at the University of Tokyo with the aim of promoting university-wide key projects and cross-disciplinary education research projects (Material 10).

【Material 10】Participation in research organizations established by the Committee for Presidential Initiatives

Outline of Research Organization	Participating Departments
＜Medical Genome Research Initiative, The University of Tokyo＞ By inviting outstanding researchers in the fields of “genomic science”, “medical science”, and “information science” from our university and collaborating with related departments, this initiative promotes innovative genomic medical science research, which is conducted with advanced genomic and information analysis technology. Its aim is to contribute broadly to society as an educational research organization, which creates interdisciplinary areas and fosters human resources by integrating genomic science/medical science and information science, as well as returning its research findings to society as genomic medicine.	Administration Office: IMSUT IMSUT and Other 18 Departments are participating.
＜Translational Research Initiative, The University of Tokyo＞ As one of Japan’s leading academic institutions, TR Initiative believes its responsibility and foremost duty is to contribute to the medical field by translating our academic research achievements to medical innovations swiftly, and in their optimal form. As its key values, the TR Initiative strives to: • Ensure that patients, their families, and medical professionals receive the maximum benefit from medical innovations.	Director of TR Initiative: Director of the University of Tokyo Hospital IMSUT and Other 12 Departments are participating.

• Deliver maximum results through an equal, cooperative partnership between academia and corporations • Create an environment in which the University's researchers fully understand and appreciate the value of TR and can work proactively towards goals of the TR Initiative.	
＜Life Science Network, The University of Tokyo＞ This is a network-type cross-sectional organization in which 17 departments within the university participate, which was created by combining the former Life Science Research Network and the former Life Science Education Support Network. In order to work on university-wide projects related to life sciences and the further development of the field itself, the organization supports education through the creation and revision of textbooks. It also holds symposiums aiming to exchange researchers within the university and to introduce its research to those outside the university.	Director of the network: Dean of Graduate School of Arts and Sciences IMSUT and other 16 Departments are participating.
＜The University of Tokyo Sports Science Initiative＞ With the advent of a "super-aged society", it is feared that problems such as skyrocketing medical costs, rising needs for nursing care, and a decrease in the working-age population will all become apparent. Under such circumstances, the challenge of how to sustain the energy of society is recognized as a global issue. With the aim of promoting cross-disciplinary research related to sports and health sciences, the Initiative works on returning the academic results to student education and society, as well as on playing a key role in coordinating between universities and research institutions in Japan and overseas.	Main Department: Graduate School of Arts and Sciences IMSUT and other 15 departments are participating.

As part of the efforts to strengthen the network in the field of infectious diseases, IMSUT has held international symposia supported by the "Japan Initiative for Global Research Network on Infectious Diseases" from the Japan Agency for Medical Research and Development (hereafter AMED) three times since FY2016, together with Osaka University, Nagasaki University and Hokkaido University, all of which have overseas bases. Also, in the field of immunology, IMSUT has successfully enhanced cooperation and cultivated young scientists at home and abroad. One example is the International Symposium on Membrane Traffic in Awajishima, where IMSUT plays a leading role and has sent six lecturers since FY2016.

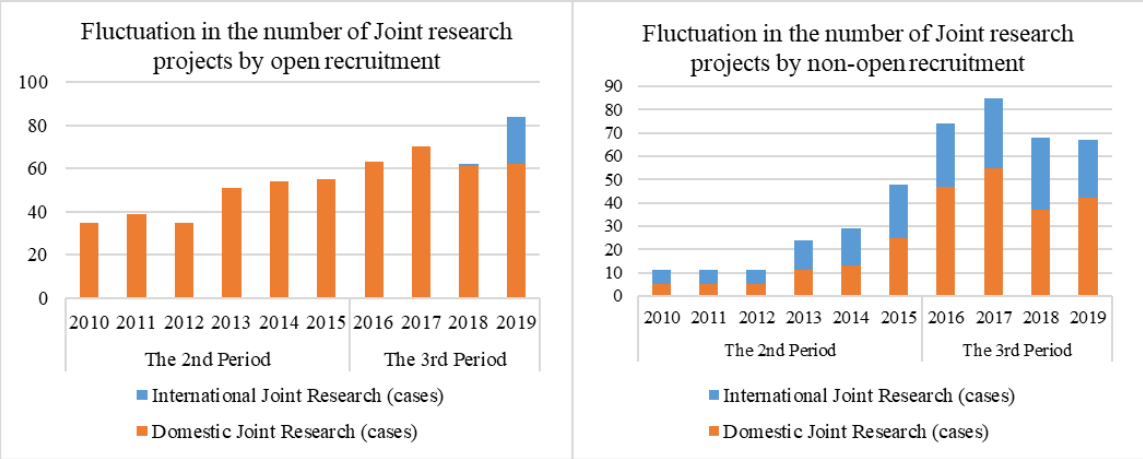
Since FY2016, IMSUT has contracted with ten principal investigators (nine professors and one associate professor) who have significant experience and expertise at other national universities, together with two project professors with excellent research performance who had reached the mandatory retirement age, and one professor with a cross-appointment at the University of Wisconsin. Meanwhile, under "the University of Tokyo Excellent Young Researcher" system, one associate professor and one assistant professor in FY2016, and one Senior Assistant Professor in FY2019 were appointed to be provided with start-up support for the research environment of young researchers. Along with this, IMSUT has promoted researcher diversity with respect to their background, age, and gender identity and the development of its research organization, such as by appointing one

female associate professor in FY2016 with a support system for female researchers.

At the Core Center in the Joint Usage/Research Project, IMSUT calls for proposals for joint research projects from both domestic and overseas research institutes and provides its internal human and material resources to promote open recruitment joint research. In preparation for the interim evaluation it was decided that the grant would be allocated in instalments, which led to a 25% reduction from the initial budget. Although the number of adopted proposals in this project decreased in FY2018, it maintained at a high level throughout the third period compare to the second period. Notably in FY2019, IMSUT began to call for international joint research proposals as an International Joint/Usage Research Center, which has resulted in 84 proposals being adopted, the largest number since the launch of the projects (Material 11).

Regarding the Functional Enhancement Center in the Joint Usage/Research Project, IMSUT conducts advanced joint research projects by non-open recruitment together with other research institutes in Japan and abroad. Although the number of adopted proposals for non-open recruitment joint research decreased in FY2018 due to a 26% reduction in the project budget under legislative and administrative measures in the field of science, 85 proposals, the highest figure since the launch of the projects, were adopted in FY2017. In FY2019, the number of adopted proposals remained the same as in FY2018 despite the impact of COVID-19 (Material 11).

【Material 11】Fluctuation in the number of joint research projects



Both the numbers of participating research institutes and accepted researchers at the Core Center and the Functional Enhancement Center were also affected by legislative and administrative measures in the field of science. However, when comparing FY2015, which was the last fiscal year

of the first period of the Joint Usage/Research Center Project, and FY2017, both participating institutes and accepted researchers significantly increased from 97 to 146, and from 136 to 224, respectively. Likewise, the total number of visitors to IMSUT increased from 2,708 in FY2016 to 7,582 in FY2018, which indicates that joint research projects were carried out continuously and vigorously. Due to the impact of COVID-19, the number of visitors in FY2019 decreased to 5,517, yet the total number of visitors from abroad soared roughly 15-fold owing to the launch of international joint research proposals at the Core Center (Material 12).

【Material 12】Acceptance status involving joint research

FY	Number of Organizations	Number of people accepted				Cumulative total number of people			
			Non-Japanese	Young Researchers (35 and under)	Graduate Students		Non-Japanese	Young Researchers (35 and under)	Graduate Students
2010	38	78	1	ND	11	232	3	ND	131
2011	50	81	1	ND	9	251	5	ND	20
2012	50	70	1	ND	9	190	3	ND	17
2013	85	107	3	15	16	414	7	70	40
2014	98	127	10	13	12	711	13	114	53
2015	97	136	4	26	16	501	10	84	42
2016	137	183	7	39	29	2,708	15	950	508
2017	146	224	11	37	30	3,698	17	1,206	1,343
2018	85	153	6	22	23	7,582	16	2,069	2,035
2019	102	168	25	38	22	5,517	244	1,858	1,017

Upon the call for joint research projects by open recruitment, IMSUT encourages participation of young researchers, postgraduates, or undergraduates (fourth year, or fifth/sixth year in six-year undergraduate programs). Adopted research collaborators are to be conferred the title of "IMSUT Joint Research Project Researcher (JRP Researcher)" and to be allowed the same access to the facilities and academic samples as IMSUT researchers, which promotes their joint use (Material 13 and 14).

【Material 13】Usage status of facilities and equipment

Name of Main Facilities/Equipment	Outline and Purpose of Facilities/Equipment					
Medical Proteomics Laboratory, Mass Spectrometer	Supports post-translational modification analysis such as protein identification and phosphorylation using a mass spectrometer that enables highly sensitive and accurate shotgun measurement, and relative quantitative analysis between different samples.					
FY	2015	2016	2017	2018	2019	Total number of users since FY2016
Number of users (of which related joint research)	27(27)	32(32)	30(30)	27(27)	6(0)	95(89)
Human Genome Center, Supercomputer System	In response to the explosive increase in the amount of data in genome research and the diversification of data types and analysis methods, we have introduced one of the largest supercomputer systems in Japan and also made it widely available to researchers who engage in genome-related research. The registered external users are from universities, independent administrative agencies, private companies, etc. It is widely used by researchers.					
FY	2015	2016	2017	2018	2019	Total number of users since FY2016
Number of users (of which related joint research)	630 (630)	716 (716)	941 (941)	1,103 (1,103)	1,408 (1,408)	4,168 (4,168)
Imaging Core Laboratory	Installed Zeiss Multiphoton Microscopy LSM710NLO. Technical guidance and analysis support.					
FY	2015	2016	2017	2018	2019	Total number of users since FY2016
Number of users (of which related joint research)	68(5)	88(1)	137(13)	59(5)	40(13)	324(32)
Imaging Core Laboratory	Installed Nikon confocal microscope A1. Technical guidance and analysis support.					
FY	2015	2016	2017	2018	2019	Total number of users since FY2016
Number of users (of which related joint research)	289(51)	192(42)	156(81)	200(70)	221(87)	769(280)
FACS Core Laboratory	Support for stem cells or immunocompetent cell sorting and analysis using Flow Cytometry.					
FY	2015	2016	2017	2018	2019	Total number of users since FY2016
Number of users (of which related joint research)	2,592 (386)	3,026 (349)	3,394 (347)	3,342 (252)	3,129 (294)	12,891 (1,242)

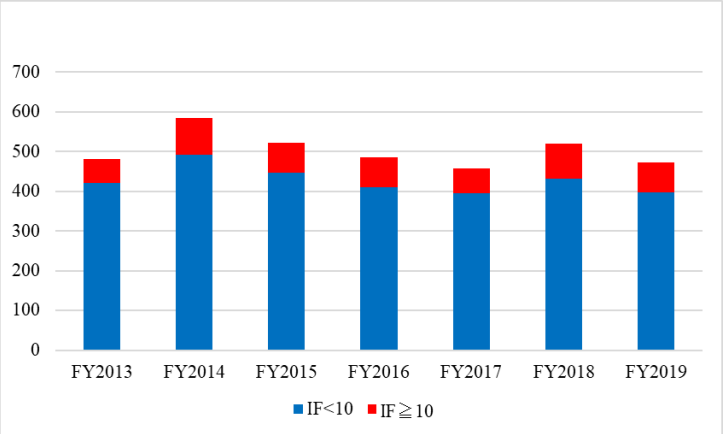
【Material 14】Status of usage/provision/collection of research resources

Research Resources	Outline and Provision Method of Research Resources					
Pathogenic Bacteria	The Pathogenic Microbes Repository Unit, International Research Center for Infectious Diseases stores 1,440 pathogenic bacterial strains, and provides them to research and educational institutions. Cryopreservation and maintenance of pathogenic bacterial strains are carried out. Check and maintain the properties of the strains regularly. Cultivate and distribute pathogenic bacteria upon request.					
FY	2015	2016	2017	2018	2019	Total number of uses since FY2016
Number of strains	1,440	1,440	1,440	1,800	1,800	
Number of uses (of which related joint research)	20(5)	27（3）	14（0）	14(0)	11（0）	66（3）
DNA (BioBank Japan, BBJ)	DNA Bank (DNA storage facility) is playing a central role in BBJ and strictly stores and manages the DNA provided by cooperating medical institutions in Japan. Contingent on an ethics review, DNAs are provided to researchers for enabling personalized medicine.					
FY	2015	2016	2017	2018	2019	Total number of uses since FY2016
Number of samples	744,991	800,406	829,878	805,285	805,279	
Number of uses (of which related joint research)	11(11)	22（18）	11（3）	20（13）	16（10）	69（44）
Genetically Modified Mice	Preparation of genetically modified model mice for human diseases on request. Analysis of human disease development mechanism in model mouse, cryopreservation of embryos, and provision of technology.					
FY	2015	2016	2017	2018	2019	Total number provided since FY2016
Number produced	52	41	16	20	20	
Number provided (of which related to joint research)	52(1)	1（0）	16（0）	20（0）	20（4）	57（4）

3) Academic Papers/Patents/Conference Presentations etc.

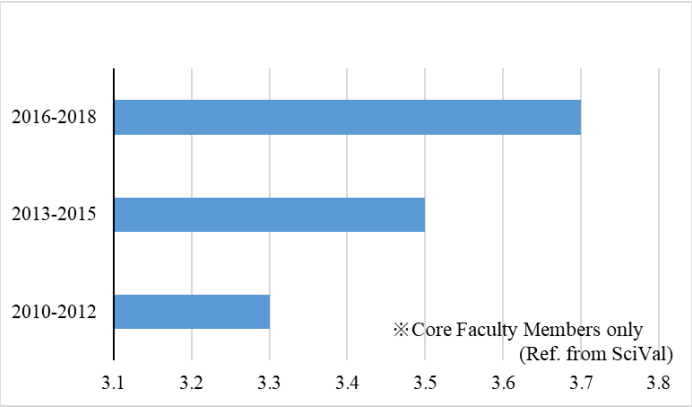
Since the second period, IMSUT has continuously published approximately 500 papers every year. For the four years from FY2016 through FY019, 1,933 English peer-reviewed papers were published, and of these, 300 papers were in journals with an impact factor of ten or above. The ratio of these papers to the total number of English peer-reviewed papers released by IMSUT increased to reach 16.76 % in FY 2018, the highest throughout the second period and the third period, which indicates that IMSUT is producing high-quality papers (Material 15). The number of papers per faculty member also increased to 3.7 papers published from FY2016 through FY2018, compared to 3.3 papers published from FY2010 through FY2012 and 3.5 papers published from FY2013 through FY2015 (Material 16).

【Material 15】Number of English peer-reviewed papers



		IF20 or more	IF10 or more	Total number of English peer-reviewed papers
FY2013	Number of papers	25	62	482
	%	5.19	12.86	
FY2014	Number of papers	28	93	584
	%	4.79	15.92	
FY2015	Number of papers	27	80	526
	%	5.13	15.21	
FY2016	Number of papers	28	75	486
	%	5.76	15.43	
FY2017	Number of papers	20	63	456
	%	4.39	13.82	
FY2018	Number of papers	27	87	519
	%	5.2	16.76	
FY2019	Number of papers	21	75	472
	%	4.45	15.89	

【Material 16】Comparison of the number of papers per core faculty member



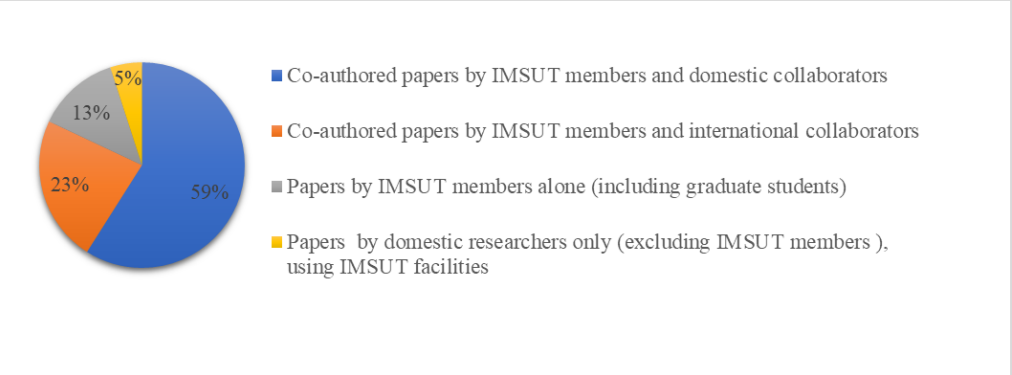
The total number of papers published through joint research at the Joint Usage/Research Center

reached 721 for the period FY2016 to FY2019, a 1.56-fold increase compared with 462 from FY2012 through FY2015 (Material 17). 82% (588 papers) of them were co-authored papers with research collaborators (Material 18), while 236 joint papers were produced by principal authors or main authors belonging to the Center. Furthermore, 33 papers with an impact factor of 20 or above were published over the four years from FY2016 to FY2019 (Material 19).

【Material 17】Number of published papers at the Joint Usage/Research Center

FY	2012	2013	2014	2015	2016	2017	2018	2019	Total number of papers since FY2016
Number of papers	94	115	145	108	142	227	187	165	721

【Material 18】Affiliation of the authors of the papers (total of 721) published FY 2016-FY2019 at the joint research center



【Material 19】Number of papers with high impact factors (IF>20) published FY2016-2019 at the joint research center

Name of journal	Number of papers	Name of journal	Number of papers
Nature	6	Nature Immunology	4
Science	1	Immunity	3
Cell	4	Lancet Oncology	1
Nature Biotechnology	3	Annual Review of Immunology	1
Nature Genetics	3	Journal of Clinical Oncology	2
Nature Medicine	4	JAMA Oncology	1

The number of national patents steadily increased to 67 at the end of FY2019 from 50 at the end of the second period, while the number of foreign patents has drastically increased to 178 from 43, respectively (Material 20).

【Material 20】Number of unexpired patents

FY	2013	2014	2015	2016	2017	2018	2019
Number of National Patents	21 (8)	36 (14)	50 (22)	51 (21)	56 (21)	62 (22)	67 (23)
Number of International Patens	25 (13)	31 (17)	43 (17)	71 (34)	111 (40)	152 (52)	178 (64)

＊The numbers in parentheses are cumulative total of joint application by the end of each fiscal year.
＊The number for FY2019 is the preliminary results as of June 4, 2020.

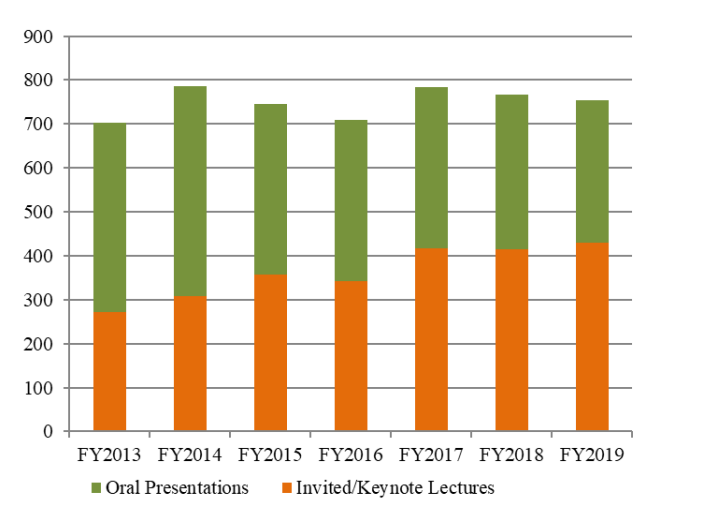
The number of patent applications at the Joint Usage/Research Center for the four years from FY2016 through FY2019 stood at three (Material 21). All of them were patents relating to medical diagnosis which embody the Center's mission to promote medical science based on translational research.

【Material 21】Patent application and registration at the joint research center

1	Application Date	Aug. 18, 2017
	Inventor	Naohiko Koshikawa, Motoharu Seiki
	Patent Application	EphA2 N-Terminus Fragment Antibody (Publication No. PCT/JP2017/029596)
2	Application Date	Sep. 20, 2019
	Inventor	Makoto Nakanishi, Yoshikazu Johmura, Tomohiko Ohta
	Patent Application	Method for Determining Prognosis of Cancer (Patent Application No. PCT/JP2019/036949)
3	Application Date	Feb. 4, 2019
	Inventor	Shinichi Yachida and others
	International Application	Method for Detecting Early Colon Cancer (Patent Application No. PCT/JP2019/003825)

Since the second period, IMSUT has vigorously given presentations at academic conferences. The average annual number of presentations given at international conferences from FY2016 through FY2019 was 168, while this number was 586 for presentation given in Japan. Notably, the number of IMSUT members who were invited to give lectures both inside and outside Japan continued to increase, reaching 429 in FY2019 compared to 357 in FY2015 (Material 22).

【Material 22】Lectures and oral presentations at academic conferences



FY2013				FY2014			
International		Domestic		International		Domestic	
Invited/ Keynote Lectures	Oral Presentations	Invited/ Keynote Lectures	Oral Presentations	Invited/ Keynote Lectures	Oral Presentations	Invited/ Keynote Lectures	Oral Presentations
97	112	174	320	105	130	204	347

FY2015				FY2016			
International		Domestic		International		Domestic	
Invited/ Keynote Lectures	Oral Presentations	Invited/ Keynote Lectures	Oral Presentations	Invited/ Keynote Lectures	Oral Presentations	Invited/ Keynote Lectures	Oral Presentations
107	88	250	300	81	80	262	286

FY2017				FY2018			
International		Domestic		International		Domestic	
Invited/ Keynote Lectures	Oral Presentations	Invited/ Keynote Lectures	Oral Presentations	Invited/ Keynote Lectures	Oral Presentations	Invited/ Keynote Lectures	Oral Presentations
112	78	306	289	115	57	299	295

FY2019			
International		Domestic	
Invited/ Keynote Lectures	Oral Presentations	Invited/ Keynote Lectures	Oral Presentations
98	49	331	276

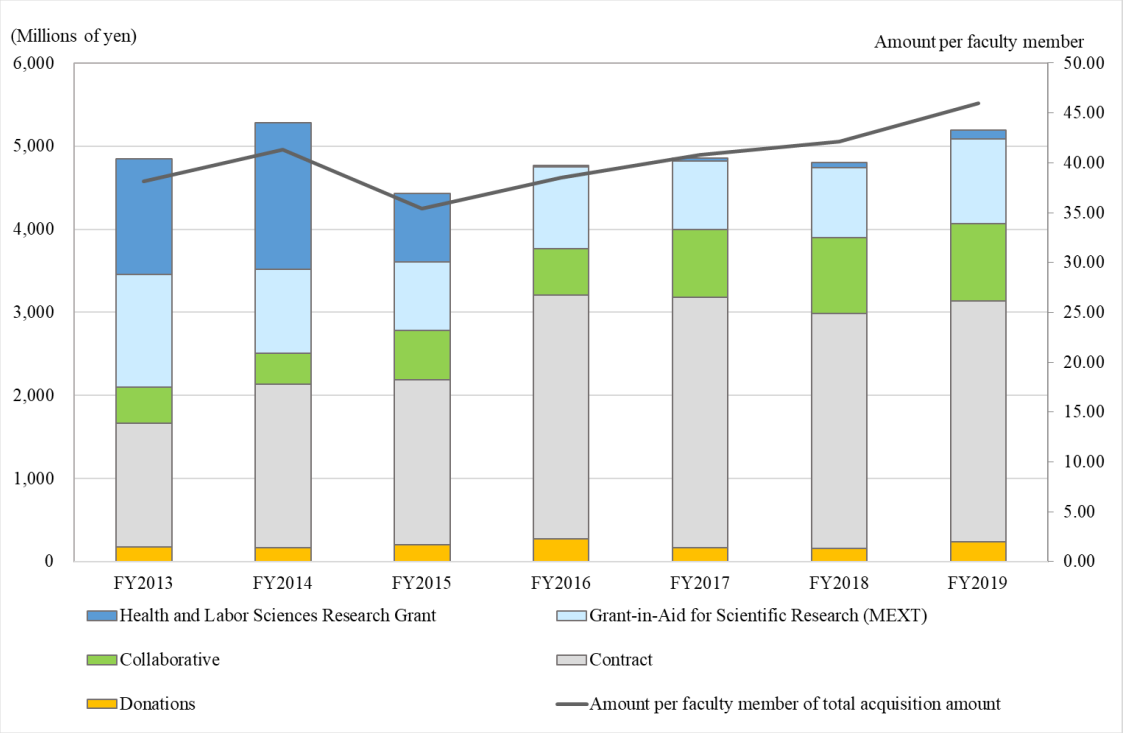
4) Research Funds

Regarding income from external sources, IMSUT has secured approximately five billion yen in total as was the case for the second period. Notably, the amount of funds for contract and collaborative research between FY2015 to FY2019 significantly increased, from 1,983 million yen to 2,893 million yen and from 598 million yen to 929 million yen, respectively (Material 23).

Also, both the number of cases and amount of income from external sources acquired per faculty member have remained high since the second period, 5.5 cases and 46 million yen respectively in

FY2019 (Material 24).

【Material 23】Amount of income obtained from external sources (per faculty member)



- The decline in the acquisition amount of Health and Labor Sciences Research Grant after fiscal 2016 was due to the establishment of AMED in 2015. The amount acquired through the public offering of AMED is included in the amount of the contract.

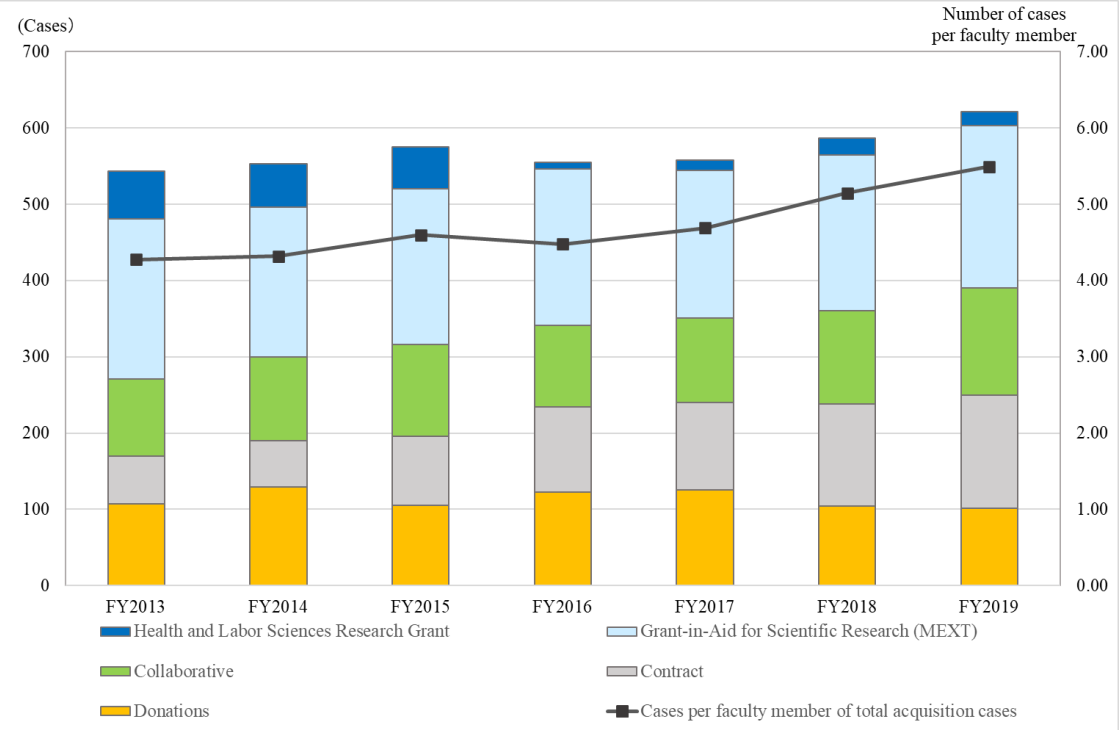
Unit: Million of yen

FY		FY2013	FY2014	FY2015	FY2016	FY2017	FY2018	FY2019
Number of Faculty members		127	128	125	124	119	114	113
Donations	Amount	180	164	202	274	167	159	242
	Amount per faculty member	1.42	1.28	1.62	2.21	1.40	1.39	2.14
Contract	Amount	1,483	1,970	1,983	2,932	3,016	2,826	2,893
	Amount per faculty member	11.68	15.39	15.86	23.65	25.34	24.79	25.60
Collaborative	Amount	440	372	598	562	816	913	929
	Amount per faculty member	3.46	2.91	4.78	4.53	6.86	8.01	8.22
Grant-in-Aid for Scientific Research (MEXT)	Amount	1,357	1,015	820	985	822	839	1023
	Amount per faculty member	10.69	7.93	6.56	7.94	6.91	7.36	9.05
Health and Labor Sciences Research Grant	Amount	1,385	1,764	826	18	34	68	105
	Amount per faculty member	10.91	13.78	6.61	0.15	0.29	0.60	0.93
Total Acquisition amount	Amount	4,845	5,285	4,429	4,771	4,855	4,805	5,192
	Amount per faculty member	38.15	41.29	35.43	38.48	40.80	42.15	45.95

- The amount column shows the amount of income from external sources acquired by all faculty members (including Project related faculty members) of IMSUT. (Includes acceptance by other than principle investigator.)
- The number of faculty members shows the number of full-time faculty members, not including project related faculty members at the end of each fiscal year.

- "Contract" includes contract research expenses, which are competitive income from external sources funded by the government such as AMED.

【Material 24】Number of cases of income obtained from external sources (per faculty member)



FY		FY2013	FY2014	FY2015	FY2016	FY2017	FY2018	FY2019
Number of Faculty members		127	128	125	124	119	114	113
Donations	Number of cases	107	129	105	122	125	104	101
	Number of cases per faculty member	0.84	1.01	0.84	0.98	1.05	0.91	0.89
Contract	Number of cases	63	61	91	112	115	134	149
	Number of cases per faculty member	0.50	0.48	0.73	0.90	0.97	1.18	1.32
Collaborative	Number of cases	101	110	120	107	111	122	140
	Number of cases per faculty member	0.80	0.86	0.96	0.86	0.93	1.07	1.24
Grant-in-Aid for Scientific Research (MEXT)	Number of cases	210	196	204	205	193	205	213
	Number of cases per faculty member	1.00	1.53	1.63	1.65	1.62	1.80	1.88
Health and Labor Sciences Research Grant	Number of cases	62	57	55	9	14	22	18
	Number of cases per faculty member	0.49	0.45	0.44	0.07	0.12	0.19	0.16
Total Acquisition cases	Number of cases	543	553	575	555	558	587	621
	Number of cases per faculty member	4.28	4.32	4.60	4.48	4.69	5.15	5.50

- The Number of cases column shows the number of cases of income from external sources acquired by all faculty members of IMSUT. (Including acceptances other than the principle investigator.)
- The number of faculty members shows the number of full-time faculty members, not including project related faculty members.
- "Contract" includes contract research expenses, etc., which are competitive income from external sources funded by the government such as AMED.

At the Joint Usage/Research Center, each research fund is mainly financed by Grants-in-Aid for Scientific Research (KAKENHI) and by the budget from AMED, while Center activity expenses such as travel expenses to and from IMSUT and conference costs are covered by Grants for Creating Research and Education Bases for the Formation of Research Centers from MEXT. After IMSUT received an "S" rating in the FY2018 interim evaluation by the Commission of research environment and infrastructure within the Scientific Subdivision on the Council for Science and Technology, a budget reallocation of 13.2 million yen was made. On top of this, IMSUT was authorized as the International Joint Usage/Research Center and received a budget reallocation of an addition 60.137 million yen (Material 25). With these funds, IMSUT has consolidated its system towards furthering the center's internationalization such as by the employment of a foreign Professor and the enhancement of communal equipment.

【Material 25】Budget Situation of the (International) Joint Usage/Research Center

【Core area of Joint Usage/Research Center】 Unit : JPY

"International Joint Research Project on Promoting of Basic and Applied Medical Sciences"

Category	FY2016 Budget amount	FY2017 Budget amount	FY2018 Initial budget amount	FY2018 Addition based on intermediate evaluation result	FY2018 Addition based on authorization as international center	FY2019 Budget amount
Joint Research Center						
Supporting expenses for joint research	4,137,000	4,137,000	2,527,000	11,480,000	52,297,000	
Research expenses for collaborators	35,000,000	35,000,000	27,000,000	-	-	
Operating expenses for center	5,860,000	5,860,000	4,420,000	1,720,000	7,840,000	
Total	44,997,000	44,997,000	33,947,000	13,200,000	60,137,000	105,559,000
						▲1.6%
			▲about 25％			
			FY2018 Total Budget: 107,274,000-			

※IMSUT was authorized as the "International Joint Research Center on 13 November 2018.

【Functional Enhancement Center】

"Establishment of a Collaborative Platform for Research and Human Resources for the Control of Infectious Diseases"

Category	FY2016 Budget amount	FY2017 Budget amount	FY2018 Initial budget amount	FY2018 Addition based on intermediate evaluation result	FY2018 Addition based on authorization as international center	FY2019 Budget amount
International Research Center for Infectious Diseases	129,430,000	122,955,000	90,995,000	-	-	90,995,000
Operating expenses for center	19,410,000	18,443,000	13,640,000			13,640,000
Total	148,840,000	141,398,000	104,635,000	-	-	104,635,000
		▲5%	▲26%			±0%

"Global Promotion of Strategic Research and Development for Mucosal Vaccines"

Category	FY2016 Budget amount	FY2017 Budget amount	FY2018 Initial budget amount	FY2018 Addition based on intermediate evaluation result	FY2018 Addition based on authorization as international center	FY2019 Budget amount
International Research and Development Center for Mucosal Vaccines	38,440,000	37,474,000	27,740,000	-	-	27,740,000
Operating expenses for center	5,760,000	5,621,000	4,150,000			4,150,000
Total	44,200,000	43,095,000	31,890,000	-	-	31,890,000
		▲2.5%	▲26%			±0%

"Organization of International Genomic Medicine Research Initiative for Innovative Therapies and Prevention"

Category	FY2016 Budget amount	FY2017 Budget amount	FY2018 Initial budget amount	FY2018 Addition based on intermediate evaluation result	FY2018 Addition based on authorization as international center	FY2019 Budget amount
Health Intelligence Center	49,912,000	48,659,000	36,008,000	-	-	36,008,000
Operating expenses for center	7,480,000	7,298,000	5,400,000			5,400,000
Total	57,392,000	55,957,000	41,408,000	-	-	41,408,000
	▲1.5%	▲2.5%	▲26%			±0%

5) Research Activities through International Collaboration

IMSUT has engaged vigorously in joint research and exchange projects. International Academic Exchange Agreements have been concluded with nine overseas research institutions as of FY2019, while joint research units were founded both at Institut Pasteur and IMSUT in FY2018. (Material 26). In parallel, based on a memorandum on activities of the Japan Program for Infectious Diseases Research and Infrastructure (AMED) with the Chinese Academy of Sciences, IMSUT scientists have been residing and working in China along with Chinese scientists. Meanwhile, joint research with close collaboration has been conducted at joint laboratories, namely the Noguchi Medical Research Institute, Ghana, and Sierra Leone University.

【Material 26】International exchange agreements

Partner Universities/Institutions	Country	Type of Agreement	Date of First Signing
Chinese Academy of Sciences	China	University Wide	2005.4.29
Institut Pasteur	France	Departmental	2006.4.18
Sun Yat-sen University	China	University Wide	2011.11.15
Arabian Gulf University, College of Medicine & Medical Sciences	Bahrain	Departmental	2013.7.14
Soonchunhyang University	Korea	Departmental	2013.9.26
The University of Chicago Medicine	United States	Departmental	2014.6.4
Vietnam National University, Ho Chi Minh City, School of Medicine	Vietnam	Departmental	2015.3.23
Khon Kaen University, School of Medicine	Thailand	Departmental	2016.12.20
Fujian Institute of Hematology, Fujian Medical University	China	Departmental	2020.6.3

Scientific symposiums are held regularly at the University of Tokyo New York Office, which IMSUT established together with the Institute of Industrial Science, the University of Tokyo in FY2015. Taking advantage of preferential tax treatment under U.S. accounting rules given for contributors to the Office regardless whether companies or individuals, IMSUT has constructed a framework for fundraising for its research projects to enhance University corporate relations in the U.S.

With the use of cross-appointment systems, two IMSUT Project Professors were appointed at Stanford University and the University of California, San Diego respectively, and one professor was appointed at the University of Chicago. Their cross-appointments have advanced interactive joint research activities between Japan and the US as well as the establishment of our worldwide research network.

6) Contribution to Academic Community

IMSUT was authorized as a Joint Usage/Research Center by MEXT in FY2010, which was followed by its approval as an International Joint Usage/Research Center in FY2018 (Material 27). Consequently, as a leading institute serving the life and medical science field, IMSUT has made a significant contribution to the academic community by offering researchers from Japan and abroad the same access to IMSUT facilities, equipment, and academic samples as its faculty members (Material 13 and 14).

【Material 27】Introduction page of the IMSUT Joint Usage/Research Center (from the MEXT website)

A mass spectrometer in the Medical Proteomics Laboratory is used to support post-translational modification analysis such as protein identification and phosphorylation by the highly sensitive and accurate shotgun method, and relative quantitative analysis between different samples. 95 researchers in total utilized this instrument between FY2016 to FY2019 (Material 13).

The supercomputer system managed by the Human Genome Center of IMSUT is widely utilized by researchers in universities, incorporated administrative agencies and companies. The average number of users per fiscal year has grown to 1,042 (4,168 in total) since FY2016. The number increased 2.2-fold between FY2015 and FY2019, from 630 to 1,408, respectively. These figures show that the system has contributed greatly to satisfying the growing demand both at home and abroad (Material 13).

Multiphoton microscopes and confocal microscopes housed in the Imaging Core Laboratory have been used by 273 researchers per fiscal year on average (1,093 in total) since FY2016. 312 of them, 28.5% of the total, used such microscopes through the Joint/Usage Research Center. Since FY2016, the number of users of the FACS Core Laboratory has grown to more than 3,222 per fiscal year on average (12,891 in total) reaching 3,342 in FY2018, with a 1.3-fold increase compared to 2,592 in FY2015. The figure decreased in FY2019 due to the impact of COVID-19 (Material 13).

As shown in the status of usage/provision/collection of research resources, the number of pathogenic bacteria possessed by the Pathogenic Microbes Repository Unit, International Research Center for Infectious Diseases increased to 1,800 strains in FY2018 from 1,440 strains in FY2015, with 17 in use (66 in total) per fiscal year on average (Material 14).

Since FY2016, an average of 17 DNA samples has been provided per fiscal year by BioBank Japan. BioBank Japan is one of the largest medical databanks in the world which stores medical data and samples such as DNA, serum, and medical records from 267,000 patients with 51 diseases (Material 14).

Genetically modified mice are to be generated and provided on request from researchers in Japan and abroad. Since FY2016, an average of 24 mice per fiscal year has been generated, and an average of 14 per fiscal year (57 in total) has been used by research collaborators (Material 14).

At the Joint Usage/Research Center, IMSUT has enhanced collaboration among its research bases by holding annual research report meetings where researchers from various fields come together, as well as by holding symposiums jointly with bases of other universities from an academic/interdisciplinary point of view. Notably, the number of meetings held for researchers increased to 55 in FY2019 from 23 in FY2016 and the number of participants nearly doubled to 1,714 from 922 (Material 28). Additionally, as part of young scientist development, IMSUT holds a Joint Usage/Research Center-Young Researcher Symposium annually to provide young researchers with the opportunity to organize a meeting on their own to stimulate open-minded discussion, along with regularly scheduled technical seminars which enable them to acquire new research techniques. In FY2019, although 16 International Joint Usage/Research Center Seminars were held by the researchers who work on joint research in Japan and abroad, some of the scheduled seminars, report meetings, and other research meetings were cancelled due to the spread of COVID-19.

【Material 28】Research meetings held at the Joint Usage/Research Center

FY	For Researchers						For the general public							
	Symposium/ Lecture Meeting		Seminar/ Workshop		Total		Symposium/ Lecture Meeting		Seminar/ Workshop		Others		Total	
	Number	Number of Attendees	Number	Number of Attendees	Number	Number of Attendees	Number	Number of Attendees	Number	Number of Attendees	Number	Number of Attendees	Number	Number of Attendees
2016	5	450	18	472	23	922	2	490	23	2,601	27	305	52	3,396
2017	8	861	19	519	27	1,380	0	0	25	1,531	25	471	50	2,002
2018	9	938	24	808	33	1,746	1	124	13	1,231	37	692	51	2,047
2019	5	525	50	1,189	55	1,714	1	140	7	2,811	30	405	38	3,356

(4) Status of Research Results

IMSUT has achieved remarkable success in both basic research aimed at integrated understanding for diseases and applied research progressing towards advanced medical development. The Division of Infectious Diseases, for example, has achieved breakthrough innovations, namely the development of novel treatment and preventive medicine for influenza virus infections and the elucidation of the herpesvirus replication mechanism inside the cell, mechanisms that inhibit host immune response, and the molecular basis of susceptibility to herpes simplex encephalitis. Meanwhile, the Department of Rheumatology and Allergy has achieved pioneering results including the identification of cells that suppress the development of autoimmune diseases, self-RNA recognition control related to SLE onset, functional analysis of IL-25 in contact dermatitis, and the mechanism underlying the establishment of mucosal immunity. In the field of cancer research, important results relating to the elucidation of pathologic molecular processes, effectiveness of treatment, and determination of prognosis have been obtained. The Division of Regenerative Medicine has successfully shed new light on the novel molecular basis by which self-renewal of hematopoietic stem cells (HSCs) is controlled, and has developed innovative technology for stem cell transplantation. Notably, IMSUT has offered invaluable advice on examining “Ethical, Legal and Social Issues” (ELSI) to support medical science in the future, which created an opportunity for deliberations on such issues at government ministries including the office of the Prime Minister and the Health, Labour and Welfare Ministry, as well as for deliberations at the national legislature on a new bill on genomic medicine.

Following these results, 300 academic papers were published in journals with an impact factor of ten or above over the four years starting in 2016 and became disseminated through the Media such as newspapers and TV programs including the Japan Broadcasting Corporation (NHK) (Material 29). IMSUT research achievements were highly evaluated by the government and academic conferences. Since FY2016, 25 awards such as the Japan Academy Prize have been received on average per fiscal year, compared to 19 during the second period (Material 30 and 31).

【Material 29】Mass media coverage of research results

Press Date	Media	Title of Article
2016/4/10	Asahi Shimbun	An IMSUT research team starts clinical trials of peptide vaccine therapy in lung cancer treatment.
2016/5/5	NHK	An IMSUT research team starts clinical trials of vaccine to prevent recurrence of lung cancer.
2016/5/24	The Nikkei/ Asahi Shimbun/ The Mainichi Shimbun/ The Yomiuri Shimbun	An IMSUT research team has developed a new technique for accurately predicting antigenic variants of seasonal influenza viruses.

2016/8/4 -8/6	The Nikkei/ NHK News 7/ The Sankei Shimbun/ The Yomiuri Shimbun	The University of Tokyo's artificial intelligence (AI) "Watson" can detect the correct leukemia type in difficult-case patients in just 10 minutes and advise doctors on treatment methods.
2017/1/26	The Mainichi Shimbun/ The Nikkei/ The Mainichi Shimbun/ The Sankei Shimbun/ The Yomiuri Shimbun	An IMSUT research team succeeded in treating diabetic mice by using iPS cells to create a mouse pancreas in the rat body and transplanting it.
2018/5/25	ABC TV	An IMSUT research team has elucidated a new mechanism of pancreatic cancer development.
2018/6/26	The Mainichi Shimbun	An IMSUT research team has succeeded in *in vivo* imaging the tissue infected with influenza virus.
2019/2/13	The Yomiuri Shimbun	An IMSUT research team has elucidated the mechanism by which the intestinal flora enhances the effect of influenza vaccine.
2019/3/10	The Yomiuri Shimbun	Sharing the biological samples and their information accumulated in Biobank Japan leads to personalized medicine.
2019/3/13	Asahi Shimbun	Members of IMSUT have created mice for modeling pediatric brain tumors using human iPS cells to elucidate its pathological condition and identified new therapeutic targets.
2019/5/30 -5/31	Asahi Shimbun	A University of Tokyo research team has discovered that hematopoietic stem cells can be cultured in large quantities with glue than with expensive culture media.
	The Mainichi Shimbun	A University of Tokyo research team has discovered that hematopoietic stem cells can be cultured in large quantities with glue. This finding may contribute to the treatment of leukemia.
2019/12/5	NHK News	The University of Tokyo starts the clinical trials of Ebola vaccine first in Japan.
	The Nikkei	The University of Tokyo starts Phase I clinical trials of its own developed Ebola vaccine.
2020/3/10	The Nikkei	IMSUT and Hitachi reduce the analysis time by about 80% compared to the conventional model in a verification aimed at speeding up genomic data analysis using Shirokane5, a supercomputer for human genome analysis.
2020/3/18 - 3/19	Nippon Television Network Corporation NEWS 24	The University of Tokyo has announced that Nafamostat, an existing Japanese acute pancreatitis drug, can be expected to prevent the transmission of new coronavirus infection (COVID-19).
	MEZAMASHI TV	The University of Tokyo has announced that a therapeutic drug for acute pancreatitis can be expected to have a therapeutic effect on COVID-19.
	The Nikkan Kogyo Shimbun	The University of Tokyo has announced that their research team has identified a drug candidate for the treatment of COVID-19 and will begin to administer it to patients as early as next month.
2020/5/14	NHK News	An IMSUT research team has discovered that cats are susceptible to the novel coronavirus.
	The Nikkei	An IMSUT research team has discovered that the novel coronavirus spreads easily among cats.
2020/6/3 -6/4	The Nikkei	A University of Tokyo research team has developed an accurate and rapid diagnostic method for the novel coronavirus infection using CRISPR-Cas3.
	The Mainichi Shimbun	Using genome editing technology, a University of Tokyo research team has developed a method that can diagnose the novel coronavirus infection in about one hour.

【Material 30】Number of awards

Awarding Body	FY 2010	FY 2011	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	FY 2019
Government	2	5	3	1	0	1	3	4	2	2
Academic Societies	10	5	7	9	8	15	10	20	18	12
Foundations	4	2	1	8	5	12	6	6	2	3
Others	0	8	1	2	3	3	5	2	2	2
Total	16	20	12	20	16	31	24	32	24	19

【Material 31】Major awards

Award Date	Name of Award	Title	Name of Awarded Faculty Member
2016/4/23	The 36th JES Research Award (The Japan Endocrine Society)	Elucidation of the mechanism and physiological significance of the control of skeletal muscle protein metabolism by Glucocorticoid	Noriaki Shimizu
2016/6/27	Japan Academy Prize (The Japan Academy)	Molecular basis of pathogenicity and control of influenza viruses	Yoshihiro Kawaoka
2016/10/8	FY2016 (The 35th) The Young Investigator Awards of the Japanese Cancer Association (The Japanese Cancer Association)	International comparison of pharmaceutical regulations for anti-cancer agents and companion diagnostics	Sumimasa Nagai
2016/11/30	The 3rd Innovator of the Year (Japan Hospital Association/Japan Association for Development of Community Medicine/ MSD)	Development of viral therapy for cancer originating in Japan	Tomoki Todo
2017/4/19	FY2017 The Young Scientists' Prize (The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology)	Studies on host proteins involved in intracellular transport of RNA viruses	Seiya Yamayoshi
2017/4/19	FY2017 The Young Scientists' Prize (The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology)	Studies on the control mechanism of intestinal homeostasis by intestinal bacteria and type 3 natural lymphocytes	Yoshiyuki Goto
2017/4/19	FY2017 The Young Scientists' Prize (The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology)	Studies on pathogenic mechanism of herpes simplex virus	Jun Arii
2017/9/30	FY2017 (The 36th) The Young Investigator Awards of the Japanese Cancer Association (The Japanese Cancer Association)	Elucidation of control mechanism of cancer microenvironment by non-protease activity of membrane type I-matrix metalloproteinase (MT1-MMP)	Takeharu Sakamoto
2017/10/25	The 2017 Sugiura Incentive Award of the Japanese Society for Virology (The Japanese Society for Virology)	Functional analysis of host proteins that contribute to the growth process of RNA viruses	Seiya Yamayoshi

2017/12/2	The 6th Takahashi Incentive Award of the Japanese Society for Vaccinology (The Japanese Society for Vaccinology)	Studies on Nasal Influenza Vaccine Combined with Adjuvant	Takeshi Ichinohe
2018/10/26	The 54th the Cultural Award for the Memorial of Saburo Kojima (Kurozumi Medical Foundation)	Elucidation of the mechanism of proliferation and pathological expression of herpes simplex virus	Yasushi Kawaguchi
2018/10/29	The 2018 Sugiura Incentive Award of the Japanese Society for Virology (The Japanese Society for Virology)	Elucidation of cell invasion and particle formation processes of herpes simplex virus	Jun Arii
2018/12/27	The 2nd Japan Medical Research and Development Awards -AMED President's Award (Japan Agency for Medical Research and Development (AMED))	Development of anti-metastatic drug for cancer targeting oxygen sensing mechanism with high safety	Takeharu Sakamoto
2019/2/22	FY2018 (The 48th) Princess Takamatsu Cancer Research Fund Prizes (Princess Takamatsu Cancer Research Fund)	Clinical Development of Oncolytic Virus Therapy Using Genetically Engineered Herpes Virus	Tomoki Todo
2019/7/25	The Kodama Prize, Japanese Electrophoresis Society Award (Japanese Electrophoresis Society)	Electrophoresis for the latest clinical medicine to hematopoietic tumors	Hiroshi Yasui
2019/8/2	The 56th Young Investigator Awards of the Japanese Society for Mucosal Immunology (The Japanese Society for Mucosal Immunology)	Analysis of human enterovirus flora and its database construction	Kosuke Fujimoto
2019/10/2	FY2019-2020 Veterinary Science Young Investigator Awards (Japanese Society of Veterinary Science)	In vivo imaging of influenza virus-infected lungs	Hiroshi Ueki
2019/10/11	The 8th Japan Society of Hematology Award (JSH Award) (The Japanese Society of Hematology)	Studies on the molecular biological analysis of hematopoietic tumors using a mouse model and the possibility of therapeutic application	Toshio Kitamura
2019/12/12	The 22nd (2019) The Japanese Society for Immunology Award (JSI Award) (The Japanese Society for Immunology)	Vaccine adjuvant: the old wisdom towards novel immunotherapeutics	Ken Ishii
2020/1/10	The 3rd Japan Medical Research and Development Awards -AMED President's Award (Japan Agency for Medical Research and Development (AMED))	Development of low-cost mass culture technology for hematopoietic stem cells	Satoshi Yamazaki

The total number of academic papers released by the Joint Usage/Research Center over the past four years has grown to 721 (Material 17), while IMSUT has applied for three patents since FY2016, based on the inventions in the joint research funded by the Joint Usage/Research Center project

(Material 21).

In FY2018, IMSUT received an "S" rating in the FY2018 interim evaluation by the Committee of MEXT. The Committee commented: IMSUT has many excellent researchers and a good range of facilities and equipment for its joint usage to conduct research activities vigorously. Also, its members are successfully implementing three projects at the Functional Enhancement Center, namely “International Genomic Medical Research Organization”, “Alliance in Research and Education for the Control of Infectious Diseases”, and “International Base for Research and Development of Mucosal Vaccines Furthermore, in the same fiscal year, IMSUT was authorized by MEXT, as the only International Joint Usage/Research Center in the fields of medical science and biology.

(5) Status of Education Activity

The number of PhD recipients increased from FY2016 to FY2018, yet the trend turned downward in FY2019 due to a gradual decrease in the number of students. Regarding the employment situation, most job applicants in FY2016 obtained work as post-doctoral fellows, while there has been an increasing number of PhD recipients who became employed as university faculty staff or as company staff in recent years (Material 32).

【Material 32】Number of doctoral degree recipients and their employment situation

FY	Number of Doctoral Degree Recipients（those employed in overseas institutions）	Faculty member at University	Postdoc	Public Institutions	Company	Others
2016	21 (4)	1 (0)	12 (3)	2 (0)	4 (1)	2 (0)
2017	27 (3)	2 (0)	10 (2)	1 (0)	10 (1)	4 (0)
2018	31 (1)	4 (0)	8 (1)	3 (0)	11 (0)	5 (0)
2019	17 (2)	3 (0)	5 (2)	1 (0)	4 (0)	4 (0)

(6) Status of Social Cooperation

IMSUT set up several Social Corporation Research Programs and Corporate Sponsored Research Programs to vigorously promote industry-academia-government collaboration. Since FY2016, three

new programs have been launched to promote the social implementation of research results targeting the development of biopharmaceutical and immunity/gene therapy, the study of the disease prophylaxis based on genome information, and the cultivation of young scientists in these areas: namely the Project Division of Advanced Biopharmaceutical Science, the Project Division of Cancer Biomolecular Therapy, and the Project Division of Genomic Medicine and Disease Prevention. Furthermore, it has been decided that three Social Corporation Research Programs (the Project Division of RNA Medical Science, the Project Division of International Advanced Medical Research, and the Project Division of Advanced Biopharmaceutical Science) shall be renewed from FY2020 onward. Meanwhile, two Corporate Sponsored Research Programs launched in FY2014 and in FY2015 (the Project Division of Molecular and Developmental Biology and the Project Division of Fundamental Study on Cutting Edge of Genome Medicine) have been renewed to promote the development of Regenerative therapy and Genomic medicine, respectively (Material 33).

【Material 33】Social Cooperation Research Programs and Corporate Sponsored Research Programs

Social Cooperation Research Programs (Period)	Purposes of Research	Research Activities
RNA Medical Science (2012.4 - 2015.3) (2015.4 - 2020.3) (2020.4 - 2023.3)	・Understanding of the possibilities and functions of RNA in the life sciences ・Exploration of the great potential of RNA ・Research into development of new RNA drugs that respond to unmet medical needs by new functional mechanisms	・Aptamer molecules that specifically bind to various target proteins has been created using systematic evolution of ligands by exponential enrichment (SELEX). ・A practical drug discovery platform has been constructed. ・Research and development for clinical trials is currently underway in the program.
Systems Immunology Research (2014.9 - 2019.3) (2019.4 - 2019.9)	・Creation of a new academic field called systems immunology which is a fusion of immunology and systems biology ・Development of young scientists in this field	Using supercomputer, ・super-high speed analysis platform for intestinal microbiota has been constructed. ・relations between symbiosis, homeostasis and diseases have been studied.
Advanced Regenerative Medicine (2014.10 - 2017.9)	・ Advancement of fundamental study of clinical research that can be expanded internationally to realize the most advanced regenerative medicine ・ Development of young scientists in this field	・Through fundamental research on regenerative medicine using mesenchymal cells, disease-specific iPS cells for pathological analysis and drug discovery have been established.
International Advanced Medical Research (2014.11 - 2017.10) (2017.11 - 2019.10) (2019.11 - 2022.10)	・ Enhancement of human resources necessary for the development of advanced medicine and consideration of the formation of bases, for the purpose of returning the research achievements of genome, cancer, infectious diseases, etc. to society	・Cutting edge medical research and the activation of the "place" necessary for its further development are currently ongoing. ・Development of young scientists in this field has been promoted.

ALA Advanced Medical Research（2015.4 - 2020.3）	Through basic and clinical application research of 5-aminolevulinic acid, the program has aimed for: ・ contribution to the development of basic medicine and medical fields ・ social contributions such as the improvement of the standards of medical institutions and medical educational institutions in Middle East Gulf countries	Preliminary experiments have been started relating to: ・detection of circulating cancer cells using 5-aminolevulinic acid ・enhancement of cell lethality by combination with oncolytic virus ・promotion of differentiation of induced pluripotent stem (iPS) cells
Advanced Biopharmaceutical Science (2017.4 - 2020.3) （2020.4 - 2023.3）	・ Study into advanced antibody creation in the biopharmaceutical research field ・ Development of specialized young scientists in this field	・To address the molecular structure problems of biopharmaceuticals such as glycan heterogeneity, the program has aimed to conduct research on the creation of protein pharmaceuticals such as antibodies, using artificial intelligence and an epoch-making biopharmaceutical creation evaluation technique. ・Development of young scientists to lead the next generation of this research field and the dissemination of international standardization technology have been facilitated by the implementation of advanced creative research.
Cancer Biomolecular Therapy （2018.4 - 2021.3）	・ Study into immunotherapy and gene therapy using various biomolecules to develop innovative treatments for cancer ・ Development of specialized young scientists through the research process	・Research and development of "advanced cancer immunotherapy" such as a technique to release the immunosuppressive state, and "gene therapy" including treatment with oncolytic virus with invasion selectivity are currently ongoing. ・The program aims to develop young scientists to lead the next generation of this research area and to give back epoch-making technology to society by the implementation of advanced drug discovery research.
Genomic Medicine and Disease Prevention （2019.7 - 2022.6）	・ Clarification of disease risk factors based on genome information and health check-up data ・ Research towards social implementation of effective disease prevention methods ・ Development of young scientists in this field	・Identification and verification of disease-related alleles among the Japanese; construction of a disease risk prediction model and examination of prevention measures; and further study of ethical, legal, and social issues (ELSI) on the social implementation of these methods are currently ongoing in the program.

Corporate Sponsored Research Programs (Period）	Purposes of Research	Research Activities
Molecular and Developmental Biology (2014.4 - 2019.3) (2019.4 - 2020.3) (2020.4 - 2021.3)	・Formation of a base for basic research into the clinical application of tissue stem cells and neural cancer stem cells; and its international development	・Creation of retinal degeneration models and elucidation of the molecular basis involved in the onset and progression of its pathogenesis ・Identification of genes that can be therapeutic targets in the development of brain tumors

Fundamental Study on Cutting Edge of Genome Medicine (2015.10 - 2018.9) (2018.10 - 2020.3) (2020.4 - 2021.3)	・ Implementation of fundamental research on system development to realize advanced genomic medicine	・Establishment of cooperation among multiple facilities ・Acquisition of informed consent in the clinic and establishment of an information protection system ・Maintenance of data/sample management

As a regional partnership, IMSUT and the Minato Ward Medical Association have been jointly holding monthly medical open lectures (23 times since FY2016, with 1,726 participants in total). On top of this, IMSUT has been promoting an ongoing relationship with the residents based on the IMSUT-Minato Ward Partnership Agreement since FY2013.

As part of IMSUT outreach activities, IMSUT provides junior high and high school students with opportunities to visit its laboratories and research centers. Since FY2016, the number of schools and students joining such activity has significantly increased (Material 34).

【Material 34】Acceptance of visits from junior and senior high school groups

FY	2016	2017	2018	2019
Number of schools students were accepted from	25	22	29	28
Number of students accepted	245	261	370	345

(7) Issues and Future Prospects

IMSUT has maintained a consistent standard in recent research activities, with regard to both quantity and quality of academic papers. Regarding the fund-raising situation, the amount of income from external sources has steadily increased. Our education programs also maintain an adequate standard in terms of both the number of postgraduates and of degree recipients. In the future, IMSUT aims to devote our efforts to further improve research and educational activities by enhancing our overall research and educational environment. Meanwhile, as of November 2018, IMSUT has been authorized by MEXT as the only International Joint Usage/Research Center in the fields of life science and biology. Our mission at the Center is to accelerate these activities, furthering not only IMSUT yet also the entire life science field in Japan, as well as to play the leading role in the development of this research network in Japan and abroad. Furthermore, IMSUT plans to expand its organization and provide full support to various projects adopted by the Grants-in-Aid for Scientific Research, such as the Scientific Research Project on Innovative Areas "Platforms for Advanced Technologies and Research Resources", the BioBank Japan Project for Genomic and Clinical Research "Management of BioBankJapan (BBJ) for utilization of the human materials and medical

information", and the Translational Research Network Program "Strategic Promotion and Expansion of a Translational Research to Establish a Global Base for Knowledge Collaboration".

II. Detailed Exposition

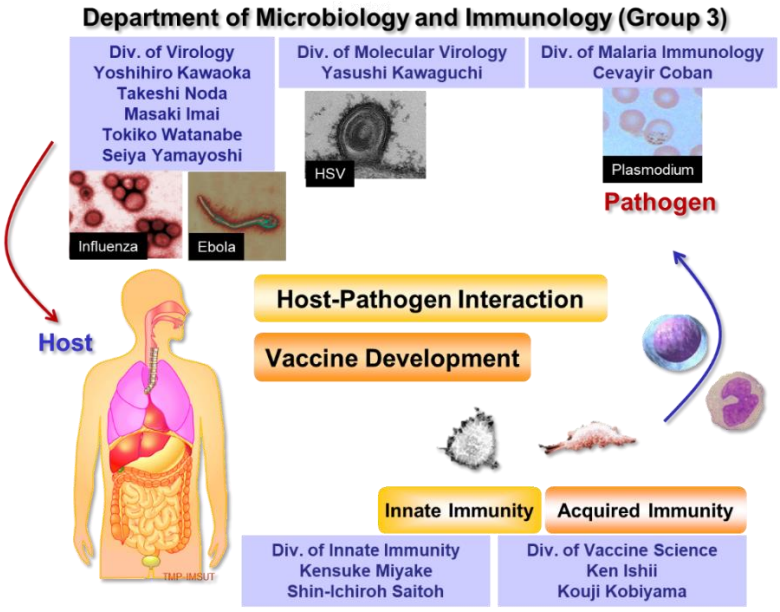
Department of Microbiology and Immunology

Chair Kensuke Miyake

（1）Missions and Features

The growing concern in emerging and re-emerging infections increases a demand for understanding and controlling such infectious diseases. Our department focuses on: the elucidation of molecular interactions between pathogens and hosts; molecular recognition of microbial products by the immune system; and molecular mechanisms controlling host defense systems. The department is composed of 5 divisions. Our department particularly studies the pathogens such as Influenza virus, Ebola virus, Herpes Simplex Virus, and malaria. We are working together to understand molecular mechanisms underlying host-pathogen interactions and develop novel vaccines or small chemicals to control infectious diseases and related immune disorders. Our research activities go beyond our institute and have been successfully running joint research projects in the area of infection and immunity with other research groups in Japan and abroad. The department is also promoting collaborative projects with IMSUT Research Hospital as well as with pharmaceutical companies for the development of drugs and vaccines. Another important mission of our department is to promote development of young independent investigators in the fields of microbiology and immunology.

This figure below shows 5 divisions in the Department of Microbiology and Immunology. Three divisions mainly focus on pathogens such as Influenza virus, Ebola virus, Herpes Simplex Virus, and malaria, whereas two divisions focus on host immune responses against pathogens. These divisions work together to understand the molecular bases underlying host-pathogen interaction and to develop novel vaccines or novel therapy for infectious diseases or related immune disorders.



（２）Organization

Division of Virology

Division of Mucosal Immunology

Division of Infectious Genetics

Division of Molecular Virology

Division of Vaccine Science

Division of Malaria Immunology

（３）Activity Reports

１）Research Activities

Each division, with its own goals, publishes papers, presents results in scientific meetings, and files patents. Details are described below.

２）Education Activities

Each division trains graduate students in its own lab and gives lectures in graduate schools.

３）Social Activities

Each division contributes to out-reach activities. For example, the Division of Virology have been organizing a seminar “Love Labo” and welcoming a visitor outside the academic community.

４）International Activities

Professor Yoshihiro Kawaoka takes advantage of cross appointment in the University of Tokyo to have concurrent appointment in University of Wisconsin in USA. Project Professor Hiroshi Kiyono also holds a post in the University of California at San Diego. Furthermore, a number of collaborations with research groups abroad, such as those in Pasteur Institute in France, are ongoing.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

Our department continues our research activities and training for young scientists to understand and control infectious diseases. To accomplish this mission, we need to recruit young talented scientists. Profs. Sasakawa, Iba, and Kiyono retired, whereas Profs. Ishii and Coban have joined in our department. Further recruitment of young talented scientists is essential for our department.

Division of Virology

（１）Members

Professor	Yoshihiro Kawaoka
Visiting Professors	Takeshi Noda, Tokiko Watanabe
Associate Professor	Masaki Imai
Project Associate Professor	Seiya Yamayoshi
Assistant Professors	Kiyoko Iwatsuki-Horimoto, Shinya Yamada
Project Assistant Professors	Maki Kiso, Hiroshi Ueki
Research Associate	Yuko Sakai-Tagawa
Postdocs	1
Graduate students	9
Technicians	1
Others	4

（２）Research objectives

Viruses can cause devastating diseases. The long-term goal of our research is to understand the molecular pathogenesis of viral diseases by using influenza and Ebola virus infections as models. Interactions between viral and host gene products during viral replication cycles determine the consequences of infection (i.e., the characteristics of the disease and whether it is limited or widespread); hence, our research has centered on studying such interactions in these viral infections. We are now also conducting research on SARS-CoV-2.

（３）Activity Reports

１）Research Activities

We are performing various molecular biology, immunology, and epidemiology studies. The following summarizes some of our achievements. In influenza research, we characterized highly pathogenic H7N9 avian influenza virus in China (Cell Host & Microbe, 2017), elucidated the influenza virus packaging mechanism (Nature Commun, 2018), established a method to predict future human influenza strains (Nature Microbiol, 2019), identified new neuraminidase antigenic epitopes recognized by human monoclonal antibodies (Nature Microbiol, 2019), found the frequent emergence of baloxavir marboxil-resistant influenza viruses in humans (Nature Microbiol. 2020), and developed a cell line that can efficiently isolate H3N2 seasonal influenza viruses without mutation (Nature Microbiol, 2019). In Ebola virus research, we developed an inactivated Ebola vaccine (Science, 2015), and identified biomarkers that predict the severity of Ebola virus disease (Cell Host & Microbe, 2017). Most recently, we reported the efficient transmission of SARS-CoV-

2 in cats (New Engl J Med, 2020) and the efficient serum treatment of COVID-19 and lack of re-infection in a hamster model (PNAS, in press).

Specifically, we published the following papers. FY2016, 17 papers (including 1 in Nat Microbiol; 1 in Nat Immunol; 1 in Proc Natl Acad Sci USA); FY2017, 19 papers (including 2 in Cell Host & Microbe; 1 in Proc Natl Acad Sci USA; 1 in Nature Commun); FY2018, 33 papers (including 1 in Cell; 1 in Nature; 2 in Cell Host & Microbe; 2 in Proc Natl Acad Sci USA); FY2019, 35 papers (including 1 in Cell; 3 in Nature Microbiol; 1 in Nature Protocol); and FY2020 as of June 01, 7 papers (including 1 in N Engl J Med)

We also filed the following patent applications:

Filing date 23 Feb 2017; Suction retainer and method for observing internal tissues

Filing date 27 Mar 2017; Adjuvant and vaccine containing the adjuvant

Filing date 22 Aug 2017; Monoclonal antibody against hemagglutinin antigen of the influenza a virus, and its antigen-binding fragment

Filing date 08 Feb 2019; Humanized cell line (PCT filed)

２）Education Activities

Our laboratory takes on average 2 new doctoral students and 2 new master's students each year. We train our students to obtain their degree without a drop or delay. Our goal is to train young scientists to work internationally. Since 2016, we have taken the following graduate students: 2 doctors and 3 masters in Apr 2016, 3 doctors and 2 masters in Apr 2017, 2 doctors and 3 masters in Apr 2018, and 3 masters in Apr 2019. From FY2017 to FY2019, we accepted and mentored 2 students from other PhD programs (internal medicine and surgical medicine).

Of the students who graduated from the master's course in FY2016 to 2019, one student went on to the doctoral course each year. Of the students who graduated from the doctoral course in FY2016 to 2019, three students became Postdoctoral Researchers of the Univ. of Wisconsin-Madison, Mt Sinai medical school, and Osaka Univ., a student became a doctor of the Infectious Disease Emergency Specialist Training Program, the Ministry of Health, Labour and Welfare, and two student became assistant professors at Tohoku Univ. and the Univ. of Tokyo.

In April 2019, one postdoctoral researcher became a researcher (PI) at the Institute of Biomedical Sciences, Academia Sinica, Taiwan, and one postdoctoral researcher was promoted to assistant professor at the Univ. of Tokyo.

３）Social Activities

We hold open seminars "LOVE LABO" and "LOVE LABO Laboratory Tour" during every summer vacation. We also host a laboratory tour of 40 high school students from Kobe High School every year. In addition, from April 21 to August 31, 2016, we exhibited panels and images at the

influenza and Ebola booth of the special exhibition "World of Invisible Viruses" at the Museum of Health and Medicine of the Univ. of Tokyo.

４）International Activities

Prof. Kawaoka also holds a professorship at the Univ. of Wisconsin-Madison, USA using the Univ. of Tokyo's cross-appointment system. We have conducted many international collaborative studies with the Univ. of Cambridge, Univ. of Pittsburgh, New York Univ., Univ. of Chicago, NIH, CDC, Vietnam NIHE, Gabriel Rene Moreno Univ. (Bolivia), Sierra Leone Univ, Erasmus Univ. Rotterdam (Nederland), and Univ. Estadual Paulista (Brazil).

We have also conducted international joint research on influenza viruses with Harbin Veterinary Research Institute as a Sub-Center of Asian Infectious Disease Research Center of IMSUT.

In addition, we held the following international symposia:

26 Aug 2017: Neo-virology: co-evolution and symbiosis of viruses

28 Aug 2018: Neo-Virology: co-evolution and symbiosis of viruses

02 Nov 2018: The 7th China-Japan Bilateral Symposium on All Influenza Viruses

19-20 Feb 2019: Influenza and Other Infections

５）Other matters to be noted

Lab members received the following awards:

Feb 2017	The 45th Annual Meeting of the Japanese Society for Immunology, Best presentation award winner (Postdoc Ueki)
Mar 2017	IMSUT Outstanding student publication award FY 2016 (D3 Nakatsu)
Apr 2017	Young Scientist Awarded by MEXT (Project Assoc Prof Yamayoshi)
Sep 2017	The Japanese Society of Veterinary Science, the 8th Vet. Microbiology Best presentation award winner (D3 Nakao, D2 Takada)
Aug 2017	Sugiura Young Investigator Award, The Japan Society for Virology (Project Assoc Prof Yamayoshi)
Apr 2018	Japanese Society for Immunology, Tadamitsu Kishimoto International travel award winner (Postdoc Ueki)
Sep 2018	The 27th Annual Meeting of the Bioimaging Society of Japan BIOIMAGING, Best imaging Carl Zeiss award winner (Postdoc Ueki)
Mar 2019	The 47th Annual Meeting of the Japanese Society for Immunology, Best presentation award winner (Postdoc Ueki)
Mar 2019	IMSUT Most outstanding student publication award FY 2018 (D3 Yasuhara)
Sep 2019	The Japanese Society of Veterinary Science, Veterinary Science Young Investigator Award winner (Project Assist Prof Ueki)

Mar 2020　Outstanding student publication award FY 2019 (D4 Takada)

（４）Challenges and Future prospects

Professor Kawaoka is scheduled to retire from his current position. Whether he will continue his research at the IMSUT of the University of Tokyo remains unknown. Nonetheless, his lab members continue to work hard to try to control influenza viruses, Ebola viruses, and SARS-CoV-2.

Division of Infectious Genetics

（１）Members

Professor	Kensuke Miyake
Associate Professor	Shin-ichiroh Saitoh
Assistant Professors	Ryutaro Fukui, Takuma Shibata
Project Assistant Professor	Ryota Sato
Graduate students	7
Technicians	3
Others	1

（２）Research objectives

Division of Infectious Genetics focuses on Toll-like receptor (TLR), pathogen sensors in the innate immune system. We would like to understand molecular mechanisms controlling pathogen sensing and TLR responses. We also would like to understand cellular and molecular mechanisms by which TLRs drive inflammatory diseases and to develop a novel therapy targeting TLRs to control such TLR-dependent diseases. Since April 2016 to March 2019, we tryed to publish papers on the relationship between TLR trafficking and type I interferon production. We focused on single stranded RNA sensor TLR7 and double stranded RNA sensor TLR3. We also tryed to publish a paper and file a patent on the control of autoimmune and inflammatory diseases with a monoclonal antibody to TLR9. As for education, we tried to train graduate students in our laboratory and by give lectures.

（３）Activity Reports

１）Research Activities

We published 28 papers including a paper in Nat Immunol, 2 papers in Immunity, 3 papers in Nat Commun, a paper in PNAS, and 3 reviews. We reported that TLR7 traffics from the perinuclear region to the peripheral region beneath the plasma membrane to induce type I interferon (IFN) (S. I. Saitoh et al., Nat Commun 8, 1592, 2017)。TLR7-trafficking depends on a GTPase Arl8b. TLR3-dependent type I IFN production, on the other hand, depends on Rab7a-dependent lysosomal trafficking to the cell periphery. (R. Sato et al., Nat Immunol 19, 1071-1082, 2018)。Furthermore, we have established anti-mouse TLR9 monoclonal antibody (mAb), which is able to inhibit TLR9 responses. The anti-TLR9 mAb protects mice from TLR9-dependent lethal hepatitis caused by TLR9 ligands (Y. Murakami et al., Sci Rep 7, 44042, 2017).

We also obtained a patent on anti-TLR7/8/9 mAb (Aug 1, 2018). Furthermore, 3 patents have been filed as below.

1. Analyses of soluble TLR7 in human samples.

2. Anti-human TLR7 mAb
3. Anti-TLR9 mAb

２）Education Activities

Four students in master course and a student in PhD course finished their courses. Prof. Miyake gave 6 lectures a year in Faculty of Sciences.

３）Social Activities

None.

４）International Activities

We are collaborating with Prof. Eicke Latz in Bonn University, Germany. A student in Bonn Univ. came to our lab and she is going to work here for 2 and half years.

５）Other matters to be noted

We are collaborating with Prof. Eicke Latz in Bonn University, Germany. A student in Bonn Univ. came to our lab and she is going to work here for 2 and half years.

（４）Challenges and Future prospects

We were able to publish a paper as aimed in the beginning of this term. We also filed and obtained patents as planned. As for education, we trained graduate students in my laboratory and gave lectures. In the next term, we would like to publish a paper on the relationship between TLR7 and histiocytosis. In parallel, we would like to develop anti-human TLR mAb for the control of an autoimmune disease in collaboration with a pharmaceutical company. The goal of our research is to understand molecular mechanisms behind pathogen sensing by TLRs, and roles of TLRs in human autoimmune diseases. For education, we would like to have all the graduate students to finish their master or PhD courses.

Division of Molecular Virology

（１）Members

Professor	Yasushi Kawaguchi
Assistant Professors	Akihisa Kato, Naoto Koyanagi, Yuhei Maruzuru
Technicians	4
Graduate Students	6
Others	3

（２）Research objectives

We have set as one of our short-term goals to have several reports on the results of our research activities each year concerning the basic research in virology published in the Journal of Virology (JVI), which is regarded as the well-established and authoritative journal in the field of virology. In addition, we aim to develop a strategy for the treatment and prevention of herpes simplex virus infections that can benefit society. Regarding our educational activities, we have set a target for 80% of our PhD students to earn their degree.

（３）Activity Reports

１）Research Activities

Research to date focusing on the herpes simplex virus has made progress in clarifying the mechanisms of viral growth and pathological expression *in vivo*. The goal of these research activities is to publish multiple reports in the JVI every year, with our research staff being recognized as the primary author (i.e. first author or corresponding author). As such, our goal from 2016 to March 2020 was to publish more than eight results reports in the JVI, and in fact, during this period, we published 27 academic papers and two review articles, with our research staff recognized as primary author in 19 of these publications.

In addition, 12 of our papers were published in the JVI, and four were published in journals with an impact factor (IF) of 10 or more (J. Clin. Invest: 1, Nat. Immunol.: 1, Nat. Commun.: 1, Cell Host & Microbe: 1). The number of research reports published in the JVI reached our initial target, and notably, four reports were published in academic journals of IF10 or higher. Thus, from the perspective of research achievements, we believe our results have exceeded our target. Maintaining this level of research productivity in the future will be a challenge, and we will strive to maintain (expand as needed) our body of research personnel and research equipment inventory.

２）Education Activities

Regarding our educational activities, we have set a target for 80% of our PhD students in the field

of viral disease control to earn their degree. In fact, 6 of 7 students (85.7%) who completed their final year of their doctoral research from 2016 to 2019 successfully earned their degrees, allowing our goal to be realized.

３）Social Activities

In this laboratory, our long-term goal is to develop a strategy for the treatment and prevention of herpes simplex virus infections that can benefit society, and in March 2019, a novel herpes simplex virus (HSV) vaccine developed from our research findings in this laboratory was licensed to a company. In the future, we will aim to produce research results promising benefits to society by working towards the concrete goal of “developing an HSV vaccine” together with our industry partners.

４）International Activities

Professor Kawaguchi concurrently serves as the Project Director of the Research Center for Asian Infectious Diseases, which promotes international collaboration between this Institute and several Chinese research institutes, and the assistant professors in this laboratory are also members of this research center. We have contributed greatly to international cooperative activities with Chinese scientists.

５）Other matters to be noted

Dr. Kawaguchi was the recipient of the 4th Terumo Foundation Award in 2016 and the 54th Kojima Saburo Memorial Award in October 2018. Assistant Professor Arii was chosen for a Commendation for Science and Technology Young Scientists’ Prize by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in April 2017 and received a Sugiura Incentive Award from the Japanese Society for Virology in October 2018. Dr. Arii joined the faculty of the Kobe University School of Medicine and was promoted to an Associate professor in August 2019. Further, Special Research Appointee Dr. Oyanagi was promoted to Assistant Professor in August 2018, and Dr. Maruzuru was promoted to Special Assistant Professor in February 2019, and then to Assistant Professor in February 2020.

（４）Challenges and Future prospects

As described above, we were able to announce the results of our research activities in this field from 2016 to March 2020, which have greatly exceeded our initial goals in both quantity and quality. Maintaining the level of research productivity seen over the last four years will be a major challenge for the future, and to meet this challenge, we will work to produce results promising benefits to society by promoting commercialization and clinical development of HSV vaccines licensed by

members of industry.

Division of Vaccine Science

（１）Members

Professor	Ken J. Ishii
Associate Professor	Kouji Kobiyama
Project Senior Assistant Professor	Hideo Negishi
Assistant Professor	Burcu Temizoz
Postdocs	1
Graduate students	3
Technicians	2
Others	2

（２）Research objectives

Primary goal of our laboratory is to understand the immunological mechanisms of the intra- and inter-cellular signaling pathways that mediate the immunogenicity of successful vaccines, as well as biological responses to adjuvants. Such knowledge will enable us to develop novel concepts, modalities and next generation immuno-preventive and/or therapeutic agents against infectious diseases, cancer and allergy as well as other non-communicable diseases.

（３）Activity Reports (2019-2020)

１）Research Activities

After moving from NIBIHON and Osaka U to IMS, U Tokyo, I successfully recruited Dr. Kouji Kobiyama from K Lay lab, Lajolla Inst, CA, USA and Dr. Hideo Negishi from T. Taniguchi Lab, U Tokyo, and Dr. Burcu Temizoz, Lab Vaccine Science, IFREC, Osaka U. It took time for us to set up the lab, but now I feel lucky and motivated to initiate new research on vaccine science including those on COVID-19 and boost our current on going research on cutting edge immunological research and development of novel vaccines and immune-therapeutics.

The recent progress during 2019-2020 are;

17 research papers, 10 invited talks in the international meetings and 27 presentation in domestic meetings. 2 patents are issued, 4 patents are filed.

The current on going projects are;

A. Extracellular nucleic acids and their immunological roles and therapeutic applications (supported by JST CREST (2018-2024, total 300M yen/5y)
B. Application of adjuvant for vaccine and immunotherapy; machine learning versus classical immunology (supported by AMED, 2019-2021, 30M yen/3y)
C. mRNA vaccine preclinical development and its mechanism of action (COVID-19, HPV, MERS,

supported by MHLW, AMED CICLE, NIBIOHN, respectively. 50M yen 2019-2020)

D. R&D of vaccine adjuvant and its immunotherapeutic application to infectious diseases, cancer and allergy. (supported by companies including Zeria Pharma, UMN pharma, Torii Pharma, Daichi Sankyo, 30M yen 2020)

２）Education Activities

During 2019-2020, we have one PhD student graduated (via Kumamoto U), One master student graduated (via Osaka U). We have 3 students currently (One PhD, two MS students at CBMS, U Tokyo). We are in charge of many lectures, including those in CBMS, School of Pharmaceutical Science, School of Medicine, U Tokyo, and those in Osaka U, NUS (Singapore), Erasmus U (Netherland),

３）Social Activities

Since we joined IMSUT 2019, the latter half has been under COVID-19 pandemic. Nevertheless, we conducted many social activities during 2019-2020.

A. Editorial activities; Associate Editor: J. Immunology, Vaccine, Frontiers in Immunology, Int. Immunology, Advisory board: EBIOmedicine, Oncotarget, npjVaccine,
B. Organizer activities; Elsevier Vaccine Congress 2019 (Journal Vaccine), ISV2019 (International society of Vacciniology), JSV2019, JSI2019, Japanese Adjuvant Research Consortium meeting 2019
C. Advisor activities; Japanese Government (MHLW, MEXT, advisor for infectious disease research, COVID-19), AMED (Program officer for Rare Disease Dep). IVI (SAG member, International Vaccine Institute, Korea), GHIT (Scientific Committee member, Global fund in Japan), 2nd Human and Translational Immunology Conference 2019 (Co-organizer,

４）International Activities

International collaboration with NIH (US), FDA (US), Lajolla I (USA), Pen State U (USA), Oxford U (UK), NUS (Singapore), Pasteur Inst (France). Erasmus Med Center (Netherland), Hacettepe U (Turkey), Bilkent U (Turkey), DNDi (Switzerland),

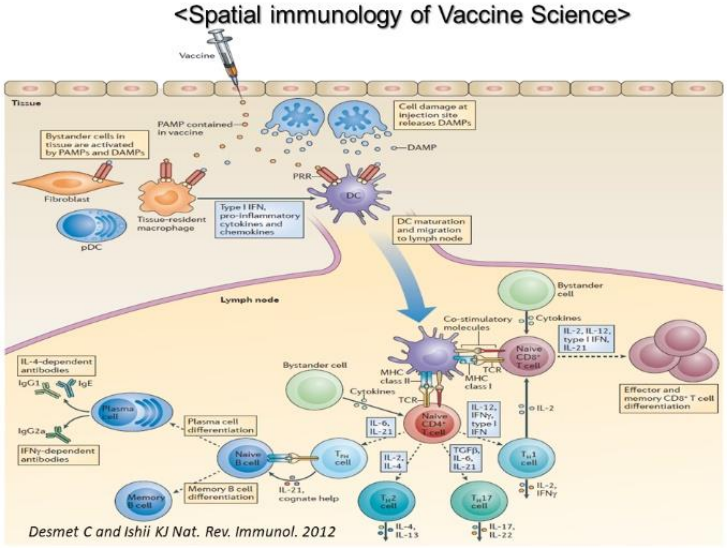
５）Other matters to be noted

I am dually affiliated at National Institute of Biomedical Innovation, Health and Nutrition (NIBIOHNhttp://www.nibiohn.go.jp/adjuvant/index-e.html), and at Immunology Frontier Research Center (IFReC), Osaka University (http://www.ifrec.osaka-u.ac.jp/en/laboratory/ken_j_ishii/)

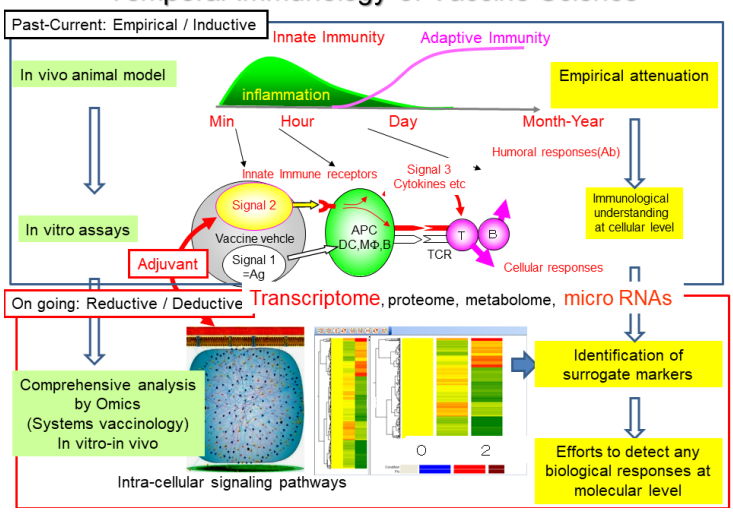
（4）Challenges and Future prospects

Vaccine target diseases are now not only restricted to a framework of infectious diseases but include a broad range of diseases such as cancer, allergy, Alzheimer's disease, and many other lifestyle-related diseases. We will continue ‘innovative’ research and development vaccines against these diseases together closely with our domestic and international collaborator accompanying active exchanges of researchers.

<Spatial immunology of Vaccine Science>



<Temporal Immunology of Vaccine Science>



Division of Malaria Immunology

（１）Members

Professor	Cevayir Coban
Project Associate Professor	Takako Negishi-Koga
Project Assistant Professor	Michelle Sue Jann Lee
Graduate students	2
Others	1

（２）Research objectives

Malaria is an infectious disease caused by *Plasmodium* parasites that often leads to severe complications such as cerebral malaria and death. Moreover, millions of people living in endemic areas suffer from asymptomatic- or post-malaria complications. In our lab, we focus on the elucidation of the mechanisms involved in the host and *Plasmodium* parasites interactions. Our final goal is to develop vaccines and vaccine modalities against malaria and other infectious disease.

（３）Activity Reports

１）Research Activities (From June 1, 2019 to June 1, 2020)

＜English original paper / Peer reviewed＞

1. *Lelliott PM, Momota M, Shibahara T, Lee MSJ, Smith NI, Ishii KJ,* ***Coban C****.* Heparin induces neutrophil elastase dependent vital and lytic NET formation. **Int Immunol.**, **2020**, doi: 10.1093/intimm/dxz084. PMID: 31879779

2. *Momota M, Lelliott P, Kubo A, Kusakabe T, Kobiyama K, Kuroda E, Imai Y, Akira S,* ***Coban C****, Ishii KJ.* ZBP1 governs the inflammasome-independent IL-1α and neutrophil inflammation that play a dual role in anti-influenza virus immunity. **Int Immunol., 2019,** Oct 20. pii: dxz070. doi: 10.1093/intimm/dxz070. PMID: 31630209

3. *Ozasa K, Temizoz B, Kusakabe T, Kobari S, Momota M,* ***Coban C****, Ito S, Kobiyama K, Kuroda E, Ishii KJ.* Cyclic GMP-AMP Triggers Asthma in an IL-33-Dependent Manner That Is Blocked by Amlexanox, a TBK1 Inhibitor. **Front Immunol, 2019**, Sep 26;10:2212. doi: 10.3389/fimmu.2019.02212. eCollection 2019. PMID: 31616416

4. *Lee MSJ, Natsume-Kitatani Y, Temizoz B, Fujita Y, Konishi A, Matsuda K, Igari Y, Tsukui T, Kobiyama K, Kuroda E, Onishi M, Marichal T, Ise W, Inoue T, Kurosaki T, Mizuguchi K, Akira S, Ishii KJ,* ***Coban C.*** B cell-intrinsic MyD88 signaling controls IFNγ-mediated early IgG2c class switching in response to a particulate adjuvant. **Eur. J. Immunol., 2019,** 49(9):1433-1440.

5. *Lelliott PM, Momota M, Lee MSJ, Kuroda E, Iijima N, Ishii KJ,* ***Coban C.*** Rapid quantification of NETs in vitro and in whole blood samples by imaging flow cytometry. **Cytometry A, 2019,** 95(5):565-578.

＜English books＞

1. *Lee MSJ,* ***Coban C***. Mucosal vaccines for malaria. In the book Mucosal Vaccines: Innovation for Preventing Infectious Diseases, 2e. Chapter 49 (p. 831-840). (Edited by Hiroshi Kiyono and David W. Pascual), **2019**.

２）Education Activities

We have newly started enrolment into lectures for undergraduate and graduate level studies at University of Tokyo. Most of them were delayed/changed due to Coronavirus pandemic.

Lectures given at Undergraduate Level:

1. ***Coban C.*** Host-Plasmodium parasites interactions Academic Frontier Lecture Series for students in Junior Division, College of Arts and Sciences, The University of Tokyo. December 14, 2019.

３）Social Activities

None.

４）International Activities

Invited Lectures (international):

1. ***Coban C.*** Immunopathology in bone during malaria infection. AAI IMMUNOLOGY2020™, May 8 – 12, **2020**, Honolulu, HI, **USA.** CANCELLED DUE TO COVID-19.
2. ***Coban C.*** Imaging immune pathoology during malaria infection. World Immune Regulation Meeting (WIRM)-XIV, March 4-7, **2020**, Davos, **SWITZERLAND.** POSTPONED DUE TO COVID-19.
3. ***Coban C.*** Understanding host-*Plasmodium* interactions for developing sterile immunity against malaria**. The** 5th SINGMALNET Singapore Malaria Network Meeting. February 20-22, 2020, **SINGAPORE.** POSTPONED DUE TO COVID-19.
4. ***Coban C.*** Host-*Plasmodium* interactions and the sterile immunity against malaria: where are we? Immunology at the Forefront. The 11th International Symposium of IFReC. January 24, **2020**, Grand Cube Osaka, Osaka, **JAPAN**.
5. ***Coban C.*** **Mysterious interactions between *Plasmodium* parasites and their host. The** 26th East Asia Joint Symposium, October 23-26, **2019**, Seoul National University, Seoul, **S. KOREA.**

Meeting organizer:

I co-organized International Joint Usage/Research Center-Young Researchers Symposium meeting with Prof. Ishii and Prof. Fujihashi in January 27th, 2020. We first time held this meeting in English and invited world famous immunologist Prof. Thirumala Kanneganti. Several Young Scientist talked about their scientific studies in this 1-day workshop.

International Speaker Invitation to IMSUT:

Since June 1, 2029 until Coronavirus outbreak, I invited several international speakers either together with support from the International Joint Research Center or alone. Seminars were held in English. Name and affiliations of speakers:

2019-10-30: Moshe Arditi (Cedars-Sinai Medical Center, USA)

2019-11-11: Pascale Cossart (Pasteur Institute, France)

2019-12-06: Shiroh Iwanaga (TMDU, Tokyo)

2019-12-17: Kazuki Tainaka (Niigata University, Brain Research Institute)

2020-02-05: Ihsan Gursel (Bilkent University, Ankara, Turkey)

2020-02-06: Katja Simon (The Kennedy Institute, University of Oxford, UK)

2020-02-06: Mayda Gursel (Middle East Tech. University, Ankara, Turkey)

５）Other matters to be noted

None.

（４）Challenges and Future prospects

As a new team in IMSUT, we are determined to develop new and outstanding immunology and parasitology research in IMSUT and nurture and develop a creative science here.

Department of Cancer Biology

Chair Yoshinori Murakami

（1）Missions and Features

Cancer develops and progresses towards malignancy through multiple steps with structural and functional alterations of multiple genes involved in regulation of cell growth, differentiation, apoptosis, and cell-cell and cell-matrix interaction. In the Department of Cancer Biology, we aim to clarify the entire picture of tumor development and progression on the basis of a molecular understanding of physiological and pathological features of these gene products. For this purpose, we take advantage of applying various multi-disciplinary approaches in addition to established molecular biological and murine genetics techniques, including proteomics, molecular imaging, structural biology, physical chemistry and mathematical sciences. The findings from our research will provide innovative targets for translational research of cancer diagnosis and treatment. Ongoing research topics in individual divisions are described as follows.

1) Division of Molecular Pathology: 1) Molecular analysis of cancer progression by aberrant cell adhesion and its application to diagnosis and treatment of cancer. 2) Genomic, epigenomic, and molecular pathological analyses of lung, breast, bile-duct, and other solid tumors and adult T-cell leukemia/lymphoma.

2) Division of Genetics: 1) Studies on molecular signals that regulate a variety of cellular activities, aiming to address how deregulated cellular signals cause neoplastic, neuromuscular or other intractable disorders. 2) Pathophysiological analyses of animal models for the above-mentioned diseases, aiming to develop new therapeutic approaches.

3) Division of Cancer Cell Biology: 1) Elucidation of *in vivo* anticancer mechanisms and development of innovative cancer therapies. 2) Studies on regulatory mechanisms of *in vivo* aging. 3) Molecular basis underlying DNA methylation abnormalities in early stages of carcinogenesis.

（2）Organization

Division of Molecular Pathology
Division of Genetics
Division of Cancer Cell Biology
Division of Molecular and Cellular Biology (-2020.3)

（3）Activity Reports

１）Research Activities

Research activities in the Department of Cancer Biology are essentially based on the curiosity-driven science by each principal investigator rather than project-oriented research shared by all divisions in the department. Each division sets individual aims and goals of its research activities with well-designed schemes and key performance indicators, including the number of papers to be published from 2016 April to 2020 March, as described in the sessions for each division. Every division has mostly achieved each goal or overcome problems if any.

２）Education Activities

Department of Cancer Biology recognized the importance of educating young scientists for continuous development of this research field in the future. For this purpose, we set the following achievement goals from FY2016 to FY2019. 1) To hold a “G2 retreat meeting” once a year, where all graduate students participate in a 2-day meeting and present and discuss their works and exchange the relevant information in English. 2) To hold a series of “G2 seminars” three times a year, where guest scientists in the relevant fields are invited to give cutting-edge lectures to encourage young scientists.

According to this plan, we held the “G2 retreat” as a 2-day meeting every year from FY2016 to FY2019, where 2 graduate students from each Division or Laboratory provided an oral presentation of 10 min in English, whereas the other students provided a short talk of 1-2 min in English. Furthermore, we invited two lecturers, Dr. Robert Whittier, Professor of Juntendo University, and Dr. Philip Hawke, Assistant Professor of University of Shizuoka, to give special lectures on English presentation skills for Japanese scientists. Dr Whittier and Dr. Hawke not only gave detailed comments in individual English presentations but also recorded videos of individual presentations and sent it to each student with special comments to brush up his/her English presentation. Thanks to the “G2 retreat meeting” and the great contribution of these 2 lecturers, the English presentation skill of the graduate students is improving greatly every year. We are going to continue this activity in the future.

Another activity, a series of “G2 seminars,” is held independently of the institutional seminar series, which are formal seminars of the Institute of Medical Science by invited lecturers. In “G2 seminars,” Professors in the Department of Cancer Biology organize and choose lecturers who make great achievements directly in the fields of cutting-edge cancer science. All the graduate students are obliged to attend the seminar and to participate in discussion. Although the number of active participants is gradually increasing, the graduate students are still shy to participate in English discussion in comparison with the presentation of their own works. Taken together, more practice would be required for graduate students to brush up their English presentation skills and to acquire an attitude towards active discussion, although we recognize that the initial goals of improvement

of English presentation by graduate students have mostly achieved in these 4 years.

３）Social Activities

Department of Cancer Biology does not set a common goal in terms of social cooperation but each division seeks programs for social cooperation, as described in the session for each division.

４）International Activities

Department of Cancer Biology does not set a common goal in terms of international collaboration but each division seeks active international collaboration and cooperation as described in the session for each division, including 4 international joint research projects.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

Challenges and Future prospects in the activities of research, social cooperation, and international collaboration are described in the sessions for each division. As to the educational activity, the Department of Cancer Biology has recognized the continuous mission of educating young scientists for sustainable development of this research field for the future. For this purpose, we will continue to hold an annual meeting of “G2 retreat” and a series of “G2 seminars.” Furthermore, we will invite participants from other departments in IMSUT to accelerate the multi-disciplinary science and research in this department.

Division of Molecular Pathology

（１）Members

Professor	Yoshinori Murakami
Project Professor	Takayuki Morisaki
Assistant Professor	Takeshi Ito
Project Assistant Professor	Masaru Koido
Postdocs	3
Graduate students	11
Technicians	3
Others	4

（２）Research objectives

Human cancer develops and progresses toward malignancy through accumulation of multiple genetic and epigenetic alterations. Understanding of these alterations is essential to developing molecular targets for prevention, diagnosis, and treatment of cancer. The Division of Molecular Pathology aims to elucidate the roles of cell-cell interaction in invasion, metastasis, immune checkpoint, and drug resistance of cancer and to develop new diagnostic and therapeutic approaches to cancer, including a serum marker of small cell lung cancer (SCLC). Genomic and epigenomic abnormalities involved in human tumors, as well as genetic susceptibility to various common diseases, are also investigated in collaboration with others to obtain a complete view of human diseases, including human cancer.

（３）Activity Reports

１）Research Activities

The Division of Molecular Pathology has been investigating the molecular mechanisms underlying cancer invasion and metastasis from the view point of cell-cell interaction and its disruption. In these four years, we developed a proto-type of a novel serum diagnostic marker of SCLC. Moreover, we recently started the projects on immune checkpoints and on resistance of cancer against molecular targeting drugs, in which cell-cell interaction plays important roles.

The goals of the research activity in this division from FY2016 to FY2020 are as follows. 1) To identify novel molecular pathways that CADM1 serves as a tumor suppressor in epithelia and as an oncogene in SCLC or adult T-cell lymphoma/leukemia, and to publish several original papers. 2) To establish a novel serum diagnostic marker of SCLC with high sensitivity and specificity by targeting a splicing variant of CADM1v8/9 specifically expressed in testis and SCLC, and to file a patent application. 3) To complete cloning of more than 150 human IgSF molecules involved in

cell-cell interaction, to assess specific interactions among these IgSFs using physico-chemical analyses, and to identify novel interactions between IgSFs with important functions in immune checkpoint and cancer metastasis. 4) To participate in large collaborative studies on the genome-wide association studies (GWAS) or sequencing analysis and to identify novel SNPs or mutations associated with various human diseases, including cancer.

The achievements in individual challenges are as follows. 1) We demonstrated the involvement of CADM1 in Hippo pathways as a possible starter of signaling from the cell membrane. We also demonstrated the suppressor function of CADM1 in Src-signaling in colon cancer by binding with c-Src binding protein (CBP). Moreover, we showed suppressor function of CADM1 in EGFR- or MET-signaling in gefitinib-resistant lung adenocarcinoma using mathematical models. These studies were published in four original papers. 2) We demonstrated the CADM1v8/9 fragments in the serum from SCLC patients caused by extracellular shedding, and generated an antibody against soluble fragments of CADM1v8/9. Then, we developed a sandwich assay to detect CADM1v8/9 in the serum from SCLC patients with high sensitivity and specificity. CADM1v8/9 is shown to be useful for monitoring SCLC after chemotherapy, which is more useful or at least equivalent to current available markers, ProGRP or NSE. We filed a domestic patent application in 2018 and a PCT application in 2019 and started collaboration with a company in Japan in 2020. 3) We have cloned 289 IgSF molecules and identified several immune checkpoint molecules serving as ligands to orphan receptors using amplified luminescent proximity homogeneous assay (Alpha) and surface plasmon imaging (SPRi) technologies, which are going to have patent applications filed. We also identified novel IgSF interactions involved in cancer metastasis and published a paper. 4) We participated in multi-institutional collaboration of GWAS or target sequencing of various human diseases, including cancer and served as co-authors of more than 30 original papers identifying key SNPs and mutations. Thus, achievements in projects 2 and 3 are more than expected and those in project 4 are satisfactory, whereas those in project 1 are steady but need more publication with higher impact. In fact, we have identified several additional cross-talks of CADM1 with novel cascades leading to promising therapeutic targets for advanced or drug-resistant cancer. We plan to publish these findings in original papers. We are also recruiting staff scientists for this division.

２）Education Activities

Prof. Murakami served as an adjunctive professor in the Graduate School of Medicine (GSM) and the Graduate School of Frontier Sciences (GSFS) and a part-time lecturer in the School of Medicine (SM), the University of Tokyo. He served and is serving as a supervisor for 6 PhD students from GSM and 5 PhD students and 12 Master Degree students from GSFS in addition to giving lectures to GSM, GSFS and SM. He also served as an inspector of the thesis for 16 PhD students and 11 Master Degree students from GSM and GSFS.

３）Social Activities

Division of Molecular Pathology concluded a joint research agreement with Koichi Tanaka Mass Spectrometry Research Laboratory, Shimadzu Corporation, Japan and conducted collaborative research on glycosylation analysis of cancer. Prof. Murakami served as a principal investigator of Biobank Japan project supported by AMED, Japan between 2014-2019 and contributed to the management and renewal of the project from 2018 to 2023 and the resultant increase in the number of distributed human DNA and serum to academic and industrial societies. He also started a collaboration with NTT Corporation, Japan, to establish a social cooperation research program, “Project Division of Genomic Medicine and Disease Prevention” as described in the relevant session.

４）International Activities

Based on the partnership agreement between GSFS and Lyon University, France, the Division of Molecular Pathology hosts 6 Master Degree graduate students from Lyon University for around 6 months every year. In addition, on the basis of the MOU between the Institute of Medical Science and Khon Kane University (KKU), School of Medicine, Thailand, this division has been collaborating with scientists in KKU on the study of cholangiocarcinoma, hosted a young scientist, and published a paper. This collaboration was renewed in 2019 as an International Joint Research Project.

５）Other matters to be noted

None.

（４）Challenges and future prospects

The research on cell adhesion and cancer progression must be completed by March 2024 when Prof. Murakami will retire. A novel serum marker of SCLC targeting CADM1v8/9 fragments is to be established and the export to the industry will be sought with a candidate company in Japan. An antigen-drug conjugate using an anti-CADM antibody will be also developed in collaboration with a candidate pharmaceutical company in USA. In the basic science, cross-talk of CADM1 and related IgSF molecules with growth factor signaling or transporter networks will be established to publish original papers and review articles summarizing the multiple functions of CADM1. Furthermore, novel promising targets in immune checkpoints are to be identified by comprehensive binding assay of IgSF molecules and at least one or two seeds applicable to cancer immune therapy will be developed. With combinatorial sequencing analyses of human genes encoding cell adhesion molecules, a concept of disorders caused by aberrant cell-cell interaction will be established. For educational activity, Prof.

Murakami will continue to devote himself to the education of graduate students and undergraduate students and will supervise at least 5 PhD students in the Division of Molecular Pathology.

Division of Cellular and Molecular Biology (-2020.3)

（１）Members

Professor	Jun-ichiro Inoue
Associate Professor	Takeharu Sakamoto
Assistant Professors	Yuu Taguchi, Mizuki Yamamoto
Graduate students	9
Others	5

（２）Research objectives

The Aims of our laboratory are 1) to elucidate the molecular mechanisms of signal transduction pathways that activate transcription factor NF-κB, which is crucial for regulation of immune system, formation of various organs and cancer development, and 2) to develop therapeutic strategies to treat various diseases by understanding physiological and pathological roles of NF-κB.

（３）Activity Reports

１）Research Activities

We have identified and been interested in Tumor necrosis factor receptor-associated factor 6 (TRAF6), which acts as an E3 ubiquitin ligase to generate Lys63-linked polyubiquitin chains that are crucial for transducing signals emanating from the TNFR superfamily or the TLR/IL-1R family leading to activation of transcription factor NF-κB and AP-1. By generating TRAF6-deficient mice, we found that TRAF6 is essential for osteoclastogenesis, immune self-tolerance, lymph node organogenesis and formation of skin appendices. We also demonstrated that NF-κB maintains cancer stem cell population in basal-type breast cancer. From April 2016 to March 2020, our goal was to publish around 5 papers, in which the first, last and corresponding authors belong to our laboratory, about one of the following five subjects: 1. Elucidation of the molecular mechanisms of NF-κB-mediated carcinogenesis; 2. Elucidation of the molecular mechanisms of NF-κB oscillation between nucleus and cytoplasm and mathematical simulation of the oscillation; 3. Elucidation of the role of NF-κB in the regulation of epithelial-mesenchymal transition of mammary epithelial cells to understand how NF-κB is involved in breast cancer malignancy; 4. Elucidation of the molecular mechanisms of regulation of inflammation by macrophages; 5. Identification of inhibitor drugs that block fusion between viral envelope and cellular membrane in collaboration with Research Center for Asian Infectious Diseases. For subject 1, we demonstrated that human T cell leukemia virus type 1 oncoprotein Tax generate Lys63- and Met1-linked hybrid polyubiquitin chains to form a macromolecular complex of IκB kinase, thereby maintaining constitutive activation of NF-κB (*PLoS Pathogens* 2017). For subject 2, in collaboration with Professor Takashi Suzuki in

Osaka University, we proposed a novel mathematical model, in which the NF-κB oscillation is robustly maintained by introducing phosphorylation of NF-κB and IκB (*J. Ther. Biol.* 2019). For subject 3, we demonstrated that TRAF6 maintains mammary stem cells and promotes pregnancy-induced mammary epithelial cell expansion (*Commun. Biol.* 2019). For subject 4, we identified Mint3, a key molecule in regulating inflammation (*Proc. Natl. Acad. Sci. USA* 2017). For subject 5, We have established experimental system to monitor fusion that mimics fusion between viral envelope and the cellular membrane. Using the fusion monitor system, we performed high through put screening of the FDA-approved library and identified Nafamostat as a potent inhibitor of MERS coronavirus infection (*Antimicrob. Agents Chemother.* 2016, *J. Biol. Chem.* 2019). We recently demonstrated that Nafamostat also blocked infection of SARS-CoV-2, a causative agent of COVID-19 (*Viruses* 2020). We have published 35 papers during the period. Among them, 15 papers include at least one of our members as the first or corresponding author. All the staffs received KAKENHI from MEXT. Prof. Inoue is a member of innovative area. Prof. Inoue and Associated Prof. Sakamoto received a grant from AMED for each. One paper that has impact factor of more than 10 was published.

２）Education Activities

Prof. Inoue was involved in education activities in three graduate school; Graduate School of Medicine, Department of Molecular Cell Biology; Graduate School of Frontier Sciences, Department of Computational Biology and Medical Sciences; Graduate School of Pharmaceutical Sciences, Department of Pharmaceutical Sciences. Prof. Inoue weekly discussed progress of experiment with his students asking them to think what to do next by yourself. During the period, 11 students have completed master course. Five students have completed doctor course and four of them received Ph. D degree. All students are actively working in their companies. In preparation for coming globalization, a portion of the regular seminar was performed in English. In 2017, a French student was joined. Thus, we think we achieved our goal in education activities.

３）Social Activities

To return scientific achievements to society, we applied a patent of viral infection inhibitor. We also collaborate with some private company to develop a diagnostic method for malignant cancer. Thus, we think we achieved our goal in social activities.

４）International Activities

During the period, Prof. Inoue went to Beijing three or four times in a year to visit China-Japan joint laboratory to pursue international collaboration. We have published 11 papers regarding this collaboration. Thus, we think we achieved our goal in international activities.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

This Division has completed and closed as of March 31, 2020.

Division of Genetics

（１）Members

Professor	Yuji Yamanashi
Assistant Professors	Ryo Ueta, Akane Inoue-Yamauchi, Takahiro Eguchi
Postdocs	1
Graduate students	6
Technicians	2
Others	2

（２）Research Objectives

Our research objective is to elucidate the molecular signals that play important roles in regulating the generation, maintenance, and functions of organisms, tissues, and cells as a path toward clarifying the molecular pathology of malignant tumors and other intractable diseases resulting from dysregulation of molecular signals. We aim to develop diagnostic and therapeutic interventions based on our findings, in order to promote societal benefit from these technologies, and to foster highly creative young scientists able to pursue a wide range of issues in the fields of life and medical sciences.

（３）Activity Reports

１）Research Activities

The Division of Genetics has attempted to identify unknown signaling molecules and pathways, focusing on those regulating cellular activities, to elucidate their functions and modes of action from a physiological or pathophysiological viewpoint. The goals of this division from April 2016 through March 2020 were as follows. First, we aimed to elucidate signal transduction mechanisms related to cancer, immunity and inflammation, bone metabolism, and formation and maintenance of neuromuscular junctions (NMJs). We mainly focused on the DOK-family of proteins that we had previously discovered. Second, we wished to promote the research and development of therapeutic methods for neurological and muscular diseases based on the knowledge we obtained regarding NMJs. Third, we aimed to publish the results as five peer-reviewed English research papers with students, researchers, and faculty members as the first, last, and corresponding authors. In fact, we published papers on the following: the roles of Dok-1, Dok-2, and C/EBP□□in intestinal inflammation (BBRC 2016; Genes Cells 2019), the roles of Dok-1, Dok-2, and Dok-3 in bone metabolism (BBRC 2018); the roles of Dok-7 in the formation, maintenance, and functional regulation of NMJs (Genes Cells 2016; J Biochem 2017; BBRC 2020); and treatment of a mouse model with amyotrophic lateral sclerosis (ALS) through enhancement of NMJ formation (EMBO Mol Med 2017). Therefore, we believe that almost all goals have been met, although no paper was

published regarding cancer within the set period. Aiming to publish this paper by 2021, we will accelerate our research by increasing the number of researchers, including graduate students, postdoctoral researchers, and technical staff, and through joint research with others inside and outside the institute.

2） Education Activities

The Division of Genetics has provided: 1) education and research training for master's and doctoral students based on the above research activities, to cultivate a wide range of knowledge in the fields of life and medical sciences; 2) deep insights into specific research subjects in order to train researchers to be able to set and solve unique research problems; and 3) young scientists able to use their abilities to contribute to the development of society. The goal of the division from April 2016 through March 2020 was to develop all the students registered in this period into such human resources. In fact, of the eleven students who joined the division as master's students, three have published peer-reviewed English-language papers and achieved PhDs, one of whom has been appointed as an assistant professor at the institute, and two have received research-based jobs in pharmaceutical companies. Two more have achieved master's degrees, one who is now employed at a pharmaceutical company, and the other who is employed at a clinical laboratory company. One student left graduate school for personal reasons. The remaining five are still at the university; three have transferred to other laboratories during their master's courses, due to a health reason or change in interest. Based on these facts, we believe that all students who achieved master’s and/or doctoral degrees successfully became the envisioned human resources. We are trying to provide more attentive education and research guidance in consideration of students whose motivation for research faded.

3） Social Activities

In the Division of Genetics, social collaborations have been carried out for the study of neuromuscular diseases. The goal of the division from April 2016 through March 2020 was to conduct drug discovery research through one or more collaborative activities. We engaged in drug discovery research jointly with a pharmaceutical company and a public interest incorporated foundation (two research activities in total) throughout the period. In this respect, we believe that this goal has been achieved.

4） International Activities

In the Division of Genetics, international collaborations have been carried out for the study of NMJs and NMJ-related disorders. The goal of the division from April 2016 through March 2020 was to conduct one or more international joint research activities. In fact, more than three

international activities were carried out throughout this period. In this respect, we believe that this goal has been met.

５）Other Matters to be noted

The patent for the DOK7 gene, invented by faculty members [Yamanashi, Yamauchi (Inoue)] and alumni of this division was acquired in Europe [2031062 (EP), published on October 24, 2018] (Japan and US patents have previously been acquired).

（４）Challenges and Future Prospects

As mentioned in “(3) Activity Reports,” the Division of Genetics has propelled research and education activities, together with social and international collaborations. The current challenges are to enhance the PR activities of our findings and to provide attentive education and research training for students. Upon achieving this, higher levels of education and research outcomes, together with the enhancement of social and international collaborations, are expected.

Division of Cancer Cell Biology

（１）Members

Professor	Makoto Nakanishi
Associate Professor	Atsuya Nishiyama
Assistant Professor	Yoshikazu Johmura
Postdocs	2
Graduate students	14
Technicians	4
Others	1

（２）Research objectives

In response to genetic and epigenetic insults, normal human cells execute various cellular responses such as transient cell cycle arrest, apoptosis, and cellular senescence as an anti-tumorigenesis barrier. Our research interests are to elucidate the mechanisms underlying the induction and regulation of cellular senescence. Our final goal is to develop innovative cancer therapies, prevention, and anti-aging strategies through regulating and/or eliminating senescent cells *in vivo* (senotherapy). We are currently focusing on identification and characterization of senescent cells *in vivo*. To do so, we have generated a mouse model in which p16-positive senescent cells are visualized by fluorescent labelling. Mechanisms underlying maintenance of genomic and epigenomic integrities such as DNA methylation maintenance are also under investigation.

（３）Activity Reports

１）Research Activities

The division of Cancer Cell Biology was inaugurated in 2016 as the 4th division in Department of Cancer Biology. Our research interests are 1) elucidation of mechanisms underlying age-associated carcinogenesis, 2) investigation of molecular basis underlying DNA methylation maintenance and genomic instability due to impaired DNA methylation, and 3) study of regulatory mechanisms underlying chromosomal segregation. For these purposes, we established various innovative technologies and materials as follows: 1) pure senescent cells in culture, 2) senolytic technology (elimination of senescent cells from an aged body) by targeting metabolic processes specific to senescent cells, 3) establishment of a mouse model in which p16-positive senescent cells are visualized by fluorescent labeling and analytical methods of their transcriptomes at a single cell level, and 4) establishment of a mouse model in which senescence can be induced by ectopic expression of p53 fused with geminin degron, which is specifically functional during S to G2 phase. Using these technologies and materials, we have uncovered the following mechanisms: 1) Innovative senolytic

technology targeting metabolic vulnerability in senescence in which glutaminolysis was activated by lysosome-mediated intracellular low pH. Inhibition of GLS1, a rate limiting enzyme of glutaminolysis, effectively induced senolysis both *in vitro* and *in vivo*. Most intriguingly, treatment of aged mice with GLS1 inhibitor ameliorated various forms of age- and senescence-associated organ dysfunction, such as age-associated glomeruloscrerosis, lung fibrosis, cardiac hypertrophy, and adipose tissue atrophy as well as senescence-associated atherosclerosis. Our results suggest that cells in a senescent state require glutaminolysis, and its inhibition offers a promising strategy for inducing senolysis *in vivo*. 2) A mechanism coupled with DNA replication machinery for the recruitment of DNMT1 to replicating chromatin in which UHRF1-mediated dual mono-ubiquitylation of PCNA-associated factor 15 (PAF15) plays an essential role. In *Xenopus* cell- free extracts, PAF15 accumulates on chromatin with dual mono-ubiquitylation (PAF15Ub2) in a PCNA-, UHRF1- and DNA replication-dependent manner. PAF15Ub2 interacts with DNMT1 with a structural mode similar to that of H3Ub2. Suppression of DNMT1 interaction with H3Ub2 in the extract shows that PAF15 and histone H3 have non-redundant roles in the recruitment of DNMT1 and subsequent DNA methylation. Consistent with this, in mammals, PAF15 is also subjected to UHRF1-dependent dual mono-ubiquitylation and is capable of binding to DNMT1. Mouse embryonic stem cells expressing PAF15 carrying substitutions of lysine to arginine at ubiquitylation sites demonstrate a marked reduction in the DNA methylation level. Together, our study reveals that PAF15 and histone H3 have non-redundant roles in the regulation of DNA methylation maintenance.

These results were published in 5 high impact journals (more than 10 impact factor) in the last three years and thus we believe that our research mission has been achieved. Now, two more papers with high impact journals are under revision. In total, 14 papers were published as peer reviewed original articles during this period. We also patented two issues including a diagnosis of luminal A-type breast cancers and a senolytic technology. We received 8 grants from MEXT and 6 grants from AMED as well as a couple of private grants during this period.

２）Education Activities

We take immense pleasure in training young researchers-to-be. Not only do we endeavor to foster appropriate research skills and attitudes to do experiments in the laboratory, but also we aim to develop and expand upon logical thinking.

Until now, we have had 9 PhD students and 15 master’s students, two of whom received their PhD and ten of whom received their MS degree. It should be noteworthy that two of our master’s students have been awarded as students of World-leading Innovative Graduate Study Program for Life Science and Technology, within which master’s student received a Best Poster Award in Foundation Memorial Symposium of our institute, a Funakoshi Ryutaro Award, and a Best Student Award in Graduate School of Science, University of Tokyo.

３） Social Activities

Breast cancer is the most frequently diagnosed cancer in women. Approximately 70% of breast cancers are positive for estrogen receptor-alpha (ER), and tamoxifen (TAM) is the standard drug for treatment of ER-positive breast cancer, especially for premenopausal women. Treatment with TAM as an adjuvant decreases the annual breast cancer mortality by approximately 30%. However, up to 25% of patients with early stage breast cancer treated with TAM experience relapse of the disease within 15 years. Hence, modification of the treatment is absolutely required for some populations. In order to overcome the above problems, we are now developing a new diagnostic kit for luminal A-type breast cancers under the collaboration with pharmaceutical companies.

４） International Activities

We are doing tight collaborative research on DNA methylation maintenance and genomic instability with a research group at the Memorial Sloan Kettering Cancer Center in US, the University of Munich in Germany, and the University of Paris in France.

５） Other matters to be noted

None.

（４） Challenges and Future prospects

Expanding our research on age-associated carcinogenesis and DNA methylation maintenance by integrating all members in our laboratory as well as materials, equipments, and technologies.

Department of Basic Medical Sciences

Chair Mutsuhiro Takekawa

（１）Missions and Features

The mission of this department is to develop new fields in basic biomedical science and to apply the results of such research to the prevention and control of human diseases. In order to elucidate the causes and mechanisms of diseases, and to develop more effective diagnostic and therapeutic strategies, it is essential to understand life processes at the molecular level. This department was established as one of three core research departments in the institute, to explore and advance life sciences without regards to specific diseases or research fields. Thus, this department is a collection of diverse and unique research groups with no limit to the direction of their research. At the same time, this department provides support to the research of other departments in the institute.

（２）Organization:

Division of Molecular Cell Signaling

Division of Neuronal Networks

Division of Cell Signaling and Molecular Medicine

（３）Activity Reports

１）Research Activities

In this department, fundamental questions pertinent to basic life processes are addressed at the levels of molecules, cells, tissues, and whole organisms. The following is a summary of the research activities of each division.

Up to the end of the fiscal year 2016, the Division of Molecular Cell Signaling studied the cellular responses to extracellular stress stimuli, including high-osmolarity stress, in budding yeast and mammalian cell models using cell biological, biochemical, and molecular genetic approaches.

The major research interest of the Division of Neuronal Networks is the molecular mechanisms of higher brain functions such as emotion, learning, and memory in mammals. The Division is especially focusing on the roles of molecules that function in neuronal information processing, using electrophysiological, biochemical, molecular biological and behavioral approaches.

The Division of Cell Signaling and Molecular Medicine studies regulatory mechanisms of biological signal transduction systems such as MAPK cascades and stress-granules that are responsible for cell-fate decisions. Since perturbation of these signaling systems is involved in various life-threatening diseases including cancer and autoimmune diseases, the Division also aims to develop new diagnostic and/or therapeutic tools for currently intractable disorders in which these

pathways are involved.

Thus, a broad range of basic medical research is conducted in this department.

２）Education Activities

The principal investigators in this department supervise many graduate students (in master's and doctoral courses) from three different graduate schools of the University of Tokyo: the Graduate School of Science; the Graduate School of Frontier Science; and the Graduate School of Medicine, and they serve as chairs or members of thesis review committees every year. The faculty members of this department also contribute to the education of undergraduate and graduate students not only at the University of Tokyo but also at other universities by lecturing in the biomedical sciences.

３）Social Activities

Some laboratories in this department promote joint research with pharmaceutical companies with the aim of developing new diagnostic tools for human diseases.

４）International Activities

Some faculty members in this department carry out international collaborations with the US, the UK, and France, and they hosted an international symposium in Tokyo in 2019.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

This department currently consists of only two divisions, as the Division of Molecular Cell Signaling has been vacant since the end of the fiscal year 2016. It is therefore obviously important to recruit new laboratories that will be leaders in the field of basic medical science. Nevertheless, the remaining Divisions will continue to pursue original, basic life science research as well as translational research aimed at overcoming currently intractable diseases. Focusing on the mechanisms of biological signal transduction associated with human diseases, we will advance a variety of research projects at molecular, cellular and organismal levels by employing new methodologies such as molecular imaging, omics, and bio-mathematical analysis.

Division of Molecular Cell Signaling (-2017.3)

（１）Members

Associate Professor	Kazuo Tatebayashi
Graduate students	1
Technicians	1

（２）Research objectives

The aim of this unit is to address how cells appropriately respond to various environmental stresses such as high osmolarity. Our research focuses on the stress-sensing mechanisms as well as the regulatory mechanisms of stress-activated MAP kinase (MAPK) signaling pathways. Our final goal is to understand the molecular bases of cellular stress responses, for developing the technology to confer environmental stress resistance to animals and plants to survive in severe environmental conditions caused by global warming, and also for developing methods of treating human diseases such as cancer and autoimmune diseases caused by dysregulation of the stress response machinery.

（３）Activity Reports

１）Research Activities

This division studied the cellular responses to extracellular stress stimuli including high-osmolarity stress using budding yeast and mammalian cells with cell biological, biochemical, and molecular genetic approaches. We focused on the sensing mechanism of high osmolarity in the osmoregulatory Hog1 MAPK pathway of *Saccharomyces cerevisiae*, to identify the interaction sites of the transmembrane osmo-sensors Sho1 and Opy2 by biochemical and genetic analyses. This study was published in PLOS ONE later (Takayama et al. 2019).

２）Education Activities

The unit member supervised a graduate student, served as a member of the evaluation committees for the assessment of PhD or MA theses and dissertations, and gave the lectures of molecular and cellular biology at the graduate school of Science, the University of Tokyo. In addition, the unit member was engaged in health and safety education for the students of this institute as a manager of the health and safety office.

３）Social Activities

None.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

This division has completed and closed as of March 31, 2017.

Division of Neuronal Network

（１）Members

Professor	Toshiya Manabe
Assistant Professors	Shizuka Kobayashi, Takahiko Chimura
Technicians	2

（２）Research Objectives

The objective of this Division is to elucidate the function of nervous systems and to publish at least three papers per year in the related research field.

（３）Activity Reports

１）Research Activities

In Division of Neuronal Network, we have examined synaptic functions and learning and memory to elucidate the mechanism of higher brain functions in the field of neuroscience. From April of 2016 to March of 2019, the aim of this Division was to elucidate the function of neurotransmitters and their receptors, signal transduction molecules and adhesion molecules that regulate properties of the central nervous system and to publish about three papers per year within the period. As concrete outcomes, we have published the papers on the topics as follows: (1) The role of cytomatrix at the active zone structural protein (CAST) in neurotransmitter release (Kobayashi et al., ***Eur. J. Neurosci.*** 44:2272-2284, 2016); (2) The role of Rho GTPase activating protein 33 (ARHGAP33) in the traffic of receptor tropomyosin-related kinase B (TrkB) (Nakazawa et al., ***Nat. Commun.*** 7:10594, 2016); (3) The role of ARHGAP32 isoform 1 (PX-RICS) in the transport of γ-aminobutyric acid type B ($GABA_B$) receptors in autistic spectrum disorders (Nakamura et al., ***Nat. Commun.*** 7:10861, 2016); (4) The role of the phosphorylation of synaptosomal-associated protein of 25 kDa (SNAP-25) in the regulation of neurotransmitter release (Katayama et al., ***Sci. Rep.*** 7:7996, 2017); (5) The role of cyclin-dependent kinase-like 5 (CDKL5) in the localization of the GluN2B subunit of N-methyl-D-aspartate (NMDA) receptors in neurodevelopmental disorders such as West syndrome (Okuda et al., ***Neurobiol. Dis.*** 106:158-170, 2017); (6) The role of cadherin 11 in the development of the middle ear (Kiyama et al., ***Lab. Invest.*** 98:1364-1374, 2018); (7) The effect of ketamine metabolites in depression that is not mediated by the regulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Yang et al., ***Biol. Psychiat.*** 84:591-600, 2018); (8) The role of the Toll-like receptor 3 (TLR3)-mechanistic target of rapamycin (mTOR) system in the infection of herpes viruses (Sato et al., ***Nat. Immunol.*** 19:1071-1082, 2018); (9) The role of lemur tyrosine kinase 3 (LMTK3) in the transport of AMPA receptors in the abnormality of behaviors (Montrose et al., ***Neuroscience*** 414:154-167,

2019). Through these studies, we believe that Division of Neuronal Network contributes considerably to this research field, and the aim of this Division has sufficiently been fulfilled.

２）Education Activities

In the Faculty of Medicine, we have given lectures and evaluated theses at the graduate school. We have also undertaken teaching of young scientists.

３）Social Activities

None.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future Prospects

We would like to carry on further analysis of other functional molecules and publish more papers. Currently, we are examining important functional molecules and would like to contribute further to this research field.

Division of Cell Signaling and Molecular Medicine

（１）Members

Professor	Mutsuhiro Takekawa
Assistant Professors	Yuji Kubota, Takanori Nakamura
Postdocs	1
Graduate students	11
Technicians	2
Others	1

（２）Research objectives

The ongoing research projects in this Division are aimed at elucidating the regulatory mechanisms of biological signal transduction systems such as MAP kinase cascades and stress granules that are responsible for cell-fate decisions. Perturbation of these critical signaling systems is involved in a variety of life-threatening diseases including cancer, autoimmune diseases, neurodegenerative disorders, and type 2 diabetes. This Division also aims to develop new diagnostic and/or therapeutic tools for currently intractable disorders in which these pathways are involved.

（３）Activity Reports

１）Research Activities

Our research is focused on intracellular signal transduction systems that dictate cell fate decisions such as cell proliferation, differentiation, survival and death. In particular, over the evaluation period we studied the regulatory mechanisms of mammalian MAP kinase signaling pathways (i.e., ERK, p38 and JNK pathways) as well as stress granule signaling, and investigated the molecular basis of human diseases including cancer, neurodegenerative disorders, and inflammation. Our major achievements include the discovery of:

• A novel human oxidative-stress sensor that mediates the delayed and sustained activation of the p38 and JNK pathways and its role in proinflammatory cytokine production during respiratory burst in macrophages (*Science Advances,* 2020).

• Oxidative stress-mediated abnormal suppression of stress granule formation and its role in neurogenerative diseases (*Nat Commun*., 2016).

• A novel role of MCRIP1, an ERK-substrate protein, in epigenetic regulation of lung surfactant protein expression during embryonic development (*Commun. Biol.*, 2019).

• Genomic loss of dual-specificity phosphatase 4 (DUSP4) in pancreatic and colonic cancers and its roles in tumor invasion and metastasis (*Cancer Res.*, 2016; *Cancer Sci.*, 2018).

• Novel post-translational modifications, such as phosphorylation and SUMOylation, of the MEK

MAPKK and its physiological relevance (*Proteomics,* 2016; *Methods Mol. Biol.,* 2017).
• A novel method (i.e., WGA-based lectin affinity gel electrophoresis) for the quantitative detection of O-GlcNAc modified proteins in cells (*PLoS ONE*, 2017; *Bio-protocol*, 2018).
• A new MEK inhibitor produced by Streptomyces sp. and its application as an anti-cancer drug (*J Antibiot.* 2018)

２）Education Activities

We have supervised approximately 25 graduate students (in master and doctor courses) from three different graduate schools at the University of Tokyo: the Graduate School of Science; the Graduate School of Frontier Science; and the Graduate School of Medicine. A number of these graduate students were awarded prizes in sevral scientific meetings. We have also contributed to the education of undergraduate and graduate students not only at the University of Tokyo but also at other universities by lecturing in the biomedical sciences.

３）Social Activities

We have promoted joint research with pharmaceutical companies with the aim of developing new diagnostic tools for human diseases.

４）International Activities

We have carried out international collaborations with the US and with European countries including the UK and France, and have hosted an international symposium entitled “First International symposium on Interdisciplinary Approaches to Integrative Understanding of Biological Signaling Networks” in Tokyo in 2019.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

We will continue to pursue not only original basic biomedical research that clarifies molecular mechanisms of fundamental biological processes, but also translational research aimed at overcoming human diseases. Since we have identified several signal transduction molecules that may be involved in human diseases including cancer, we will explore their physiological and pathological roles at the molecular, cellular and organismal levels, and apply the findings to the development of effective diagnostic and/or therapeutic tools.

Human Genome Center

Director Satoru Miyano (-FY2019)
Acting Director Yuji Yamanashi (FY2020-)

（１）Missions and Features

The mission of Human Genome Center is to promote human genome research and personalized medicine. We manage the supercomputer system SHIROKANE, which support the medical and life sciences' research activities in Japan and international collaborative research.

（２）Organization

Laboratory of Genome Database
Laboratory of DNA Information Analysis (-2020.3)
Laboratory of Molecular Medicine
Laboratory of Genome Technology
Laboratory of Sequence Analysis
Laboratory of Functional Analysis in Silico
Department of Public Policy
Division of Medical Data Informatics (2020-)
Division of Health Medical Intelligence (2020-)
Division of Metagenome Medicine (2020-)

（３）Activity Reports

１）Research Activities

With the social implementation of genomic medicine, we have promoted personalized genomic medicine based on genomic and medical information. To make a significant contribution to human society through the diagnosis, prevention and development of treatments for disease, we have been in the following researches by utilizing the supercomputer for large-scale data analysis and the artificial intelligence technology to extract knowledge from big data; we are the pioneer in Japan. In this context, we have taken the lead in ELSI issues. The Center as a whole publishes about 100 papers in a year, with several papers per year with IFs more than 30.

1. Promotion of next-generation genomic research for personalized genomic medicine and medical informatics research: By utilizing ultra-speed sequencing technology, supercomputers, and artificial intelligence, we have made a number of remarkable achievements in cancer genome research. Furthermore, we have developed information technologies based on supercomputers and artificial intelligence in order to promote researches for clinical sequencing and its implementation.

We have conducted researches of medical informatics and based on the achievements we have trained researchers and physicians who have skill to organize, analyze and translate genome and medical information in personalized genomic medicine.

2. Public policy science for ethical, legal and social issues (ELSI): We have conducted research on various issues that arise at the interface with society in promoting life science and medical research. The understanding of the public and the construction of a social consensus on the maximizing usage of personal genetic information are essential for the promotion of personalized genomic medicine and advanced medical care. Therefore, through empirical and comparative policy research, we have promoted researches on the prevention of misuse and abuse of personal genetic information, disclosure of diseases and sharing patients and medical practitioners' decision-making processes, access right to their own genome and medical information, and appropriately priced health care, and made policy proposal based on the obtained results. A total of 10 commissioned projects were carried out.

２）Education Activities

We have been conducting hands-on workshops for users of Human Genome Center's supercomputer SHIROKANE about 10 times a year.

３）Social Activities

We have contributed to a total of 16 government committees related to ELSI and research ethics.

４）International Activities

We participated and contributed to the International Cancer Genome Consortium (ICGC).

５）Other matters to be noted

The number of users, which had been hovering around 500 in the past, exceeded 1,000 by improving the operation of Human Genome Center's supercomputer SHIROKANE and improving its services. We worked on power-saving operations of the supercomputer system, and as a result, contributed to the evaluation of power savings for the University of Tokyo.

（４）Challenges and Future prospects

By the integration of Health Intelligence Center into Human Genome Center, reorganization of the center that enables to create personalized medicine in the Society 5.0 era ahead of the world is the primary issue. Based on this integration and renewal, we will address the following four areas.

1. The challenge of addressing important issues in cancer genomics, such as the unveiling mechanisms of generating cancer heterogeneity, and the development of fundamental infrastructure

for genomic data and data sharing.

2. Promoting artificial intelligence research for clinical translation of new dimensional genomic information (integrated genomic information from human genome, commensal bacteria and virus genomes).

3. Proceeding medical informatics research, which organizes, analyzes, and interprets new dimensional genomic, medical, and health-related information and training researchers and physicians who translate it for personalized medicine.

4. ELSI research addressing a variety of issues, which arise at the contact point between medical research such as advanced medicine including new dimensional genomic medicine and society.

Laboratory of DNA Information Analysis (-2020.3)
Laboratory of Genome Technology
Laboratory of Genome Database
Laboratory of Sequence Analysis
Division of Computational Science (Health Intelligence Center) (-2020.3)

（1） Members

Professors	Satoru Miyano (-2020.3),
	Tatsuhiro Shibata (Laboratory of Genome Technology) (2020.4-),
	Kenta Nakai(Laboratory of Genome Database) (2020.4-),
	Seiya Imoto (Laboratory of Sequence Analysis) (2020.4-)
Associate Professors	Rui Yamaguchi (Laboratory of DNA Information Analysis) (-2020.3),
	Tetsuo Shibuya (Laboratory of Sequence Analysis)(-2020.3)
Assistant Professors	Yaozhong Zhang (Laboratory of DNA Information Analysis),
	Kotoe Katayama (Laboratory of Sequence Analysis),
	Chizu Tanikawa (Laboratory of Genome Technology),
	Atsushi Niida (Division of Computational Science)
Project Assistant Professor	Taku Onodera (Laboratory of Sequence Analysis)
Postdocs	5
Technicians	2
Others	8

（2）Research objectives

Technological innovations, including next-generation sequencers, have produced biomedical big data with ultra-high dimensionality and heterogeneity. In particular, cancer genomics research has become large-scale based on whole-genome sequencing of an individual. In this situation, the mission of four laboratories in HGC and one division in HIC directed by Miyano is to develop computational/informatic strategy for medical informatics and proceed researches for the implementation of personalized medicine by utilizing genomics, systems biology, supercomputing, and artificial intelligence.

（3）Activity Reports

1）Research Activities

In addition to the management expenses grants for Human Genome Center, we have obtained competitive external funds to conduct research on the following subjects.

- A commissioned project from MEXT, "Post K-Computer Priority Issue 2 - Integrated

computational life science to support personalized and preventive medicine" (Core institute: IMSUT, PI: Satoru Miyano)

- Grant-in-Aid for Scientific Research on Innovative Areas "Conquering Cancer through Neo-dimensional Systems Understanding" (N0. 4701) PI as a whole.
- AMED Practical Research Project for Rare/Intractable Diseases. "Development of analysis platform for understanding cause of intractable hematopoietic diseases and improving their diagnosis using omics analysis and artificial intelligence technologies" (PI: Satoru Miyano)
- Collaborative research on cancer genomics with other organizations
- Conducting clinical sequencing studies and medical informatics research (Collaboration with Advanced Clinical Research Center, Health Intelligence Center, and IMSUT Hospital)
- Promotion of genomic medicine at Medical Genomics Research Initiative, The University of Tokyo.
- JST Center of Innovation Program "Self-Managing Healthy Society (The University of Tokyo)". We joined this project from 2015 and have promoted researches on clinical sequence and metagenome analysis of intestinal microbiome. This project will be continued until academic year of 2022.
- Joint management of Health Intelligence Center (directed Division of Health Medical Computer Science)
- Research to understand the cancer genome using AI (Utilizing Watson for Genomics and collaborative research with Fujitsu Laboratory)
- Development of MYCODE by the collaborative research with DeNA Life Science, and promotion of MYCODE Research, which is a research platform for internet cohort.

Researches funded by competitive external funds were evaluated and they are highly regarded.

From 2016 to 2018, we published about 50 papers per year and totally about 150 papers were published in three years. In 2016, Satoru Miyano was awarded as a winner of the Uehara prize (Jointly awarded with Prof. Seishi Ogawa at Kyoto Univ., “Understanding molecular mechanism of cancer by advanced genomics”).

２）Education Activities

As a cooperative laboratory of Department of Computer Science, Graduate School of Information Science and Technology, we contributed to training of about 10 graduate students from 2016 to 2018, who are now working in academia and industry with keeping high activity.

３）Social Activities

In the project “Innovative AI Hospital System (Program Director: Prof. Yusuke Nakamura)” of

Cross-ministerial Strategic Innovation Promotion Program (SIP), Cabinet Office, Satoru Miyano is served as a sub-Program Director and makes effort to promote the project. Also, Satoru Miyano is a member of “Cancer Genomic Medicine Consortium” of Ministry of Health, Labour and Welfare, and he manages office of a nonprofit organization “Health and Medical care Promotion (Chairperson of the board of directors; Prof. Hiroshi Shiku)” (board of director). Satoru Miyano has been contributing to promote the collaborative research among industry, government and academia.

４）International Activities

As a member of International Cancer Genome Consortium (ICGC), we have been operating Human Genome Center supercomputer system SHIROKANE as a computational resource. This method of operation is a model for the six facilities that provide computational resources worldwide.

We collaborated with University of Chicago on joint research on cancer immunity and on a symposium on big data analysis in the University of Tokyo's Strategic Partnership. The Center for Research and Advanced Studies of the National Polytechnic Institute (CINVESTAV) in Mexico and us have organized an annual hands-on seminar on bioinformatics and systems biology using SHIROKANE. In addition, Boston University, Humboldt University, the University of Tokyo, and Kyoto University have held the International Workshop on Bioinformatics and Systems Biology for students on a rotating basis since 2000. In 2016, we held this workshop at IMSUT. We have been involved in discussions to create an international data sharing ecosystem (Anderson WP et al. Nature 2017).

５）Other matters to be noted

None.

（４）Challenges and Future prospects

As Professor Miyano will be retiring at the end of March 2020, these four laboratories will follow to the future vision of the Institute of Medical Science, the University of Tokyo. It may be a great loss for the researchers and technical staffs who have been trained over a long period of time to leave IMSUT, but it may be a necessary process for creating an innovative future.

Laboratory of Molecular Medicine

（1）Members

Professor	Tatsuhiro Shibata
Associate Professor	Atsushi Niida
Graduate students	1
Technicians	3

（2）Research objectives

To discover novel therapeutic, diagnostic and prevention targets and molecular pathways, we will perform comprehensive molecular-genomic analysis of intractable diseases including cancer that are frequent and critical health issues in Japan and other Asian countries. Furthermore, we aim to discover novel concepts and mechanisms in these diseases through the development of new bioinformatics tools including machine-learning algorithms for analyzing multiple omics data and mathematical modeling.

（3）Activity Reports

1）Research Activities

Pan-Cancer Whole Genome analysis by the international consortium

As part of the International Cancer Genome Consortium (ICGC), we characterized mutational signatures using 84,729,690 somatic mutations from 4,645 whole-genome and 19,184 exome sequences that encompass most types of cancer (5, 6). We identified 49 single-base-substitution, 11 doublet-base-substitution, 4 clustered-base-substitution and 17 small insertion-and-deletion signatures. We revealed associations of signatures to exogenous or endogenous exposures, as well as to defective DNA-maintenance processes.

Metagenomic landscape in human colon carcinogenesis

We performed fecal metagenomic and metabolomic studies on samples from a large cohort of 616 participants who underwent colonoscopy to assess taxonomic and functional characteristics of gut microbiota and metabolites (8-10). Microbiome and metabolome shifts were apparent in cases of multiple polypoid adenomas and intra-mucosal carcinomas, in addition to more advanced lesions. We found two distinct patterns of microbiome elevations. We also identified metagenomic and metabolomic markers to discriminate cases of intra-mucosal carcinoma from the healthy controls.

Development and application of analytical informatics tools

We have developed a novel deep leaning algorithm to diagnose cancer types based on molecular genetic alterations (7). We have developed an original simulating model for tumor evolution (1).

Using our own pipelines for RNA sequencing data, we have assisted collaborative molecular researches in our institute (2-4).

Epigenetic landscape of the liver cancer genome

We analyzed correlation between the occurrence of epigenetic features and genetic aberrations by whole-genome bisulfite, whole-genome shotgun, long-read, and virus capture sequencing of 373 liver cancers.

References (selected publications in FY2019-present)

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2. Takeda R, et al. HHEX promotes myeloid transformation in cooperation with mutant ASXL1. **Blood**. 2020 Jun 3:blood.2019004613. doi: 10.1182/blood.2019004613.
3. Hirata M, et al. Integrated exome and RNA sequencing of dedifferentiated liposarcoma. **Nat Commun**. 2019 Dec 12;10(1):5683. doi: 10.1038/s41467-019-13286-z.
4. Hayashi Y, et al. Antitumor immunity augments the therapeutic effects of p53 activation on acute myeloid leukemia. **Nat Commun**. 2019 Oct 25;10(1):4869. doi: 10.1038/s41467-019-12555-1.
5. Alexandrov LB, et al. The repertoire of mutational signatures in human cancer. **Nature**. 2020 Feb;578(7793):94-101. doi: 10.1038/s41586-020-1943-3.
6. ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium. Pan-cancer analysis of whole genomes. **Nature**. 2020 Feb;578(7793):82-93. doi: 10.1038/s41586-020-1969-6.
7. Jiao W, et al. A deep learning system accurately classifies primary and metastatic cancers using passenger mutation patterns. **Nat Commun.** 2020 Feb 5;11(1):728. doi: 10.1038/s41467-019-13825-8.
8. Yachida S, et al. Metagenomic and metabolomic analyses reveal distinct stage-specific phenotypes of the gut microbiota in colorectal cancer. **Nat Med.** 2019 Jun;25(6):968-976. doi: 10.1038/s41591-019-0458-7.
9. Thomas AM, et al. Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation. **Nat Med.** 2019 Apr;25(4):667-678. doi: 10.1038/s41591-019-0405-7.
10. Wirbel J, et al. Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer. **Nat Med.** 2019 Apr;25(4):679-689. doi: 10.1038/s41591-019-0406-6

2） Education Activities

Teaching staff in World-leading INnovative Graduate Study Programs for Life Science and Technology (WINGS LST)

Committee Member of the Life-Science Organization and Genome Medical Science Organization in the University of Tokyo

３）Social Activities

None.

４）International Activities

Participation in the International Cancer genome Consortium (ICGC/ICGC-ARGO)

Participation in the Mutographs consortium by UK Sanger Institute and WHO IARC

５）Other matters to be noted

Organizing Committee Chair of the 49th International Symposium of the Princess Takamatsu Cancer Research Fund

Committee member of the Promotion of Clinical Development for Rare Cancers under the direction of the Pharmaceuticals and Medical Devices Agency (PMDA) Science Board

（４）Challenges and Future prospects

We will further continue and expand molecular genomic analyses of the intractable diseases and attempt to discover novel therapeutic/diagnostic/prevention molecular targets. New activities include mutational signature analysis for cancer prevention, mathematical modeling of tumor evolution for diagnosis and new pathological views on tumor heterogeneity, single cell analysis and metagenomic analysis for biomarker discovery and pathobiology of disease-associated immune system.

Laboratory of Functional Analysis *in Silico*

（１）Members

Professor	Kenta Nakai
Associate Professor	Sung-Joon Park
Project Assistant Professor	Luis Augusto Eijy Nagai
Graduate students	10
Technicians	1
Others	3

（２）Research objectives

The research objective of this laboratory is to conduct computational (*in silico*) studies on the functional aspects of genome information. Thus, our scope includes the structural analysis of the molecular function of each gene product as well as the analysis of its regulatory information for understanding its cellular role, played through the inter-gene networks. Currently, we rather focus on the analysis of gene regulatory information through the analyses of multiple types of NGS data, such as ChIP-seq, Hi-C, WGBS, ATAC-seq and scRNA-seq.

（３）Activity Reports

１）Research Activities

In recent years, one of our major research interests was to understand how various kinds of epigenetic features, including DNA methylation (CpG/CpH), histone marks, TADs and A/B compartments, can specify cell type-specific gene expression. Similarly, we have also studied how DNA sequences can specify such epigenetic information. Methodologically, we have sought the possibility of finding new biologically-relevant discoveries from combined public data, which are now quite plenty, though we have also been quite keen in promoting collaborative works with other labs. As for our quantitative targets from April 2016 to March 2020, we have set them as 1) to publish original research papers, either the first author or the corresponding author of which is a lab member; and 2) to publish at least one paper in a journal with its impact factor equal to or more than 10. The numbers of papers that satisfy the condition 1) were: 2-4-5-3 for the four years while those that satisfy the condition 2) were 0-3-1-0 (of the three papers for fiscal year 2017, two were published in the database issue of *Nucleic Acids Research*, which might be regarded as exceptional; in 2019, one paper was published in *Dev. Cell* (IF9.6)). Therefore, though we could (almost) succeed on average while failed in several years. One of the situations that we can improve is that the topics of our works may have been too diverged considering the size of our lab. Although it is important to respect spontaneous research activity of each member, we should more focus on our major topics

and enhance our mutual synergy. Since one of our staffs has been renewed recently and since the background of the staff has thus been switched from protein science to artificial intelligence, we expect that more focused research activities would become possible.

２）Education Activities

In our lab, we accept graduate students from two departments: the department of computer science in the graduate school of information science and technology, U. Tokyo and the department of computational biology and medical sciences in the graduate school of frontier sciences, U. Tokyo. In total, the numbers of students who have succeeded in getting their Master and PhD degree, respectively, in each fiscal year from 2016 to 2019 were: 1-2-1-3 for Master degree and 1-2-3-0 for PhD degree. In addition, we have accepted 1-3-4-5 international internship students (from France and India) from 2016 to 2019 (in 2020, one had to go back to his home country earlier and two could not come because of the COVID-19 problem). It is noteworthy that we accept students from a variety of countries, which include China, Korea, Spain, Cuba, Brazil, Iran, and Malaysia. Thus, considering the size of our lab, it can be said that our lab has contributed actively to education. It should be also added that Prof. Nakai has been a main contributor of the annual certification examination program for technicians in bioinformatics, held by the Japanese Society of Bioinformatics, for more than a decade.

３）Social Activities

So far, collaboration with private companies has not been so active but we have accepted several graduate students who have their job position elsewhere (such as a pharmaceutical company). Moreover, from May 2020, we have accepted a visiting researcher from another pharmaceutical company.

４）International Activities

We have conducted several international collaborations. As a rather successful example, we published a paper in *Cell* in 2017, through a collaboration with a group of Harvard University (at that time). Notably, Prof. Nakai has been repeatedly elected as an ExCo member of APBioNet (Asia Pacific Bioinformatics Network, which is an organization for fostering the growth of bioinformatics in the Asia-Pacific region) for many years and have contributed to their activities. He has also been taking responsibility in serving as a PC member (or sometimes as a co-chair) of various international conferences, such as InCoB, BIBM, IWBBIO, GIW and APBC. He is on the editorial board of DNA Research, PeerJ, and Mathematical Biosciences.

５）Other matters to be noted

Prof. Nakai has served as a reviewer of several grants funded by national agencies, such as MEXT, JST and AMED, as well as an external evaluation committee member of several institutions, such as NIBIOHN. He has been a selection member of the young scientist award by the Ministry of Education (MEXT).

（４）Challenges and Future prospects

We are aware that the amount of acquired external funding has been decreasing. Also, the number of invited talks from major conferences is decreasing, too. The situation may improve because we are now applying to several big grants but it seems to be a good opportunity to consider our new challenges. As noted above, one important issue is to direct our diverged research activities to more focused ones. Another is to take part into some leading international conferences in our field, knowing what areregarded as the cutting-edge topics and advertising our activities.

Department of Public Policy

（１）Members

Professor	Kaori Muto
Associate Professor	Yusuke Inoue
Project Assistant Professor	Akiko Nagai
Postdocs	2
Graduate students	6
Others	6

（２）Research objectives

The Department of Public Policy aims to conduct theoretical, experimental, and policy research. We respect the viewpoints of patients and the public with regard to the ethical, legal, and social implications (ELSI) of the application in society of research results relevant to the fields of medical studies and emerging technology. In terms of research ethics involving human participants and clinical ethics regarding decision-making in medical practice, we contribute to the society.

（３）Activity Reports

１）Research Activities

To date, the Department of Public Policy has conducted theoretical, experimental, and policy research involving ELSI, research ethics, and clinical ethics. From April 2016 to March 2019, the goals for the Department were to reconstruct ELSI research and research ethics, which tend to be biased toward research ethics support as academic research. We have promoted collaborative research within Japan and abroad. During this period, the Department achieved a virtuous circle of research and support through the plan–do–check–act cycle, and substantial outcomes may be considered to have been obtained in the form of 27 European-language papers, 10 Japanese-language papers, and four textbooks published.

２）Education Activities

A total of five compulsory and elective subjects in the Graduate School of Frontier Sciences, two required lectures in the Graduate School of Interdisciplinary Information Studies and one elective subject in the College of Arts and Sciences were offered.

From April 2016 to March 2019, the Department produced two master’s candidates and one doctoral candidate in the Graduate School of Frontier Sciences as well as three master’s and two doctoral candidates in the Graduate School of Interdisciplinary Information Studies. Furthermore, five postdoctoral researchers in the Department were promoted to researchers and faculty members independently capable of research ethics support.

Within the Institute of Medical Science, the Department cooperates in the management of the Office of Research Ethics and contributes to its implementation of education and training involving research ethics.

３）Social Activities

From April 2016 to March 2019, professors and associate professors of the Department of Public Policy contributed to a total of 30 governmental and other committees on ELSI and research ethics. They also contributed to the activities of academic associations across disciplines, such as the Japan Association for Bioethics (director), Japanese Society of Health and Medical Sociology (director), Japan Society of Human Genetics (councilor), Japan Association of Medical Law (director), and Japanese Society for Hygiene (councilor).

Moreover, the Department has conducted a total of six collaborative projects and research studies with patient groups and support groups for cancer and intractable diseases.

４）International Activities

With regard to ELSI research and research ethics involving stem cell research and genomic medicine, the Department is conducting collaborative research with the University of Edinburgh and the University of Oxford in the United Kingdom and with Seoul National University in South Korea and Monash University in Australia.

５）Other matters to be noted

The Japan Agency for Medical Research and Development has commissioned the Department to conduct a total of 10 projects involving medical ethics. Through the results, the Department has contributed to research ethics consulting in Japan on issues including cancer, intractable diseases, brain science, dementia, regenerative medicine, and genomic medicine. Furthermore, within the Institute, the Department has provided support for the management of BioBank Japan in its ethical aspects in addition to contributing to the administration of the Office of Research Ethics.

（４）Challenges and Future prospects

Although ELSI research and research ethics in Japan have not drawn much attention from academia overseas, many topics, such as stem cell research, have garnered considerable interest abroad, and international collaborative research is beginning. The Department plans to work toward the realization of leading large-scale international collaborative research projects.

Division of Medical Data Informatics

（1）Members

Professor	Tetsuo Shibuya
Postdocs	1
Graduate students	3
Technicians	1

（2）Research objectives

Our objective is to develop fundamental data informatics technologies for medical data, such as big data technologies, artificial intelligence, privacy preserving technologies, and algorithm theory. Medical data, especially genome data are increasing exponentially in medical science from basics to clinical research. Our aim is to innovate the entire medical science with novel data informatics solutions.

（3）Activity Reports

1）Research Activities

Our division started in March 2020. We are developing fast, accurate, and scalable algorithms for analyses on large genome databases. We have developed a succinct data structure called BOSS for genome assembly, which is used worldwide in various metagenome projects, including researches on SARS-COV-2. We are also working on artificial intelligence and privacy preserving technologies for analyzing clinical text data.

2）Education Activities

We had 5 students in 2019 and 2 of them graduated with master degrees. Currently we have 3 students. All the students are from department of computer science, graduate school of information science and technology. We also give lectures at college of arts and sciences, and at department of information science, faculty of science.

3）Social Activities

We are serving as the committee chair for the Bioinformatics Technician Certification Exam sponsored by Japanese Society for Bioinformatics.

4）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

The amount of medical data, especially genome data is still increasing rapidly. Currently we consider data up to around the size of 100,000 individual genomes, but we suppose it could reach the country-wide size, which should be 1,000 times larger or more, around in next 10 years. We need next generation data informatics technologies scalable to the size until then. In this point of view, data informatics should be one of the keys to the next generation medical science. We are aiming to contribute to the medical research from basics to clinics by supplying novel data informatics technologies.

Division of Health Medical Intelligence

（1）Members

Professor	Seiya Imoto
Project Associate Professor	Yao-zhong Zhang
Assistant Professor	Kotoe Katayama
Graduate students	2
Technicians	5
Others	2

（2）Research objectives

This division was started from April 2020 with the mission realizing genomic medicine based on the integrated data from genomes of human and commensal microbes. Development of computational data analysis methods including artificial intelligence for genomic, health, and medical big data is one of our main focuses. We promote integrative analysis of human whole genome, RNA and other omics data, commensal microbes including bacteriome and virome, and health and medical-related big data. Furthermore, health medical intelligence aims at using the analysis results of such big data to create personalized action plan of individuals.

（3）Activity Reports

1）Research Activities

- Development of omics data analysis methods for whole genome, transcriptome, epigenome, proteome and metabolome especially in cancer researches. We were heavily involved in ICGC/TCGA PanCancer Analysis of Whole Genomes (PCAWG) project and developed several computational methods for cancer immunogenomics, such as HLA genotyping from WGS, detection of neoantigen, and TCR repertoire analysis.
- Implementation of genomic medicine by collaborative research with IMSUT hospital and Advanced Clinical Research Center. Hematological and gastric cancers are our target. Using artificial intelligence and supercomputer, we achieved 2 days and 16 hours of turn-around-time when we apply WGS.
- Development of artificial intelligence for interpreting the analysis results of human genome and microbiome based on huge amount of literature information. For cancer genome, we collaborate with Fujitsu Laboratory and developed an artificial intelligence to support physicians to search for literature, which are useful to determine treatment plan and to assist physicians to extract essential information from literature. We succeeded in showing this AI can reduce the time physicians spent for this task to around half.

- Development of artificial intelligence for the analysis of long-read sequencing data produced from cutting-edge sequencing technologies, e.g., Oxford Nanopore. Usually, long-read sequence data have more noise than short-read. Our developed U-net based neural network can perform accurate base-calling.
- Analysis of intestinal viruses, which are mostly bacteriophages. Although intestinal bacteria have been analyzed in worldwide, intestinal bacteriophages are not well studied and recognized as “viral dark matter”. Our interest covers the development of analysis methods for sequence data derived from bacteriophages and unveiling host bacteria-parasite (bacteriophage) associations to implement next generation phage therapy.
- Development of a computational method based on deep learning for the integrative analysis of pathological image data and genomic sequencing data. We use TCGA data of multiple types of cancers for this purpose. This is a collaborative research with researchers of Monash University, Australia.
- Health check-up data analysis integrated with genomic and microbiome data. We have received 15 years of health checkup data (approximately 30,000 records, WGS, intestinal and oral flora, health checkup information, lifestyle habits, etc.) from Hirosaki University, and we are developing a risk prediction model for lifestyle-related diseases.
- In an effort to return analysis results to individuals, we are working with DeNA Life Sciences that conducts direct-to-consumer genetic testing MYCODE to analyze SNP information from approximately 100,000 users. We created a research platform called MYCODE Research to promote new research method on internet cohort.
- SARS-Cov-2 virus genome and host human genome analysis. Prof. Imoto is a proposer of the Coronavirus Task Force (https://www.covid19-taskforce.jp/en/home/) and is served as a principal investigator of TCR analysis section of COVID-19 patients. The Coronavirus Task Force is an on-going project. For SARS-Cov-2 virus genome, we have collected the sequences obtained from COVID-19 patients from GISAID database and now (July 2020) more than 68,000. We focus on the diversity of viral sequences changing over time and across places.
- Risk assessment of mass-gathering events in With-Corona era is now an important issue. We collaborate with researchers who are experts in exposure analysis of environmental field. We are performing simulations to assess the risk of infection and the effectiveness of each of actions for prevention.

２）Education Activities

Accepting graduate students from Department of Computer Science (2 in 2020); and we provide research guidance related to bioinformatics. We also provide training to motivated graduate students who want to study bioinformatics in experimental laboratories (several students each year). We

provided several bioinformatics related lectures to graduate and undergraduate students in the University of Tokyo. Undergraduate students at the University of Tokyo who are interested in data science are asked to visit the laboratory on a regular basis for guidance. We also provide the Japanese Society of Internal Medicine's Educational Lecture Series in 2020.

３）Social Activities

- Chairman of the third annual meeting of Japanese Medical AI Society (29-30 January 2021 (In the second meeting, more than 1,000 participants we have. The third one is now planed as on-line style))
- A mediator of IBM Fuji Meeting
- Vice chancellor of Hitachi Academic System Society

４）International Activities

- ICGC/TCGA PanCancer Analysis of Whole Genomes (PCAWG)
- Collaborative research with Center for Research and Advanced Studies, Mexico (Prof. Martha Espinosa-Cantellano) was accepted and supported by the IMSUT International Joint Research Center’s project (2019 and 2020)
- Collaborative research with China Medical University, Taiwan Genome Project (Dr. Ro-Ting Lin) was accepted and supported by the IMSUT International Joint Research Center’s project (2020)
- Collaborative research with Monash University (Assc. Prof. Jiangning Song) for Image and Genome Analysis was started.
- Intestinal microbiome research with Boston Brigham and Women's Hospital, UC San Diego, and Pasteur Institute.
- Bioinformatics education program with Japan (Kyoto University and us), USA (Boston University), Germany (Humboldt-Universität zu Berlin, etc.)

５）Other matters to be noted

- Presentation and Panel Discussion at Tokyo Forum 2019’s session “Healthy Aging Society”
- Press Releases (from April 2020)
  - with Osaka City Univ about the Cell Host & Microbe paper of intestinal microbe project in July 2020
  - with Corona Task Force about COVID-19 study May 2020

（4）Challenges and Future prospects

By COVID-19, we recognize that we are facing with a global crisis. We address several issues related with COVID-19 such as viral sequence analysis, patients' immune response analysis based on genomic data, vaccine development and risk assessment of mass-gathering events by simulations. The completion of these studies as soon as possible is essential for the normalization of research activities and life. The current genomic medicine especially for cancer genomic medicine in Japan is limited in panel sequence analysis. On the other hand, we have been promoting the use of whole genome sequencing data for obtaining more accurate diagnosis and treatment plan. Although we have obtained several achievements based on the current studies, for expanding genomic medicine to other diseases than cancer, we consider the use of the information of commensal microbes are important. We call a genomic medicine based on the integrated data of human genomic and medical data and information of commensal microbe new dimension genomic medicine, which we will promote in the next five years. Also, by considering with Post-Corona era, bringing pathological microbiota from abroad is a serious issue of Japan, especially for multi-agent resistant bacteria (MAR), which are generated by indiscriminate use of anti-bacterial drugs. WHO estimated that the number of death by MAR will be greater than that by cancers in 2050. By extending the achievement of our Cell Host & Microbe paper (we showed that prophage enzyme, endolysin, determined by metagenome sequencing data can kill *C. difficile* specifically), we will compile phage-derived enzymes that can kill pathological bacteria specifically and create next generation phage therapy for MAR.

Division of Metagenome Medicine

（１）Members

Project Professor	Satoshi Uematsu
Project Assistant Professor	Kosuke Fujimoto
Technicians	1
Others	2

（２）Research objectives

１）Construction of a database of intestinal bacteria and virus in healthy subjects

２）Development of therapeutic methods for dysbiosis-related diseases by metagenomic analysis

（３）Activity Reports

１）Research Activities

1. Construction of a database of intestinal bacteria and virus in healthy subjects

In collaboration with Professor Seiya Imoto at the Human Genome Center, we are constructing an ultra-high-speed analysis pipeline for intestinal bacteriome and virome by using IMSUT Supercomputer Shirokane. Using this pipeline, we are analyzing the stools of Japanese healthy people and creating the world's first database of intestinal bacteriome and virome in the same stool. Many enteric viruses are bacteriophages that infect enterobacteria, and we are also advancing host identification of bacteriophages based on sequence data. We are building the basis for a new bacteriophage therapy that can control intestinal bacteria.

2. Development of therapeutic methods for dysbiosis-related diseases by metagenomic analysis

In recent years, dysbiosis is present not only in intestinal diseases such as inflammatory bowel disease, but also in autoimmune diseases, diabetes, cardiovascular diseases, and autism, and it is clear that they are closely related to the pathological condition. have become. Our laboratory conducts metagenomic analysis of intestinal bacteria and viruses in dysbiosis-related diseases, and is engaged in searching for microorganisms related to pathological conditions and developing new therapeutic methods.

２）Education Activities

We accept 3 PhD students at the dual post.

３）Social Activities

We are collaborating with EA Pharma Co., Ltd and Meiji Co., Ltd.

４）International Activities

IMSUT has signed an agreement with the Pasteur Institute to create a joint unit for both parties. Prof. James Di Santo, the counterpart of the other party, made the joint research contract together with us. We are now conducting a joint research project to analyze the nasal microflora of allergic patients in France.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

A database of intestinal flora and virus flora will be published. In the future, it will be necessary to control intestinal bacteria using phages for various diseases. In addition, we believe that phage therapy will be an indispensable treatment method against multidrug-resistant bacteria, which has become a global problem. We think that it is necessary to carry out social implementation of phage therapy in Japan and, if possible, to establish a center in the Institute of Medical Science to practice phage therapy.

Center for Experimental Medicine and Systems Biology

Director Yasuhiro Yamada

（１）Missions and Features

The Center for Experimental Medicine and Systems Biology was established in 2007, renewed from The Center for Experimental Medicine organized in 1998. The current center consists of five laboratories, Division of Stem Cell Pathology, Division of Genome Engineering, Laboratory of Innate Immunity, Laboratory of Reproductive Systems Biology, and Laboratory of Genetically Engineered Mouse Research.

Although an accurate and complete genome sequence of various organisms have been made available, the function of genes, the epigenetic mechanisms that control gene expressions, the role of genomic elements, including non-coding elements, are not fully understood, especially at an organismal level. The purposes of the center are to establish *in vivo* experimental platforms for various research fields and develop animal models for investigating human diseases. Our center has a mission to provide scientists at IMSUT and other academic institutes with genetically-engineered rodent models for studying various aspects of biology as well as human diseases. Our effort should promote the interdisciplinary research that connects a wide range of research fields, including stem cell biology, immunology, and cancer biology, which eventually contributes to the development of novel therapies for human diseases.

（２）Organization

Division of Stem Cell Pathology
Laboratory of Innate Immunity
Laboratory of Reproductive Systems Biology
Division of Genome Engineering
Laboratory of Genetically Engineered Mouse Research
Laboratory of Developmental Genetics (-2018.3)
Laboratory of Systems Biology (-2019.3)

（３）Activity Reports

１）Research Activities

We have generated and provided genetically-engineered mouse models for scientists at IMSUT as well as other academic institutes. We also provided various mouse models as a member of the Advanced Animal Model Support, which is supported by Grant-in-Aid for Scientific Research on Innovative Areas Platforms for Advanced Technologies and Research Resources from MEXT.

The following is a summary of genetically-engineered mouse models that we provided during the past four years.

FY 2016: 54

FY 2017: 14

FY 2018: 20

FY 2019: 34

Our center is also developing novel technologies for establishing advanced animal models for biomedical research. For example, we devised doxycycline-inducible Cas9 platforms that efficiently enable conditional genome editing at multiple loci in adult mice.

２）Education Activities

Our center has hosted training of genome-editing in mouse embryos and gene targeting in mouse ES cells for young researchers and graduate students at IMSUT as well as other academic institutes. Laboratories/Divisions in Center for Experimental Medicine and Systems Biology have accepted master course and PhD course students in Graduate School of Medicine, Graduate School of Frontier Sciences, and Graduate School of Sciences.

３）Social Activities

None.

４）International Activities

Researchers in our center are actively conducting international collaborative projects, including collaborations with investigators at Harvard University, Johns Hopkins University, UCLA, and Max Planck Institute.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

Genetically-engineered mice have offered the opportunities of not only analyzing the complex gene function *in vivo*, but also providing various human disease models, with which new therapeutic approaches can be explored. In April 2020, Division of Stem Cell Pathology, Laboratory of Reproductive Systems Biology, and Division of Genome Engineering established a core team to further facilitate generation of genetically-engineered mice and rats. The team takes advantage of the embryo engineering technologies as well as genome editing technologies to devise the *in vivo*

experimental systems that link the basic science and medicine. The team will provide scientists at IMSUT and other academic institutes with advanced animal models. To further promote the activity, we will also develop technologies for rapid, efficient, and complex genome editing in rodents.

Laboratory of Developmental Genetics (-2018.3)

（１）Members

Professor	Nobuaki Yoshida
Associate Professor	Hirotake Ichise
Assistant Professor	Taeko Ichise
Postdocs	1
Graduate students	1
Technicians	2
Others	2

（２）Research objectives

Medium- to a long-term goal: To create gene manipulated mice by developmental engineering technology, to clarify the mechanism of homeostasis maintenance in the living body, paying particular attention to lymphatic vessel development, immune function, and spermatogenesis.

Short-term Goal: To publish about 10 original papers during the period from 2016 to the end of the lab-closing in 2018.

（３）Activity Reports

１）Research Activities

The objectives of our lab are to elucidate the homeostasis maintenance mechanism of the living body, especially on lymphatic vessel development, immune function, and spermatogenesis by using gene manipulated mice. We also run many joint researches through the development and provision of gene manipulated mice.

From April 2016 to March 2018, when our lab has closed, the goal of our lab is to elucidate the molecular basis of B cell antibody production by analyzing of alternative splicing and histone epigenetics, development mechanism of lymphatic vessels, and to find out essential genes and their molecular roles that maintain sustainable spermatogenesis. We aimed to achieve at least 10 publications within the period. Also, we aimed to set up a genome-editing technique by CRISPR/Cas9 using fertilized embryo, e.g., inducing indel mutation, short nucleotide recombination using ssODN, or insertion of large cassette sequences using dsODN.

The number of papers we have published was seven in 2016, but no original paper was published in 2017. Therefore, it cannot be said that the achievement of the outcome was sufficient compared with the initial goal. The reason for this is that the number of postdocs and graduate students decreased in 2017 because of lab closing in the next year, 2018. On the other hand, in 2019, after the lab closed, two ongoing projects were published as original papers, so we believe that we have

almost reached the goal finally. On the other hand, regarding genome editing with CRISPR/Cas9, 13 strains of indel loss-of-function mutation mice, and 3 strains SNPs-edited mice using ssODN were developed during the period. On the other hand, the insertion of large cassette using dsODN could not be developed so far. Thus, it cannot say that the initial goal could be achieved. This might because genome editing of fertilized eggs by CRISPR/Cas9, especially for large sequence knock-in, was in a start-up phase and it needs to be optimized.

２）Education Activities

For graduate student education, we encourage students to acquire techniques to develop gene manipulation mice that our lab is good at and to be a person who can discover and solve problems by themselves through research. The goal of the master's program is to develop at least one gene manipulated mouse line and have one oral presentation in any academic meetings until they finish their degrees.

From 2016 to 2019, one Ph.D. student has received a doctor's degree, and a master course student is currently in the second year. The students who finished the doctoral program presented her research results by an oral presentation in 2018, thus she could achieve the goal. On the other hand, a master's student, so far, has not presented in an academic conference. One of the reasons for this is that the time to submit the abstract of the academic conference coincided with the peak period of job hunting, and he could not have enough time to prepare his data.

３）Social Activities

None.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

This Laboratory has completed and closed as of March 31, 2018.

Division of Stem Cell Pathology

（１）Members

Professor	Yasuhiro Yamada
Assistant Professor	Sho Ohta
Postdocs	2
Graduate students	9
Technicians	3
Others	1

（２）Research objectives

Epigenetic regulation involving multiple chemical modifications plays critical roles during mammalian development and ensures stable gene expression, which is required for maintenance of cellular identity. In addition, alterations in epigenetic modifications have been observed in many diseases such as cancers. Our research focuses on studying the epigenetic regulation in various biological aspects in multicellular organisms. Particularly, taking advantage of mouse genetics and iPS cell technology in combination with genome-wide analysis of epigenetic modifications, we are investigating the role of epigenetic regulation on the cellular differentiation, the maintenance of cellular identity, and the pathogenesis including age-related diseases such as cancer at the organismal level.

（３）Activity Reports

１）Research Activities

Since its inception on December 2017, Division of Stem Cell Pathology has investigated the role of epigenetic regulation in various biological aspects in multicellular organisms, including mammalian development and diseases. The following are major research achievements:

a) Distinct responses to cellular senescence determine cell type-specificity of cancer development

Cell type-specificity of cancer development has long been recognized. We established induced pluripotent stem cells (iPSCs) from murine clear cell sarcoma (CCS) cells harboring cancer-associated genetic abnormalities and generated sarcoma-iPSC mice. Sarcoma-iPSC mice developed secondary sarcomas only in soft tissue but exhibited oncogene-induced senescence in the other tissues. We showed that cell type-specific enhancers play a critical role in cell type-specific induction of senescence. We propose that distinct responses to premature senescence are the basis for the cell type-specificity of cancer development. ***Nature Commun***. 10(1):3999, 2019.

b) Modeling pediatric brain cancer using human iPS cells

Atypical teratoid/rhabdoid tumor (AT/RT), which harbors SMARCB1 mutation and exhibits a characteristic histology of rhabdoid cells, has a poor prognosis. We established human SMARCB1-deficient pluripotent stem cells (hPSCs). SMARCB1-deficient hPSCs efficiently gave rise to AT/RT-like brain tumors in the mouse brain. We found that activation of an embryonic stem cell (ESC)-like signature confers a rhabdoid histology and causes a poor prognosis. SMARCB1-deficient hPSCs offer the human models for AT/RT, which uncover the role of the activated ESC-like signature in the poor prognosis and unique histology of AT/RT. ***Cell Reports***. 26, 2608–2621, 2019.

c) Unveiling epigenetic abnormalities in pluripotent stem cells

Imprinting control regions (ICRs) are protected from *de novo* methylation in somatic cells. We conducted a comprehensive analysis of ICR methylation during somatic cell reprogramming. We found that several ICRs are often *de novo* methylated in reprogrammed pluripotent stem cells (PSCs). Mechanistically, ablation of *Dnmt3a* prevented PSCs from *de novo* ICR methylation. Notably, the ICR-preferred DNA hypermethylation was observed in pediatric cancers, while adult cancers exhibit genome-wide DNA hypermethylation. These results may have important implications in the pathogenesis of pediatric cancers and the application of PSCs. ***Stem Cell Reports***. 12(5):1113-1128, 2019.

d) *In vivo* reprogramming drives pancreatic cancer

The faithful shutdown of the somatic program occurs in the early stage of reprogramming. We showed that the transient expression of reprogramming factors in pancreatic acinar cells results in the transient repression of acinar cell enhancers, which are similarly observed in pancreatitis. Notably, the transient expression of reprogramming factors in *Kras* mutant mice was sufficient to induce rapid formation of pancreatic ductal adenocarcinoma. In contrast, the forced expression of acinar cell-related transcription factors inhibited development of precancerous lesions in *Kras*-mutated acinar cells. These results underscore a crucial role of dedifferentiation-associated epigenetic regulations in the initiation of pancreatic cancers. ***Nature Commun***. 9(1):2081, 2018.

２）Education Activities

During the period from December 2017 to March 2019, we accepted graduate students from Kyoto University where Prof. Yamada belonged to before December 2017. During the period, one PhD student received a degree. This doctoral study (***Cell Reports***. 26, 2608–2621, 2019) was highly evaluated and the student won the award at the Japan Brain Oncology Society. In addition, two master's degree students completed the course and entered the doctoral course in 2019, continuing

their research in this field.

３）Social Activities

Prof. Yamada is a member of Science Council of Japan, a councilor of Japanese Cancer Association, The Japanese Society of Pathology, and The Japanese Society for Epigenetics.

４）International Activities

A joint project with Prof. Miguel Esteban at Chinese Academy of Sciences (CAS) is currently ongoing as a JSPS-CAS joint program (Project title: Molecular roadmap of in vivo reprogramming at the single-cell level). Our group is also collaborating with investigators at Harvard University, UCLA, and Max Plank Institute. Prof. Yamada is a member of publication committee of International Society for Stem Cell Research (ISSCR) and a Board Member of Cancer Research, an official journal of the American Association for Cancer Research (AACR). Prof. Yamada co-organized Stem Cell Crossroads, a Cold Spring Harbor Asia (CSHA) meeting in 2018.

５）Other matters to be noted

In April 2020, Division of Stem Cell Pathology, together with Laboratory of Reproductive Systems Biology and Division of Genome Engineering, established a core team to facilitate generation of genetically-engineered rodents.

（４）Challenges and Future prospects

We will investigate the role of epigenetic regulation on the cellular differentiation, the maintenance of cellular identity, and the pathogenesis including age-related diseases such as cancer at the organismal level. We will try to develop a novel therapeutic approach targeting epigenetic regulation to treat patients.

As a member of Center for Experimental Medicine and Systems Biology, we will contribute to scientists at IMSUT and other academic institutes through providing advanced animal models. To achieve this, we will develop technologies for efficient and complex genome editing in rodents.

Laboratory of Innate Immunity

（1）Members

Professor	Kensuke Miyake
Associate Professor	Shin-ichiroh Saitoh
Assistant Professors	Ryutaro Fukui, Takuma Shibata
Project Assistant Professor	Ryota Sato
Graduate students	7
Technical assistants	3
Others	1

（2）Research objectives

Laboratory of Innate Immunity focuses on Toll-like receptor (TLR), pathogen sensors in the innate immune system. We would like to understand molecular mechanisms controlling pathogen sensing and TLR responses. We also would like to understand cellular and molecular mechanisms by which TLRs drive inflammatory diseases and to develop a novel therapy targeting TLRs to control such TLR-dependent diseases. Since April 2016 to March 2019, we tried to publish papers on the relationship between TLR trafficking and type I interferon production. We will focus on single stranded RNA sensor TLR7 and double stranded RNA sensor TLR3. We also tried to publish a paper and file a patent on the control of autoimmune and inflammatory diseases with a monoclonal antibody to TLR9. As for education, we tried to train graduate students in our laboratory and by give lectures.

（3）Activity Reports

1）Research Activities

We published 28 papers including a paper in Nat Immunol, 2 papers in Immunity, 3 papers in Nat Commun, a paper in PNAS, and 3 reviews. We reported that TLR7 traffics from the perinuclear region to the peripheral region beneath the plasma membrane to induce type I interferon (IFN) (S. I. Saitoh et al., Nat Commun 8, 1592, 2017) TLR7-trafficking depends on a GTPase Arl8b. TLR3-dependent type I IFN production, on the other hand, depends on Rab7a-dependent lysosomal trafficking to the cell periphery. (R. Sato et al., Nat Immunol 19, 1071-1082, 2018) Furthermore, we have established anti-mouse TLR9 monoclonal antibody (mAb), which is able to inhibit TLR9 responses. The anti-TLR9 mAb protects mice from TLR9-dependent lethal hepatitis caused by TLR9 ligands (Y. Murakami et al., Sci Rep 7, 44042, 2017).

We also obtained a patent on anti-TLR7/8/9 mAb (Aug 1, 2018). Furthermore, 3 patents have been filed as below.

1. Analyses of soluble TLR7 in human samples.
2. Anti-human TLR7 mAb
3. Anti-TLR9 mAb

２）Education Activities

Four students in master course and a student in PhD course finished their courses. Prof. Miyake gave 6 lectures a year in Faculty of Sciences.

３）Social Activities

None.

４）International Activities

We are collaborating with Prof. Eicke Latz in Bonn University, Germany. A student in Bonn Univ. came to our lab and she is going to work here for 2 and half years.

５）Other matters to be noted

Prof. Miyake is on the board of trustees of the Japanese Society of Immunology since Oct 2018.

（４）Challenges and Future prospects

We were able to publish a paper as aimed in the beginning of this term. We also filed and obtained patents as planned. As for education, we trained graduate students in my laboratory and gave lectures. In the next term, we would like to publish a paper on the relationship between TLR7 and histiocytosis. In parallel, we would like to develop anti-human TLR mAb for the control of an autoimmune disease in collaboration with a pharmaceutical company. The goal of our research is to understand molecular mechanisms behind pathogen sensing by TLRs, and roles of TLRs in human autoimmune diseases. For education, we would like to have all the graduate students to finish their master or PhD courses.

Laboratory of Reproductive Systems Biology

（１）Members

Professor	Masahito Ikawa
Associate Professor	Manabu Ozawa
Postdocs	1

（２）Research objectives

Germ cells, i.e., sperms and eggs, are unique types of cells that are differentiated only for the purpose to transfer genetic information to the next generation. The research aims of our laboratory are to clarify the molecular system of how germ cells are developed, maintained, or fertilized to make a new generation. Also, based on the basic information obtained from animal models, we also aimed to uncover the causes of human infertility and develop therapeutic methods.

（３）Activity Reports

１）Research Activities

So far, our laboratory has conducted research to elucidate mechanisms that orchestrates germ cell development, spermatogenesis, and fertilization in mammals. Also, since our laboratory is a core member of the "Gene Manipulated Mouse Section", which is the core laboratory of the IMSUT, we have carried out many collaborative researches with other fields through making gene-manipulated mice.

From April 2016 to March 2019, the goal of our lab is to elucidate the molecular basis that regulates continuous spermatogenesis or fertilization by using genome-editing mice models and to achieve at least 5 publications or 15 publications per each year or throughout the period, respectively. In addition, we are trying to develop gene manipulated mice 20 or more annually on average in “Gene Manipulated Mouse Section”, and to develop 60 or more mice line during the period.

The actual number of original papers published was 4 in FY2016, 3 in FY2017, and 9 in FY2018, and the total number of original papers are considered to have been sufficiently achieved the initial goal. On the other hand, in FY2016 and FY2017, we could not reach the target of more than 5 publications within the year. The reason is that 2016 was the year in which the laboratory was started up, and many research projects had just begun. It is expected that the results of those research projects will come out in the near future, so we will continue to research with the goal of more than 5 original papers per year. The activities of the “Gene Manipulated Mouse Section” were 54 in FY2016, 14 in FY2017, and 20 in FY2018. Therefore, we believe that we could achieve the initial goal in total. On the other hand, the number of preparations in FY2017 did not reach the annual target number. This might because genome editing of fertilized eggs by CRISPR/Cas9 was in a start-

up phase and it took time to optimize it. Since the technology is currently tuned-up for developing gene-editing mice stably, we will continue to support collaboration with similar goals at the beginning.

２）Education Activities

For graduate student education, we encourage students to acquire techniques to develop gene manipulation mice that our lab is good at and to be a person who can discover and solve problems by themselves through research. The goal is to have at least one oral presentation in an academic meeting until they finish their degrees.

During this period, one Ph.D. student has received a doctor’s degree, and a master's student is currently in the second year. The students who finished the doctoral program presented her research results by oral presentation in 2018, thus she could achieve her goals. On the other hand, a master's student has, so far, has not presented at academic conferences. One of the reasons for this is that the time to submit the abstract of the academic conference coincided with the peak period of job hunting, and he could not have enough time to prepare.

For future improvement, we will encourage students to have a strong awareness of conference presentations from the beginning of the research.

３）Social Activities

None.

４）International Activities

We are actively promoting collaborative research with overseas laboratories, mainly by developing and providing gene manipulated mice lines. From 2016 to 2019, we provided gene manipulated mice to four American laboratories as joint research. We will continue to actively promote international collaboration.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

As a short-term goal, we aim to consistently publish more than 5 original papers annually on average.

Also, as a medium- to a long-term goal, we aim to uncover the entire development and fertilization of mammalian germ cells using gene manipulated mice model. Furthermore, in the future, we will promote joint research with the clinical field for human medical applications.

Laboratory of Systems Biology (-2019.3)

（１）Members

Associate Professor	Susumu Nakae
Postdocs	1
Graduate students	1
Technicians	1
Others	2

（２）Research objectives

Our research focus is the understanding of the pathogenesis of rejection and immune disorders such as allergy and autoimmunity using gene-modified mice.

（３）Activity Reports

１）Research Activities

The goal from April, 2016 to March, 2019 is that we investigate the role of certain cytokines in the development of allergic disorders such as asthma and dermatitis, and autoimmune disorders such as arthritis and aortitis. The goal of the outcome is to publish one paper each year as a corresponding author by the researcher of our laboratory. In fact, we reported 9 publications as a corresponding author, and 27 publications (19: Japan and 8: other countries) as collaborators during the period. Thus, in terms of the number of published papers, we achieved more than the goal. Regarding the quality of publications, one of the 9 reports was published in the journal with <10 impact factor. In terms of this, we will improve the research environment so that we can report more high-quality researches.

２）Education Activities

Three students of master's course (at Graduate School of Frontier Sciences, The University of Tokyo) and 3 students of PhD course (at other universities except The University of Tokyo) conducted researches in our laboratory from April, 2016 to March, 2019. Two of master's course had completed their master's degree, and then, got a job at a pharmaceutical company and national institute, respectively. One of master's course got a job without completing master's degree.

PhD students have to publish their thesis reports in international journals during the period of thesis to obtain a PhD degree. Two of PhD course published it during the period of thesis, and had completed their PhD degree. Although one of PhD course could not publish it during the period of thesis, he finally had completed PhD degree after publication of the thesis report.

To publish the PhD thesis report during the period of thesis (3-4 years), we are sometimes forced

to reduce the quality of research to prioritize the acceptance of articles in international journals. To avoid such situation, we will establish a system that enables an efficient instruction.

３）Social Activities

None.

４）International Activities

9 publications with collaborators in US, Euro and Korea from April, 2016 to March, 2019.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

This Laboratory has completed and closed as of March 31, 2019.

Division of Genome Engineering

（１）Members

Professor	Tomoji Mashimo
Senior Assistant Professor	Kazuto Yoshimi
Technicians	1

（２）Research objectives

Genome engineering technologies, such as Zinc finger nucleases (ZFNs), TAL effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPR)-associated (Cas) nucleases (CRISPR/Cas), have been widely used in life science and medical science. Now, we are developing novel genome editing tools, such as CRISPR-cas3, which can overcome the limitations of current technology. Utilizing the different genome-editing tools, we are also developing the efficient genome editing strategies, which can modify different genes in various living organisms with high efficiency.

（３）Activity Reports

１）Research Activities

The genome editing system could be powerful tools for development of effective cancer treatment. We have reported that genome editing using Class 1 CRISPR-Cas3 system is possible in human cells as a novel independent genome editing technology from Class 2 CRISPR-Cas9 system. We also established a new combinational method of NHEJ and HDR mediated by the CRISPR-Cas9 system, named Combi-CRISPR, which facilitates the efficient and precise of KIs the plasmid DNA cassettes in mice and rats.

２）Education Activities

None.

３）Social Activities

None.

４）International Activities

None.

５）Other matters to be noted

None.

（4）Challenges and Future prospects

We will continue to develop novel diagnosis strategy and more clinical application by using CRISPR-Cas3 technology. Now we are working on chimeric antigen receptor T (CAR-T) cell therapy by utilizing CRISPR-Cas3. This effective cancer immunotherapy applies genetically modified T cells and precisely target and kill cancer cells.

Advanced Clinical Research Center

Director Toshio Kitamura

（１）Missions and Features

We aim to develop diagnostic procedures and therapies of diseases through investigating the etiologies of diseases. To this end, we investigate the molecular bases of pathologies of a variety of diseases in the Advanced Clinical Research Center, and collaborate with medical stuffs of the Research Hospital in making good use of the research achievements.

（２）Organization

Division of Molecular Therapy
Division of Cellular Therapy
Division of Infectious Diseases
Division of Clinical Genome Research
Division of Innovative Cancer Therapy
Division of Advanced Medicine Promotion
Division of Advanced Genome Medicine
Division of Genetic Therapeutics (-FY2017)
Division of Bioethics

（３）Activity Reports

１）Research Activities

Purpose: To clarify the etiologies and develop new therapies based on the basic research.

Achievements: Basic research on gene therapy lead to clinical research, and the clinical trial has been started. A trial to use AI in diagnostics has been succeeded in the initial phase, and attracted much attention from the public. The paper on the mouse model of clonal hematopoiesis has attracted much attention from the scientific field, was introduced by a special review article in New England Journal of Medicine. We have provided the model mouse to many laboratories for collaboration.

２）Education Activities

Purpose: To nurture physician scientists, and to contribute to development of novel therapies and basic research.

Achievement: We have an average of 30 graduate students (master and doctoral courses), give doctoral grades to 5~10 graduate students, some of whom go abroad for their postdoctoral works. At present, there are about 10 researchers stay in the foreign countries for their research.

３）Social Activities

Purpose: To collaborate with pharmaceutical countries to develop new drugs, and to give seminars to public and middle/high school students.

Achievement: We collaborate with more than 10 domestic and foreign pharmaceutical companies and biotech venture companies to develop novel drugs. As for outreach activities, we give about 10 seminars to the public. In addition, we accept 10~15 groups of high schools or middle high schools annually (in total 50~100 students) and introduce them with the history of our institute as well as recent achievements of our institute. These activities are organized by the director of research hospital and the director of Advanced Clinical Research Center, and many researchers and medical doctors are voluntarily involved in these activities.

４）International Activities

Purpose: Each laboratory collaborates with laboratories in the foreign countries, and publish papers.

Achievement: We annually publish papers in collaboration with foreign groups in prestigious journals including Nature, J Experimental Medicine, Blood and Leukemia.

５）Other matters to be noted

A trial to use AI in analyzing DNA mutations of AML succeeded in obtaining useful information concerning the diagnostics and therapies, which attracted much attention and was reported in TV news and newspapers. The paper on the mouse model of clonal hematopoiesis has attracted world-wide attention the scientific field, and was introduced by a special review article in New England Journal of Medicine. Phase I and II trials for the therapy of brain tumors (glioma and glioblastoma) by lytic herpesvirus vectors has been completed and are now ongoing, respectively, attracting much attention of the field.

（４）Challenges and Future prospects

Our Research Hospital and Advanced Clinical Research Center has been leading the fields of bone marrow transplantation, G-CSF therapy, cord blood transplantation, and therapy of HIV infection. In addition, lytic virus therapy against brain tumors are now on-going. Many research activities would lead to new therapies in the future.

Division of Infectious Disease is now setting up the laboratory with the new professor. In 2 years, two professors (Divisions of Molecular Therapy) will leave the institute which are mainly involved in clinical hematology and basic research concerning hematology. Therefore, it is critical to choose two professors to support clinical and basic parts of hematology of this institute.

Division of Molecular Therapy

（１）Members

Professor	Arinobu Tojo
Associate Professor	Satoshi Takahashi
Assistant Professors	Muneyoshi Futami, Masamichi Isobe
Graduate students	9
Technicians	5
Others	2

（２）Research objectives

Our research has been focused on the development of novel therapeutic options against intractable malignant disorders including leukemia, lymphoma and various cancers. For this purpose, we are making every effort to master the mechanisms of normal and neoplastic stem cells on the basis of molecular and cellular biology as well as medical informatics. We also try to develop novel therapies in the field of regenerative medicine using bone marrow-derived mesenchymal stromal cells.

（３）Activity Reports

１）Research Activities

Our research activities cover the following topics:

1. Artificial Intelligence (AI)-guided clinical sequencing for leukemia and related diseases
2. Analysis of hematological abnormalities using genetically engineered mice and search for therapeutic targets by integration of iPS cell technology and genome analysis
3. Development of universal cellular drugs using genome editing technology
4. Development of novel therapeutic modality for relapsed/refractory myeloma

We have promoted research on these topics through collaboration with researchers and companies inside and outside IMSUT, and the research outcomes have been published in Nature, JAMA Oncol, Blood, Blood Adv, PNAS, Cancer Res, Oncogene, Sci Rep, Mol Ther Oncolytics, and other journals. We published 5 peer-reviewed original articles in 2016, 9 in 2017, and 13 in 2018.

２）Education Activities

Our division cooperates with Graduate School of Medicine, UTokyo in education of doctoral students. We have 6 doctoral students in 2016, 10 in 2017 and 11 in 2018. Most of them are M.D, and our goal is to help them become respectable physician scientists. In addition, we encourage non-MD students to apply for postdoctoral positions in academia or research positions in industry.

As a result, 3 students in 2016, 1 in 2017, and 2 in 2018 have completed the doctoral course, all of whom obtained Ph.D. During this period, one Japanese and one overseas student were adopted for Graduate Program for Leaders in Life Innovation (GPLLI), and two others were adopted as JSPS research fellows (DC2), one of whom thereafter went abroad as a postdoctoral fellow. The remaining two are working as postdoctoral fellows in domestic laboratories.

３）Social Activities

We conducted collaborative researches with several pharmaceutical companies in each fiscal year in the fields of cell therapy and cancer drug discovery, resulting in acquisition of intellectual property in two issues. We also collaborated with several project divisions, which belong to Corporate Sponsored Research Program or Social Cooperation Research Programs, to help them achieve their research projects toward social implementation.

We contributed to establish the Clinical Flow Cytometry Laboratory (IMSUT-CFC), which is now operated by LSI Medience Co. as outsourcing business and helped IMSUT-CFC undertake clinical and research testing services from outside the institute (research facilities, hospitals, and companies).

We participated in UTokyo program “Self-Managing Healthy Society”, which is one of Center of Innovation Science and Technology based Radial Innovation and Entrepreneurship Program (COI-STREAM) by MEXT and contributed development of precision medicine based on whole genome sequencing.

４）International Activities

We conducted an international collaboration with a research group at the University of Georgia, USA, and published our findings in Nature.

５）Other matters to be noted

In order to realize genomic medicine, we are promoting clinical research termed as AI medicine in which artificial intelligence (AI) is applied to interpret enormous data from NGS analysis of cancer genome and to find therapeutic options deduced from driver mutations. Our trial for AI medicine was introduced by various media including newspapers and TV program with a significant impact.

（４）Challenges and Future prospects

In the field of clinical hematology, especially for hematological malignancies, a number of innovative drugs have been developed in recent years. A number of these drugs including CAR-T cells were already approved for insurance coverage via clinical trials. Although the prognosis of some

patients with hematological diseases is improving, there are still many disorders that have no standard treatments and unfavorable prognosis. To solve this problem, it is essential to identify therapeutic targets using multi-omics data and to establish animal models recapitulating pathophysiology of these diseases.

Division of Cellular Therapy

（１）Members

Professor	Toshio Kitamura
Assistant Professors	Tomofusa Fukuyama, Yosuke Tanaka
Postdocs	5
Graduate students	9
Technicians	2
Others	2

（２）Research objectives

To clarify the etiologies of hematological malignancies through establishment and investigation of mouse models, and to seek for the novel therapeutic strategies.

To investigate hematopoietic stem cells and leukemic stem cells to develop a strategy to completely cure hematological malignancies without bone marrow transplantation. The research includes screening for novel drugs, to seek for effective combination therapies, to identify the molecular mechanisms of drugs, and anti-tumor immunity.

（３）Activity Reports

１）Research Activities

Purpose: To devise the novel strategies for therapy of hematological malignancies including AML, MPN (including) CML, MDS, and CMML based on the results of basic research.

Achievements: We demonstrated that an MDM2 inhibitor is effective for the MLL-AF9-induced AML model and that HIF1a inhibitor or anti-PDL1/PD1 antibodies enhance the therapeutic effect of the MDM2 inhibitor (Hayashi et al. Nat Commun, 2019). Concerning MDS, we demonstrated that forced expression of an EZH2 mutant lacking its catalytic activity or of ABC-G2, derepressed by EZH2 mutations, induced MDS-like diseases in the mouse BMT model (Kawabata et al. Leukemia, 2018). We also published a paper that presents the first evidence that the mutant ASXL1 (ASXL1-MT) is indeed expressed in MDS/AML cells (Inoue et al. Exp Hematol, 2016). We also reported that the ASXL1-MT-KI mouse is healthy but preleukemic, mimicking clonal hematopoiesis (Nagase et al. J Exp Med, 2018). We also published a paper showing that binding of ASXl1-MT and BAP1 stabilizes and activates BAP1, leading to derepression of downstream genes including HoxA9 and Myb, which then transform the cells (Asada et al. Nat Commun, 2019).

２）Education Activities

Purpose: To recommend graduate students or postdoctoral fellow to go abroad for their research

after getting doctoral grades or publishing papers. To help graduate students to get jobs as researchers in pharmaceutical companies.

Achievements: During 2016 through 2020, 9 graduate students obtained doctoral grades, and among them five got position as postdoctoral fellow, 2 in Canada from this year and 3 in USA from next April. One master student obtained a job as a researcher in a pharmaceutical company.

３）Social Activities

The lab annually offer 6~8 open seminars including one concerning epigenetics open to general public.

４）International Activities

The lab has close connections with several foreign laboratories, several in USA and three in Europe to do collaboration, exchange ideas and people. With Abdel-Wahab lab at Memorial Sloan Kettering Cancer Center, we have many collaborations and published two papers (Inoue et al. Leukemia, 2015; Nagase et al. J Exp Med, 2018) and another collaborative paper (Fujino et al.) is now under revision. We also have close collaboration with Dr. Machiejewski at Cleaveland Clinic, and has published a paper (Takeda et al. Blood, in press). In addition, we published a collaborative paper with Dr. Gottgens lab in UK (Fukushima et al. Cell Rep, 2019).

The lab has also close relationship with Dr. Melnick lab at Weil-Cornell Medicine, Dr. Helin lab and Dr. Levine both at Memorial Sloan Kettering Cancer Center, Dr. Skoda lab at University of Basel, Dr. Schroeder lab at EZH Zurich, Dr. Scadden lab at Harvard and Dr. Goodell lab at Bailer Medical College. We sent postdocs to Dr. Scadden lab, Dr. Abdel-Wahab lab, Dr. Melnick lab, Dr. Helin lab (in Copenhagen at that time), and are going to send postdocs to Dr. Goodell lab, Abdel-Wahab lab, and Scadden Lab. We also sent a graduate student to Schroeder lab for a couple of months for formal collaboration.

５）Other matters to be noted

We filed a patent application for the ASXL1-MT-KI mouse.

The lab hosted US-Japan Hematology Meeting in Hawaii in March, 2017, 9th JSH International Symposium at Kyoto in July, 2018, and 24th meeting for hematopoietic malignancies at Kobe in January, 2019. The rock band “Negative Selection”, composed of Hematology and Immunology professors including Professor Toshio Kitamura as a drummer, gave gigs at the gathering parties for the latter two. In particular, in 9th JSH International Symposium, we played several hit songs of Eagles, Pink Floyd, and Deep Purple together with Dr. Radek Skoda from Switzerland and Dr. Margaret Goodell from USA.

（４）Challenges and Future prospects

We plan to utilize results of mouse models to develop new strategies and drugs to cure patients with hematological malignancies in concert with pharmaceutical companies. In most cases, mouse models rather accurately mimic the human disease. However, it is not clear how far we can extrapolate mouse models to human diseases. Therefore, it is critical to simultaneously use human samples in the experiments. Therefore, we are now seeking many hospitals who can supply samples from patients with hematological malignancies.

Division of Infectious Diseases

（１）Members

Professor	Hiroshi Yotsuyanagi
Associate Professor	Takeya Tsutsumi
Assistant Professors	Michiko Koga, Makoto Saito
Postdocs	1
Graduate students	7
Technicians	5
Others	1

（２）Research objectives

In addition to HIV research and international infectious disease research, which have been mainly focused on in our division, hepatitis virus research will also be conducted.

（３）Activity Reports

１）Research Activities

- HIV research

Until the current professor's appointment (July 2016), HIV research in our division mainly focused on analysis using clinical samples before introduction of antiretroviral therapy (viral gene analysis/immunological analysis of peripheral blood mononuclear cells). Until July 2017, the experiment could be operated only on a small scale., therefore we focused on building a research base for, (1) a database of these existing data (joint research with Dr. Tetsuro Matano, National Institute of Infectious Diseases) (2) pathogenesis of co-infection of HIV and hepatitis virus, (3) the relationship between the onset of complications after the introduction of antiretroviral therapy and host immunity. Concerning (2) and (3), we aimed to publish one original paper each.

Regarding (1), about 90% of the data in our division that can be uploaded to the server installed at the National Institute of Infectious Diseases has been completed. Regarding (2), we could publish only original paper in Japanese. As of March 2019, we will urgently turn into a paper for a project that is in progress (two English papers were published in FY2019). Regarding (3), we were able to publish one original paper. However, this is based on the analysis of existing databases, and the goal is to disseminate the data based on the basic research in our division that is currently underway in FY2019.

- International infectious diseases research

Regarding international infectious diseases, as of July 2016, the activities of the Department of Infectious Diseases and Applied Immunology in IMSUT Hospital (participation in research groups,

provision of rare drugs) were left. For this reason, the goal was to first start collaboration with researchers (malaria, Chagas disease) inside and outside the institute, which are related to our division, and build a system to start research. Research on malaria started in 2017. We will disseminate research results in the future.

- Hepatitis virus research

With the goal of continuing the research on viral hepatitis in HIV-infected persons and publishing the original paper, we reported one English paper as described above. In addition, we set up an experimental system to continue HCV research using conventional HCV transgenic mice, put it on an orbit, and if possible, publish one English paper. The results based on work after 2016 have not been produced yet, and it is one goal for FY2019.

２）Education Activities

There were 4 graduate students at the time of the professor's arrival in 2016, but since it was difficult to conduct an experiment immediately in our division as mentioned above, 3 students were asked to be instructed at the external research institute. Another student who was on leave returned to their first year in 2017 and is conducting research activities in our division. Her goal is to complete a dissertation. By March 2019, the presentation of the first half of the dissertation was performed at the academic conference, and writing of the thesis is underway, and progress is proceeding smoothly. Prof. Yotsuyanagi is also in charge of the Graduate School of Frontier Sciences, and gives lectures, but currently no graduate students belong to our division.

３）Social Activities

None.

４）International Activities

None.

５）Other matters to be noted

As an activity of the Department of Infectious Diseases and Applied Immunology in IMSUT Hospital, we conducted educational activities for citizens and opened an outpatient clinic for overseas travels.

（４）Challenges and Future prospects

For two and a half years until March 2019, a great amount of time was spent building a system for conducting research in our division. The system is almost established, and it is possible to carry out research and disseminate the results in the future. There are some projects as mentioned above, and it

is necessary to publish the papers from each project regularly.

Division of Clinical Genome Research

（１）Members

Professor	Yoichi Furukawa
Associate Professor	Tsuneo Ikenoue
Project Senior Assistant Professor	Kiyoshi Yamaguchi
Assistant Professor	Kiyoko Takane
Graduate students	3
Technicians	2

（２）Research objectives

Our research objectives include elucidation of mechanisms underlying gastrointestinal tumors and development of new modalities for their diagnosis, treatment, and prevention. In addition, we have been carrying out a research project for the implementation of precision medicine in our hospital through genomic analysis of cancer and individual genome.

（３）Activity Reports

１）Research Activities

In our laboratory, we have been investigating molecular mechanisms underlying gastrointestinal tumors such as colorectal, biliary tract, and pancreatic cancer.

One of our research projects is the elucidation of molecular mechanisms involved in colorectal carcinogenesis caused by activated Wnt signaling. Using expression profiles of colorectal cancer cells treated with β-catenin siRNA and ChIP-seq data with anti-TCF7L2 antibody, we identified several genes directly upregulated by β-catenin/TCF7L2 complex including FERM domain containing 5 (*FRMD5*). Additionally, we disclosed that elevated *FRMD5* expression in colorectal cancer is associated with poor prognosis. We further identified interferon induced protein with tetratricopeptide repeats 2 (*IFIT2*) as a gene downregulated by Wnt signaling, and found that reduced IFIT2 expression increased cell proliferation and suppressed apoptosis. Further investigation unveiled that *IFIT2* is transcriptionally regulated by interferon regulatory factor 1 (IRF1), and that IRF1 is destabilized by the Wnt signaling through reduced UAF1 expression and suppressed USP1 deubiquitinase activity. These data shed light on new mechanism of Wnt signaling pathway. Besides these basic studies, we have been working on the development of Wnt inhibitors. We previously performed a high throughput screening for Wnt inhibitors using a library containing 20,000 compounds, and identified several hit compounds. For the optimization of the hit compounds, we are now collaborating with medicinal chemists in Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS), the University of Tokyo.

In addition, we have been generating cancer mouse models and analyzing tumors developed in the mice. In a project, we established liver-specific knockin mice carrying a cancer-associated hotspot mutation of *FBXW7*, which developed intrahepatic bile duct tumors. We are now analyzing the role of *FBXW7* mutation in cholangiocarcinogenesis.

In 2015, we started a precision medicine project for patients with solid cancer/hematological malignancies in collaboration with doctors in IMSUT hospital and bioinformaticians in Human Genome Center. In this project, we performed whole genome/exome sequencing and took advantage of an artificial intelligence, IBM Watson for Genomics, for the interpretation of mutations and selection of anticancer drugs. In addition, we performed genetic screening for endometrial cancer using liquid-based cytology samples in collaboration with Sapporo Medical University. We also participated in international collaboration with the Pharmacogenomics Research Network (PGRN) in USA, and searched for genetic variants associated with efficacy and/or adverse effect of drugs. The collaborative studies consequently identified SNPs associated with adverse effects of bevacizumab in adjuvant chemotherapy for breast cancer, and those associated with serum VEGF-A levels.

２）Education Activities

Professor Furukawa has been taken charge of master and doctor-course education of Graduate School of Medicine and Graduate School of Frontier Sciences in the University of Tokyo. In addition, he has been in charge of an adjunct professor in Oita University and Iwate Medical University. He gave several lectures and seminars in these universities. Associate professor Ikenoue is a faculty member of Graduate School of Medicine. They have trained a number of master and doctor-course students through the participation in their research projects.

３）Social Activities

Professor Furukawa has been playing a vital role as an associate editor of Cancer Science and Human Genome Variation, journals supported by Japanese Cancer Society and Japanese Society of Human Genetics, respectively. He is working as a board member of these societies. He is involved in a project for promotion of genome-based medicine for cancer in Japan, and has given lectures for medical doctors, nurses, and laboratory technicians. He was invited as an adviser in a meeting for 100 thousand whole genome-project in Japan in 2019. Professor Furukawa and associate professor Ikenoue are collaborating in the development of guidelines for hereditary tumors such as Cowden disease and Peutz-Jeghers syndrome in Japan.

４）International Activities

Professor Furukawa has been collaborating with the Pharmacogenomics Research Network

(PGRN) in USA for more than six years.

５）Other matters to be noted

We opened a summer seminar for young students in elementary and junior high schools in 2019. Students participated in the seminar with their parent(s), enjoyed lectures of genome, DNA analysis, and genetic variations, and performed experiments using DNA from their parent. We do hope that early education of genomic variations will help their understanding of difference in individuals.

（４）Challenges and Future prospects

We will keep on working for the elucidation of molecular mechanism underlying gastrointestinal tumors, and analyzing function of genes associated with the development and progression of gastrointestinal tumors. Additionally, we will try to clarify new molecules, pathways, mechanisms regulated by activated Wnt signaling in cancer, and make challenges for the identification of novel target molecules for the treatment of tumors. In the development of Wnt inhibitors, we will investigate small molecules structurally related to the hit compounds, and perform analysis of structure–activity relationship for their optimization.

In the research of mouse models, we plan to establish novel genetically engineered mice models. In addition, we will test efficacy and adverse effect of new compounds using our intrahepatic cholangiocarcinoma model in collaboration with pharmaceutical companies. Challenges will be started for the development of a treatment model targeting oncogene(s) by adenovirus expressing guide RNA with dCas9.

We will continue the project of precision medicine for patients with solid cancer/hematological malignancies, and assess the effectiveness of WES/WGS with AI for the selection of treatment.

Division of Innovative Cancer Therapy

（１）Members

Professor	Tomoki Todo
Project Associate Professor	Minoru Tanaka
Assistant Professor	Seisaku Kanayama
Assistant Professors	Yoshinori Sakata, Hirotaka Ito
Postdocs	1
Graduate students	2
Technicians	4
Others	3

（２）Research objectives

With the steady increase in the mortality rate of cancer, it is difficult to cure intractable cancers and cancers that have recurred after standard treatment, and there has been an urgent need for developing an innovative modality that can lead to the cure of disease. We developed genetically engineered oncolytic viruses that only replicate and destroy cancer cells. In particular, G47Δ, a genetically engineered oncolytic herpes simplex virus type 1 with triple mutations, has high safety features and a robust antitumor effect, and is being applied in the clinical trials. Through the development of various next-generation viruses that exert different anti-tumor functions and utilization of cancer stem cells isolated from malignant brain tumors, we aim to develop an innovative cancer treatment that is applicable to a wide variety of cancers and will overcome recurrence and metastasis in the near future.

（３）Activity Reports

１）Research Activities

Oncolytic virus therapy has been suggested to be effective for all solid tumors in pre-clinical studies, and is expected to be a new cancer treatment modality that is universally applicable. We have been dedicated to developing a series of next-generation oncolytic viruses preclinically and delivering them on the clinical pipeline. In 2016, G47Δ was designated as a ‘Sakigake’ breakthrough therapy drug by the Ministry of Health, Labour and Welfare of Japan, and further as an orphan drug for malignant glioma in 2017, allowing its priority review and fast-track drug approval. With an unprecedented high therapeutic efficacy in the interim analysis of the phase II clinical trial for glioblastoma, the new drug application of G47Δ as the first-in-the-world, Japan-made oncolytic virus product for malignant glioma is expected in 2020. A new clinical trial for malignant melanoma using T-hIL12, a recombinant herpes simplex virus type 1 gene expressing human interleukin 12, also started in 2020.

２）Education Activities

A wide range of graduate students from each department of internal medicine and surgery have applied, and a variety of preclinical researches have been conducted while considering the practical needs in each disease. Most of the graduate students have received their degrees, which yields core human resources who will be responsible for viral therapy in the future.

３）Social Activities

The principle investigator is anointed as the president of the Japan Society for Gene and Cell Therapy, where he strives to spread gene therapy and viral therapy in Japan, and acts as a bridge between regulators, researchers and companies. We have also been making a social contribution by cooperating in making a public comment on “Ethical guidelines for research that uses genetic information modification technology for human fertilized embryos” related to the research that uses technology that modifies genetic information such as genome editing technology.

４）International Activities

We have frequently exchanged ideas through international conferences.

５）Other matters to be noted

Specimens (tumor tissue, blood, saliva, urine, etc) from the clinical trials of G47Δ for glioblastoma, olfactory neuroblastoma, malignant pleural mesothelioma, were analyzed to evaluate the safety and efficacy.

（４）Challenges and Future prospects

There has been a remarkable progress in the practical application of in vivo gene therapy and oncolytic virus therapy. In recent years, several products have been put on the market for rare diseases (hereditary diseases) and cancers, and new entry of many pharmaceutical companies have made the development race more intense. In particular, the scale of market for oncolytic virus therapies is expected to be 1 billion dollars per drug. We are trying to seek the profits of research to the Japanese society by realizing the application of G47Δ in all cancer patients as early as possible.

Division of Advanced Medicine Promotion

（１）Members

Professor	Fumitaka Nagamura
Associate Professor	Masanori Nojima
Graduate students	2
Technicians	1

（２）Research objectives

Translational Research (TR) is the clinical application of the results of basic research. One of the major missions of IMSUT is to promote TR. Division of Advanced Medicine Promotion cooperates with Center for Translational Research to provide consistent support for conducting TR, from basic research to conduct of clinical trials, and this includes the supports of patent applications and conducts of preclinical studies. Professor Nagamura mainly researches regulations and support methods as regulatory science. And Associate professor Nojima mainly does biostatistical analysis and support methods using biostatistics. As the numerical goals of research, at least five conference presentations and at least three papers a year have been settled. Our long-term goals are that several kinds of supported “seeds” will be approved by regulatory authorities.

（３）Activity Reports

１）Research Activities

The biggest feature of the seeds we support is that most of them are classified as new modalities, such as genetically modified Herpes Simplex Virus-1 and that Measles Virus as oncolytic therapy, Rice-based vaccine for traveler’s diarrhea, artificial adjuvant vector cells for hematologic malignancies, umbilical cord derived mesenchymal stroma cells for inflammatory/immune diseases. Under such situation, the main topic of our researches is regulatory science for new modalities and biostatistical methods for early clinical trials. We prepare for “Regulatory Science consultation on R&D strategy” of Pharmaceuticals and Medical Devices Agency in all seeds, and utilized the experience and information obtained from consultations for research. We made seven presentations at domestic conferences in 2016, 12 presentations at domestic conferences and seven at international conferences in 2017, 11 at domestic conferences and three at international conferences in 2018, and six presentations at domestic conferences and two at international conferences in 2019. Regarding the paper, we published 24 papers in 2016, 23 papers in 2017, 14 papers in 2018, and 22 papers in 2019. Another research interest is the education on TR, and we created the education syllabus on TR and conducted a survey on TR education in graduate school. So far, we believe the goal of the research has been fully achieved. Other research interests include the development of diagnostic

methods using machine learning methods. As a graduate school faculty, an epidemiological study using the receipt data provided by the Ministry of Health, Labour and Welfare has been conducted.

２）Education Activities

Educations for non-MD researchers and workers are critical for the development of human resources engaged in TR. We have been in charge of graduated school lectures of “Basic of Translational Research”, “TR as clinical trial” and “Laws and regulations for TR” of department of computational biology and medical sciences, graduate school of frontier sciences and “Nursing for translational research” of division of health sciences and nursing, graduate school of medicine. We also take part in the project to create educational materials for workers engaged in vector manufacturing for gene therapy and that to conduct annual workshop on bioethics of regenerative medicine. For researchers and workers at IMSUT and IMSUT hospital, we provide e-learning on TR and conduct several seminars.

３）Social Activities

Because there are few biostatistical education in Japan, we give biostatistics courses at other medical institutes. We have released an explanation of terms on TR and teaching materials, including materials for researchers and physicians related to TR on our webpage.

４）International Activities

We have been involved in the Nipa Vaccine development project, which had adopted by CEPI (Coalition for Epidemic Preparedness Innovation) in 2018. Our role is to handle the matters related to clinical trials. This project has been conducted by a consortium composed of the University of Tokyo, Stanford University, European Vaccine Initiative, and International Centre for Diarrhoeal Disease Research, Bangladesh.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

The range we have been treating is very wide, from the patent application to clinical trial. On the other hand, the member of our division is very limited. Our challenge is to increase the number of staff and treat various problems. One solution is to get external research funding for employment, and the other is to aggressively target new modalities to increase the attractiveness of our research. Our future prospect is to secure adequate human resources by above activities, and to set up a research system which responding to novel areas of TR.

Division of Advanced Genome Medicine

（1）Members

Associate Professor	Yoshihiro Hirata
Graduate students	2

（2）Research objectives

Pathogenesis analysis and new therapy development for inflammatory diseases and malignancies of digestive systems; for example, development of two novel diseases models, two new therapies, and publication of six original papers during this term.

（3）Activity Reports

1）Research Activities

After arrival in September 2017, we performed several research projects mostly based on genetically engineered mouse models. As major achievements, 1) We have shown the pathogenic role of dendritic cell E-cadherin, and proposed a novel neutralizing antibody therapy using originally developed mouse colitis model, 2) We have elucidated the mechanism and cell origin of gastric metaplasia, which is known to be the precursor of gastric cancer. In total, nine original papers were published. Therefore as an evaluation of achievements, 1) development of two novel diseases models for pathogenesis analysis was achieved (gastritis model and colitis model), 2) development of two novel therapies using mouse models fell short (one novel therapy against colitis using E-cadherin neutralizing antibody), 3) number of publication was achieved (nine original papers).

As for an unachieved goal (novel therapy proposal against gastric metaplasia), we have set up new research projects for the next term; generation of a new gastric metaplasia model with the inducible gene modification, which enables temporal-spatial, comprehensive analysis of gastric metaplasia process. We believe this model will lead to the clear understanding of the mechanisms and elucidate a novel therapy for reversal or prevention of metaplasia.

2）Education Activities

Our division took charge of Fundamental Exercise I for the graduate students of School of Fontier Sciences, in which about 50 students annually got experienced in practical Medicine through the rounding at IMSUT Hospital. We also offered similar practical Medicine course to ten students of the department of Psychology, Faculty of Human Science, Bunkyo University. Each exercise course was evaluated by the students, and mostly got satisfactory responses. We also adjusted the shortcomings in the course, such as inconvenient time scheduling, unnecessary repetition of lecture contents, with the lecturer or hospital staff. This kind of refinement by feedback will be continued

to improve the quality of Fundamental Exercise I.

Graduate students who attended our division is going through the research project in which each student pursue his/her own goal to explore the pathogenesis and the treatment of gastroduodenal inflammatory and malignant diseases. They got practical lessons on biology, molecular biology, and gastroenterology through practices and lectures.

３）Social Activities

Our division offered a field trip for the high school students.

４）International Activities

Two publications, Hayakawa et al (gastroenterology), Kinoshita et al (Am J Physol Gastroint Liver Physiol), were performed in collaboration with the researchers in the USA. Our original cell line (SIAC1 cell) was donated to the German researcher for the collaboration.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

This division included only one faculty member, and the lack of manpower have led to the insufficient achievements in both research and educational activity. Currently, collaboration with other laboratories of the IMSUT, University of Tokyo Hospital, or others, have helped to keep research activities. Thorough acquisition of new research grant and addition of faculty member and graduate students, we try to improve research and educational activities of the division.

Division of Genetic Therapeutics (-2018.3)

（１）Members

Professor	Keiya Ozawa
Project Professor	Shin-ichi Muramatsu
Senior Assistant Professor	Sumimasa Nagai

（２）Research objectives

The main project of our division was to promote clinical development of novel gene therapy for cancer and chronic intractable diseases. We engaged in clinical development of immuno-gene therapy with chimeric antigen receptor (CAR)-modified T cells for relapsed and refractory hematological malignancies and gene therapy for neurological disorders using adeno-associated virus (AAV) vectors.

（３）Activity Reports

１）Research Activities

1. Immuno-gene therapy with CD19-directed CAR-modified T cells (CD19-CAR-T cells) for adult patients with relapsed and refractory B-cell non-Hodgkin lymphoma

It has been reported that CD19-CAR-T cell therapy is highly effective for relapsed and refractory B cell malignancies. In order to develop this novel promising gene therapy in Japan, we conducted clinical study of CD19-CAR-T cell therapy for adult patients with relapsed and refractory B-cell non-Hodgkin lymphoma in collaboration with Jichi Medical University and Takara Bio Inc. (NCT02134262). This first clinical study of CAR-T cell therapy in Japan has started in 2015.

2. Gene therapy for amyotrophic lateral sclerosis and spinocerebellar ataxia type 6

In sporadic amyotrophic lateral sclerosis (ALS) patients, down regulation of the RNA-editing enzyme, adenosine deaminase acting on RNA 2 (ADAR2), is death-causing molecular abnormality that occurs in motor neurons. Gene delivery of the ADAR2 using tyrosine-mutant AAV9/3 (AAV.GTX) vector in conditional ADAR2 knockout mice effectively prevented progressive motor dysfunction without any adverse effects. We have started to produce GMP grade AAV.GTX vectors that express ADAR2 for a clinical trial. In collaboration with Chicago university, we have developed miR-based gene therapy for spinocerebellar ataxia type 6 (SCA6). SCA6 is caused by abnormal expansions of the polyglutamine tract within a second *CACNA1A* gene product, α1ACT. Selective translational block of SCA6-associated α1ACT by delivering miR-3191-5p protected from the Purkinje cell degeneration and ataxia in a mouse model

(Miyazaki Y. et al, Sci Transl Med, 2016).

By lending our expertise on gene therapy for Parkinson disease, we have supported an open-label phase1/2 study of gene therapy for children with aromatic L-amino acid decarboxylase (AADC) deficiency in National Taiwan University. AADC is an essential enzyme for dopamine synthesis. The primary phenotypes of AADC deficiency include severe developmental delay and movement disorders. AAV vector-mediated gene delivery into the putamen resulted in marked improvement of motor functions (Chen YH, et al. Lancet Child Adolesc Health, 2017).

3. International comparison of regulations on regenerative medical products and anticancer drugs

Several expedited regulatory review projects for drugs and regenerative medical products have been developed in the US, the EU, and Japan. Understanding the global regulatory frameworks is important for the conduct of translational research and clinical development of new therapeutic products efficiently. Regulatory frameworks for the marketing authorization of oncologic drugs, generic anticancer drugs, and gene and cellular therapy products in Japan, the EU, and the US were examined. (Nagai S, et al. Int J Hematol 2016, Nagai S, et al. Invest New Drugs 2016, Yang YT, Nagai S, Chen BC, et al. Lancet Oncol 2016, Nagai S, et al. Curr Gene Ther 2017, Nagai S, et al. Invest New Drugs 2018)

２）Education Activities

None.

３）Social Activities

Our division organized the 1st ~ 5th IMSUT-CGCT (Center for Gene & Cell Therapy) symposium as the secretariat.

４）International Activities

S.M. contribute to European society for gene and cell therapy (ESGCT) as a reviewer of abstracts and an invited speaker of annual congress in 2016.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

This Division has completed and closed as of March 31, 2018.

Division of Bioethics

（１）Members

Associate Professor	Ayako Kamisato
Postdocs	2
Others	1

（２）Research objectives

The objectives of our division are to study how medical science or medical care should develop in society and what are needed for them to develop including regulations, and then to give practical feedbacks through policy proposals or tools development to society.

The following are the specific research themes.

(1) Human embryo research/human embryo genome editing

(2) Creation of human and animal chimeras

(3) Improvement of quality of ethical review

(4) Protection of human subjects

（３）Activity Reports

１）Research Activities

Regarding the above theme (1)

- As a member of the Expert Panel on Bioethics of Council for Science, Technology and Innovation set by Cabinet Office, Dr. Kamisato engaged in following policy makings;
  - Supplementary report on the revision of the Basic Principles on Handling of Human Embryos: regarding the use of genome modification techniques including genome editing in assisted reproductive medicine research. March 2018
  - Second Report on the revision of the Basic Principles on the Handling of Human Embryos: regarding the use of genome modification techniques including genome editing in assisted reproductive medicine research. June 2019
- As a member of the Council on Research Using Genome Editing Technology for Human Fertilized Embryos set by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Dr. Kamisato engaged in making following guidelines;
  - Guidelines for Research Using Gene-altering Technologies on Human Fertilized Embryos
- As a member of the Council on Research Using Genome Editing Technology for Human Fertilized Embryos set by the Health, Labour and Welfare Ministry (MHLW) , Dr. Kamisato engaged in making following guidelines;
  - Guidelines for Research Using Gene-altering Technologies on Human Fertilized Embryos

- As a member of the Council on Clinical Use of Using Genome Editing Technology for Human Fertilized Embryos set by the Ministry of Health, Labour and Welfare Ministry (MHLW) , Dr. Kamisato engaged in making proposal.

Regarding the above theme (2)

- As a member of the Council on Specified Embryos set by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Dr. Kamisato engaged in revising following guidelines;
  - Guidelines on the Handling of Specified Embryos

Regarding the above theme (3)

"Ethical Guidelines for Medical and Health Research Involving Human Subjects" and "Regulation for Enforcement of Clinical Trials Act" require researchers and research ethics committee (REC) members to receive ethical education and training programs at least once a year. We established the original program for researchers and REC members with support from the Japan Agency for Medical Research and Development (AMED) since FY 2019. We have already produced and released 14 video programs.

Regarding the above theme (4)

"Center of Healthy Aging Innovation project" promoted by Hirosaki University is one of the projects of JST Center of Innovation (COI) Program. One goal of this project is to build a platform of big data on health. We support the researchers involved in this program from the aspect of research ethics, such as giving research ethics consultation, making tools for public enlightenment.

２）Education Activities

Concurrent lecturer of Graduate School of Frontier Sciences, The University of Tokyo
Part-time lecturer of several universities
Holding many workshops for REC members
Conducting many educational lectures

３）Social Activities

None.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

From the results of the questionnaire survey conducted by us in 2018, the need for public awareness activities regarding medical research to the general public has emerged. In order to build good relationships of trust between the general public and medical researchers and to promote medical research, we will continue our research and give back the result to society.

Center for Stem Cell Biology and Regenerative Medicine

Director Hideki Taniguchi

（１）Missions and Features

Stem cell research has been a major part of regenerative medicine in the 21st century. This includes transplantation therapy with artificial or whole organs as well as research into cancer and other disease areas. The Center for Stem Cell and Regenerative Medicine was launched as a core research center for stem cell-based medicine. It aims to facilitate the transition of outcomes from stem cell biology research into pre-clinical and clinical studies. Furthermore, there is also hope for developing innovative approaches to treat to cancer and various other diseases.

（２）Organization

Division of Regenerative Medicine
Division of Stem Cell and Molecular Medicine
Division of Stem Cell Transplantation
Division of Stem Cell Signaling
Division of Stem Cell Processing
Division of Stem Cell Pathology
Division of Stem Cell Biology
FACS Core Laboratory
Stem Cell Bank
Division of Stem Cell Therapy (-FY2016)
Division of Stem Cell Dynamics (-FY2018)
Division of Stem Cell Cellomics (-FY2019)

（３）Activity Reports

１）Research Activities

In each division, activities such as publication of papers, presentations at conferences and application/acquisition of patents are actively promoted in line with the respective goals of each project. For detailed information please see the description of each division with the results shown below.

2016 April to 2017 March (Director: Dr. Hiromitsu Nakauchi)
2017 April to 2019 March (Director: Dr. Yoshinori Murakami)

Relating to hematology, it was discovered that the essential amino acid Valine is critical for the

maintenance of hematopoietic stem cells (Taya et al. *Science*). In collaboration with the Weissman Lab at Stanford University, we revealed that hematopoietic stem cells are localized to the side of the vascular niche. (Chen et al., *Nature*). Furthermore, from research conducted in the division of stem cell therapy regarding organ regeneration, it was discovered that primed ES / iPSCs and progenitor cells committed to the endoderm lineage has the capacity to form chimeras by only transient expression of an apoptosis inhibitor (Masaki et al. *Cell Stem Cell*). A breakthrough results was made by demonstrating that a mouse pancreas can be generated inside a rat and that the islets derived from the pancreas can be transplanted into a diabetic mouse to normalize blood glucose levels for long periods without immunosuppression. (Yamaguchi and Sato et al. *Nature*). A review article on organ regeneration in xenogeneic animals was published in Nature (Wu et al. *Nature*).

2019 April~ (Director: Dr. Hideki Taniguchi)

In April 2019, Professor Hideki Taniguchi was appointed as the Director of the Center for Regenerative Medicine. Alongside Professor Yasuhiro Yamada of the Graduate School of Stem Cell Pathology, the resulting collaborative efforts further strengthened the ongoing stem cell research at the center. More recently in relation to hematology, a highly cost effective method of expanding hematopoietic stem cells without aging was reported. The method relied upon the use of polyvinyl alcohol (PVA), the main component of liquid glue, rather than expensive materials such as serum or albumin that are routinely used in cell culture. (Wilkinson et al. *Nature*). In collaboration with Columbia University, there was success in generating a functional lung from pluripotent stem cells using a next-generation blastocyst complementation method and a novel pluripotent stem cell culture system (Mori et al. *Nature Med*). Taken together, this research center has consistently produced high-level research results.

２）Education Activities

In each division, the training of graduate students is actively ongoing. The center has also been open to visits from junior and senior high school students to offer some exposure to a scientific research environment. In the past year, 57 graduate students (13 international) were trained and 15 visits were accepted.

３）Social Activities

Joint research with companies is ongoing in each division. In the past year, 21 collaborations (joint research with companies/contract research) were established and executed.

４）International Activities

A number of international cooperative research activities in different fields are taking place. For

more information, please see specific descriptions from each division. In the past year, a total of 17 international collaborations were conducted at the center, including the following.

- The International Academic Exchange Agreements with Fujian Institute of Hematology a research project entitled "Co-development of novel cancer immunotherapy for hematological cancers such as multiple myeloma".
- The International joint research project of the International Joint Usage/ Research center of the Institute of Medical Science entitled "Virus-specific T-cell therapy for cord blood transplant patients".
- Research on ASXL1 with Dr. Omar Abdel-Wahab under an international joint research agreement with Memorial Sloan-Kettering Cancer Center.
- Research on pluripotent stem cells with Dr. Austin Smith under an international joint research agreement with University of Cambridge.
- The international joint research project of the International Joint Usage/ Research Center of the Institute of Medical Science entitled "Development of innovative culture method for hematopoietic stem cell expansion" with Lund University and "Single-cell epigenomics for the characterization of HSC aging" with Marseille Cancer Research Center.
- The International joint research project of the International Joint Usage/ Research center of the Institute of Medical Science with Sun Yat-sen University entitled "New treatment strategy in acute on chronic liver failure using iPSCs-derived liver organoids.
- The Bilateral Programs with Chinese Academy of Sciences (CAS), a joint research project entitled "Elucidation of the molecular basis of in vivo reprogramming by single cell analysis".

５）Other matters to be noted

Dr. Beate Heissig was one of only a few foreign female senior faculty members. She trained a large number of international students and published excellent papers.

Annually the FACS Core Lab is used by more than 2000 internal and external researchers.

（４）Challenges and Future prospects

With regards to basic research on stem cells, a number of truly novel and innovative results has been published. In the future, it is hoped that further progress can be made on research aiming at the proliferation of human hematopoietic stem cells. With the support of the Institute of Medical Research Hospital, the goal is to facilitate the realization of safer transplantation medicine.

Division of Stem Cell and Molecular Medicine

（１）Members

Professor	Atsushi Iwama
Assistant Professors	Motohiko Oshima, Yaeko Nakajima, Masayuki Yamashita
Postdocs	2
Graduate students	11
Technicians	2
Others	1

（２）Research objectives

1. We aim to develop methods to manipulate hematopoietic stem cells through an understanding of their self-renewal mechanism.

2. We aim to establish a new treatment method by conducting research on the aging of hematopoietic stem cells and hematopoietic malignancy from an epigenetics point of view.

（３）Activity Reports

１）Research Activities

We, Division of Stem Cell and Molecular Medicine, have conducted research in order to elucidate:

a) the molecular basis for the self-renewal mechanism of hematopoietic stem cells,

b) epigenetics for the characteristic changes of hematopoietic stem cells associated with aging,

c) epigenetic abnormality in the pathogenesis of hematopoietic malignancy.

From March 2018, the time I transferred here and set up a laboratory, until March 2019, the objective for our division has been to research the working mechanism of epigenetic molecules that control the self-renewal of hematopoietic stem cells and the pathogenic mechanism of hematopoietic malignancy caused by dysregulation of self-renewal and differentiation of hematopoietic stem cells. As for results, we planned to publish 1 to 2 English scientific papers during the stated period.

In fact, we were able to unravel the function of Phf6 as a new epigenetic control gene for the hematopoietic stem cells (Blood 2019, IF 16.4） and elucidated how a dysfunction of Bcor affects the onset of myelodysplastic syndrome, which is an aging-related myeloid malignancy (Blood 2018 IF 16.4). We wound up publishing 8 scientific papers (6 papers above IF 10).

From that viewpoint, we believe we have made fruitful achievements in those areas of research.

However, we have yet to publish papers on epigenetic analysis for characteristic change of hematopoietic stem cells associated with aging, and there is some delay in this research.

For this matter, we plan to increase the number of researchers who will mainly work on the said theme and strengthen the research promotion system as well as optimize the quality of our research by conducting a single cell epigenetic analysis and so forth.

２）Education Activities

We instructed 1 Master student from Department of Computational Biology and Medical Sciences, 2 PhD students from Faculty of Medicine and 5 PhD students outsourced from Faculty of Medicine, Chiba University. We taught a class for each of Faculty of Liberal Arts and Department of Computational Biology and Medical Sciences.

３）Social Activities

None.

４）International Activities

We conducted a joint research with Dr. Duprez at Marceille Cancer Center in France and unraveled the function of transcription factor PLZF in regulating enhancer activity associated with the aging of hematopoietic stem cells.

５）Other matters to be noted

As head of the Grant-in-Aid for Scientific Research on Innovative Areas ‘Establishing a new paradigm of the pathogenesis of diseases through the understanding of stem cell aging’, I endeavored to consolidate and promote this area of research.

（４）Challenges and Future prospects

There is a delay in the epigenetics analysis on the characteristic changes of hematopoietic stem cells associated with aging. For this matter, we will strengthen the research promotion system by increasing the number of researchers. At the same time, we will improve the quality of research by conducting single cell epigenetic analysis and so forth. We also plan to start a project to discover how inflammation is associated with self-renewal, differentiation and transformation of hematopoietic stem cells and promote the research.

As a result of the above projects, we expect to publish 3 highly impactful scientific papers and 3 additional papers on unraveling the pathogenesis and treatment method of hematopoietic malignancies associated with the inflammation and aging of hematopoietic stem cells by 2021. Among those papers mentioned above, we aim to publish 1 to 2 papers above IF 20. Moreover, we intend to acquire 2 research funds from AMED for projects on the self-renewal control of hematopoietic stem cells as well as the aging of hematopoietic stem cells.

Division of Regenerative Medicine

（1）Members

Professor	Hideki Taniguchi
Project Associate Professor	Tomoyuki Yamaguchi
Assistant Professor	Yunzhong Nie
Project Assistant Professor	Yasuharu Ueno
Postdocs	1
Graduate students	7
Technicians	4
Others	2

（2）Research objectives

In our lab, we are developing a method for creating and transplanting human tissues or organs generated from human induced pluripotent stem cells (human iPSCs). Our goal is to establish this method as a new therapeutic modality as an alternative to whole organ transplantation. Between 2008 and 2009, a quality evaluation method for liver organoids generated from human iPSCs (human iPSC liver bud) was developed. This included the establishment of a method for detecting undifferentiated iPSCs, which is necessary for the clinical application of human iPSC liver bud, and to examine the therapeutic efficacy after transplantation for treating urea cycle disorders and liver cirrhosis. In addition, in order to evaluate the feasibility of utilizing the same differentiated cells to elucidate the pathology of infectious diseases, we aimed to establish an infection model using these liver buds to evaluate hepatitis B virus (HBV) infection.

（3）Activity Reports

1）Research Activities

1. Development of a quality evaluation method for human iPSC liver buds

To achieve therapeutic effect in treating liver diseases, it is necessary to transplant a large number of human iPSC liver buds. In order to ensure safety by excluding the presence of residual undifferentiated iPSCs that may cause tumor formation, it is necessary to establish a technique for detecting and evaluating undifferentiated cells within the liver buds. LIN28A was previously reported to be a marker of undifferentiated iPSCs, but we confirmed that expression is retained through the early stages of hepatocyte differentiation. Therefore, it is necessary to identify novel markers suitable for the detection of undifferentiated iPSCs (purity test). Overall three different markers for characterizing undifferentiated cells were identified. It is now possible to detect the presence of undifferentiated cells at a frequency of 0.005% (reported at the 18th Annual Meeting

of the Japanese Society for Regenerative Medicine, Japan Foundation for Applied Enzymology). Single cell RNA sequence data analysis of human iPSC liver buds was performed. Subsequently a novel marker that enables prediction of human iPSC liver bud function during the human iPSC liver bud production process was identified. These evaluation methods are currently being considered for implementation as part of the manufacturing process in the future.

2. Examination of the therapeutic efficacy of human iPSC liver bud for treating urea cycle disorders and cirrhosis

Verification of the therapeutic efficacy of human iPSC liver bud transplantation involves two stages. First, a method for evaluating metabolic abnormality in mouse models of urea cycle disorders was established. Thereafter, the therapeutic efficacy of human iPSC liver buds was investigated using Ornithine Transcarbamylase (OTC) deficient mice. It could be confirmed that ammonia metabolism of OTC deficient mouse improved after subrenal transplantation of human iPSC liver buds, and the therapeutic effect after transplantation was confirmed. An investigation into the mechanisms revealed that that engrafted tissue showed OTC activity, which was confirmed by a metabolic flux analysis method that was developed in this laboratory. Furtheremore, preparation for the clinical application of human iPSC-derived liver bud is well under way in cooperation with Yokohama City University. Study results are being compiled and documents such as Standard Operating Procedures (SOP) have been prepared. This is alongside writing a regenerative medicine provision plan as well as other related documents. These will be submitted as supporting documents for an application to be examined by the regenerative medicine committee of the National Center for Child Health and Development.

3. Establishment an infection model for HBV

Human iPSC liver buds can recapitulate the tissue structure and metabolic functions of human liver thus applications can extend to its establishment as a pathological model. An investigation into the practical utility of these liver buds for assessing HBV infection revealed that HBV can persistently infect human iPSC liver buds long-term and reproduce characteristic changes in hepatocytes associated with HBV infection (Nie YZ, Taniguchi H et al, ***EBioMedicine***. 35:114-123, 2018). From these results, it was confirmed that human iPSC liver buds are useful for elucidating the infection mechanisms of HBV.

２）Education Activities

7 students (3 master course, 4 doctor course) were trained in educational research activities. Five of them are international students.

３）Social Activities

Collaboration with various companies is crucial for promoting clinical application of human iPSC liver bud. Recently, in collaboration with Ajinomoto Co., Inc., we established a protocol for producing human iPSC liver buds that complies with GCTP (Good Gene, Cellular, and Tissue-based Products Manufacturing Practice) standards. This allows production of manufactured cells to a grade that is required for clinical trials. In addition, discussions are advanced in strengthening our collaboration with Healios Co., Ltd., which is a biotechnology company with a strong track record of conducting multiple clinical trials.

４）International Activities

Joint research is being conducted with Zhongshan University, Guangdong Province, China. This institution processes a large number of clinical liver transplantation (about 320 cases / year) and owns a large-scale facility for cynomolgus monkeys. Meetings have been held discussing such topics as how a close cooperation system can be established. From the next fiscal year, Zhongshan University clinicians and researchers will be accepted into the Center for Stem Cell Therapy to begin acceleration of the joint research partnership.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

Although preparations for clinical trials are well under way, further progress will be highly dependent upon securing new grants. International join research is vital to facilitate the exchange of ideas and scientific expertise. Collaboration with Zhongshan University allows our method of generating and transplanting iPSC-derived organoids to be evaluated in larger mammals such as cynomolgus monkeys. Provision of education will be equally important to train the next generation of young researchers who can carry out the research associated with this laboratory. This includes recruiting international graduate students. As part of the recruiting efforts, plans have been made to create an internationally appealing website and to actively promote the introduction of laboratories on open campuses.

Division of Stem Cell Transplantation

（１）Members

Professor	Arinobu Tojo
Associate Professor	Satoshi Takahashi

（２）Research objectives

We are conducting clinical stem cell transplantation, especially using cord blood as a promising alternative donor for clinical use and investigating optimal strategies to obtain the best results in this area. We are also generating pre-clinical study to utilize virus-specific CTL for immune competent patients such as post-transplantation. Our goal is as allogeneic transplantation to be safer therapeutic option and to extend for older patients.

（３）Activity Reports

１）Research Activities

Our division plays a clinical part of Center for Stem Cell Biology and Regenerative Medicine, and is in charge of treatment of hematological disorders, especially relapsed/refractory hematological malignancies. We have been conducting allogeneic stem cell transplantation (alloSCT) using a variety of stem cell source including cord blood (CB), bone marrow (BM) and mobilized peripheral blood (PB), and mainly focus on the preferential use of cord blood, since we are one of the pioneers of cord blood transplantation in adults. The clinical outcome of adult CBT in our institution is comparable to the best one in both Japan and western countries (5-year event-free survival is around 60% for acute leukemias). Our publications on adult CBT have had many citations so far. The annual number of alloSCT between 2016 and 2018 is shown in the following table.

FY	The number of alloSCT			Total
	BM (unrelated)	PB	CB	
2016	3 (0)	0	18	21
2017	2 (0)	1	17	20
2018	2 (1)	1	18	21

In addition, we are conducting a physician-initiated clinical trial of cord-derived mesenchymal stromal cell (C-MSC) therapy for therapy-resistant severe acute graft versus host disease (aGVHD) and a commercially-sponsored phase I/II clinical trial of CD19-targeted CAR-T cell therapy for relapsed/refractory B cell acute lymphoblastic leukemia (B-ALL).

Based on our clinical database of alloSCT, we have extensively studied factors affecting on the clinical outcomes and complications in CBT and published many original articles in peer-reviewed international journals; 7 papers in FY2016, 10 in FY2017, and 12 in FY2018.

２）Education Activities

Education and instruction to residents and clinical research fellows is achieved as On-the-Job-Training (OJT). We supervised 4 senior residents in 2016, 3 in 2017, and 2 in 2018 according to the clinical hematology program. All these residents were qualified to be board certified hematologists of Japanese Society Hematology (JSH).

３）Social Activities

We have been in charge of coordination in the Japan Marrow Donor Program (JMDP) and involved in confirming the eligibility and final consent of unrelated volunteer donors for BM collection. IMSUT Hospital is a BM collection facility authorized by JMDP, and then we conducted BM harvest from 4 unrelated volunteer donors in FY2016, 2 in FY2017 and 3 in FY2018.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

Although alloSCT is progressing steadily, there still remain to be solved many problems including availability and safety of donors, engraftment failure of donor cells, regimen-related toxicities, relapse, GVHD, opportunistic infections and late complications. Among those, the most important issue is prevention of relapse after alloSCT. To challenge this issue, several modalities are being applied into clinic. These include liquid biopsy of minimal residual disease, novel antibody drugs and CAR-T cells and so on. In recent years, HLA-haploidentical related donors are becoming popular as alternative donors, and GVHD treatment with MSC, fecal microbiota transplantation (FMT) as well as novel agents are being developed. In these situations, we will take a problem-oriented approach to improve clinical outcome and safety of alloSCT.

Division of Stem Cell Processing/Stem Cell Bank

（１）Members （as of March 31, 2020）

Professor	Hideki Taniguchi
Postdocs	2
Technicians	2

（２）Research objectives

Division of Stem Cell Processing / Stem Cell Bank has been working on its activities, aiming at the followings. 1) To improve efficacy and safety in innovative treatment modalities that include stem cell gene therapy and allogeneic hematopoietic transplantation based on basic / pre-clinical studies; 2) To develop new treatment strategies including drug discovery for intractable disorders in a broad collaboration through disease studies utilizing induced pluripotent stem (iPS) cell-based technologies.

（３）Activity Reports

１）Research Activities

Through 2016 April ~ 2019 March, we had four publications describing the researches that were conducted for the improvement of hematopoietic stem cell-based medicine (J Exp Med. 2016;213:1865, Stem Cells. 2017;35:989, ACS Synth Biol. 2018;7:1709, Stem Cell Rev. 2018;14:101-9). In addition, we had three papers published regarding disease-modeling studies utilizing iPS cells, (Hum Gene Ther Methods. 2016;27:197, Stem Cell Reports. 2017;8:1155, Stem Cell Reports. 2018;11:380). Besides the above publications, the results obtained through iPS cell-based research have been reported at either domestic (21) or international (5) academic meetings. As Stem Cell Bank, we established 23 lines of disease-related iPS cells with their quality as research materials assured by a series of defined analytical assessment. To contribute to wide applications of disease-specific iPS cells to research fields, we deposited 16 lines of those iPS cells to RIKEN Bio-Resource Center.

２）Education Activities

Five Ph.D. students worked on each research theme that used human iPS cells, whereas one young M.D. investigator conducted hematopoietic stem cell research. Each of them succeeded in earning a doctoral degree at the end.

３）Social Activities

One of the tasks assigned to Stem Cell Bank is to promote dissemination and enlightenment of iPS cell-related technologies. To support the on-site management of iPS cell-research at each

laboratory, we had a substantial number of young investigators visiting or staying for days to months at our place to learn the technologies. Such training was given to investigators from many locations, such as other campuses (Hongo and Komaba) of the University of Tokyo, Tokyo Medical and Dental University, Tsukuba University, Hamamatsu University School of Medicine, and Showa University. Also, we have established our unique instruction manual, in which researchers can find the information necessary to handle human iPS cells appropriately for their research purposes. These user manuals have already been distributed to a certain number of investigators.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

Although the generation of iPS cells has become a common practice in many laboratories, the method we developed has proved highly valuable to the field with its extremely high iPS cell establishment efficiencies (Stem Cell Res Ther. 2019; 10:185). Until recently, our special technical skills related to iPS cell research have mainly been utilized for investigations targeting hematopoietic / immune disorders. It is now highly desirable to extend the iPS cell-related study focuses on other research fields, including those treating cancers, endodermal organs, or the others. Also, fruitful collaboration with other IMSUT-specialties, e.g., genomic medicine, infectious disease research, and proteomics, is expected to make this unique iPS cell study platform more invaluable for a wide variety of applications in medical science.

Division of Stem Cell Signaling

（１）Members (common with those with Division of Cellular Therapy)

Professor	Toshio Kitamura
Postdocs	5
Graduate students	9
Technicians	2
Others	2

（２）Research objectives

Purpose: To establish and characterize a knock-in mouse expressing a G0 marker mVenus-p27K- which we previously developed (Oki et al. Sci Rep, 2014).

Achievement: We established and characterized a knock-in mouse harboring mVenus-p27K- with the lox-P cassette. We orally reported this in several academic meetings and published a paper (Fukushima et al. Cell Rep, 2019).

（３）Activity Reports

１）Research Activities

Purpose: Characterization of knock-in mouse of G0 marker and its application in research for leukemic stem cells (LSCs).

Achievements: We established a knock-in mouse harboring mVenus-p27K- with the lox-P cassette, and crossed this mouse with Vav-Cre mouse to generate mice where mVenus-p27K- is expressed in hematopoietic cells. Analyses of this mouse revealed that about 90% of long-term hematopoietic stem cells (LT-HSCs) are in G0 phase as reported. After commitment to more mature progenitors, cells in the G0 phase decrease in frequencies. Interestingly, most MEP (megakaryo-erythroid progenitors) are cycling, leaving only 10% MEP in the G0 phase. In the peripheral blood, all cells are terminally differentiated and G0 marker-positive. In addition, we also found that calcium concentrations are high in G0 marker-positive HSCs, and that calcium ionophore could keep HSCs in G0 phase (Fukushima et al. Cell Rep, 2019).

We utilized the G0 marker mouse in investigation of CML-LSCs, and found that G0 marker-positive and CD27-positive fraction contains most LSCs in BCR-ABL-positive LSK cells (manuscript in preparation).

２）Education Activities (common with those with Division of Cellular Therapy)

Purpose: To recommend graduate students or postdoctoral fellow to go abroad for their research after getting doctoral grades or publishing papers. To help graduate students to get jobs as

researchers in pharmaceutical companies.

Achievements: During 2016 through 2020, 9 graduate students obtained doctoral grades, and among them five got position as postdoctoral fellow, 2 in Canada from this year and 3 in USA from next April. One master student obtained a job as a researcher in a pharmaceutical company.

３）Social Activities (common with those with Division of Cellular Therapy)

The lab annually offer 6~8 open seminars including one concerning epigenetics open to general public.

４）International Activities (common with those with Division of Cellular Therapy)

The lab has close connections with several foreign laboratories, several in USA and three in Europe to do collaboration, exchange ideas and people. With Abdel-Wahab lab at Memorial Sloan Kettering Cancer Center, we have many collaborations and published two papers (Inoue et al. Leukemia, 2015; Nagase et al. J Exp Med, 2018) and another collaborative paper (Fujino et al.) is now under revision. We also have close collaboration with Dr. Machiejewski at Cleaveland Clinic, and has published a paper (Takeda et al. Blood, in press). In addition, we published a collaborative paper with Dr. Gottgens lab in UK (Fukushima et al. Cell Rep, 2019).

The lab has also close relationship with Dr. Melnick lab at Weil-Cornell Medicine, Dr. Helin lab and Dr. Levine both at Memorial Sloan Kettering Cancer Center, Dr. Skoda lab at University of Basel, Dr. Schroeder lab at EZH Zurich, Dr. Scadden lab at Harvard and Dr. Goodell lab at Bailer Medical College. We sent postdocs to Dr. Scadden lab, Dr. Abdel-Wahab lab, Dr. Melnick lab, Dr. Helin lab (in Copenhagen at that time), and are going to send postdocs to Dr. Goodell lab, Abdel-Wahab lab, and Scadden Lab. We also sent a graduate student to Schroeder lab for a couple of months for formal collaboration.

５）Other matters to be noted (common with those with Division of Cellular Therapy)

We filed a patent application for the ASXL1-MT-KI mouse.

The lab hosted US-Japan Hematology Meeting in Hawaii in March, 2017, 9th JSH International Symposium at Kyoto in July, 2018, and 24th meeting for hematopoietic malignancies at Kobe in January, 2019. The rock band “Negative Selection”, composed of Hematology and Immunology professors including Professor Toshio Kitamura as a drummer, gave gigs at the gathering parties for the latter two. In particular, in 9th JSH International Symposium, we played several hit songs of Eagles, Pink Floyd, and Deep Purple together with Dr. Radek Skoda from Switzerland and Dr. Margaret Goodell from USA.

（４）Challenges and Future prospects (common with those with Division of Cellular Therapy)

We plan to utilize results of mouse models to develop new strategies and drugs to cure patients with hematological malignancies in concert with pharmaceutical companies. In most cases, mouse models rather accurately mimic the human disease. However, it is not clear how far we can extrapolate mouse models to human diseases. Therefore, it is critical to simultaneously use human samples in the experiments. Therefore, we are now seeking many hospitals who can supply samples from patients with hematological malignancies.

Division of Stem Cell Dynamics (-2019.3)

（１）Members

Professor	Beate Heissig
Postdocs	1
Others	1

（２）Research objectives

The aim of the laboratory is to get a comprehensive understanding of the regulatory mechanisms of how proteases and angiogenic factors control cell behavior in normal and pathological conditions, namely 1) inflammation, 2) cancer growth, 3) and stem cell fate. Proteases perform highly selective and limited cleavage of specific substrates including growth factors and their receptors, cell adhesion molecules, cytokines, apoptotic ligand, and angiogenic factors. Understanding the target molecules of proteases provides critical insights into basic biological cellular functions including proliferation, differentiation, and migration. Ultimately, it is our mission to identify novel therapeutic targets for diseases like cancer or inflammatory diseases and to find novel ways to expand hematopoietic and mesenchymal stem cells. During the period 2016-2019, we focused on understanding the function of two serine proteases, namely plasmin and tissue-type plasminogen activator in the field of inflammatory diseases and stem cell biology.

（３）Activity Reports

１）Research Activities

The aim of the laboratory is to get a comprehensive understanding of the regulatory mechanisms of how proteases and angiogenic factors control cell behavior in normal and pathological conditions, namely 1) inflammation, 2) cancer growth, 3) and stem cell fate. Proteases perform highly selective and limited cleavage of specific substrates including growth factors and their receptors, cell adhesion molecules, cytokines, apoptotic ligand, and angiogenic factors. Understanding the target molecules of proteases provides critical insights into basic biological cellular functions including proliferation, differentiation, and migration. Ultimately, it is our mission to identify novel therapeutic targets for diseases like cancer or inflammatory diseases and to find novel ways to expand hematopoietic and mesenchymal stem cells. During the period 2016-2019, we focused on understanding the function of two serine proteases, namely plasmin and tissue-type plasminogen activator in the field of inflammatory diseases and stem cell biology. The research group consisted of the PI, a post-doc and graduate students.

Our research led to a total of 6 original manuscripts, including 2 with IF over 16, and 1 review article (Adv Drug Deliver Review IF 16). My group showed that plasmin and tissue-type

plasminogen activator contribute to inflammation (Blood IF 16.4, FASEB J IF 6), enhance mesenchymal stem cell expansion (Blood IF 16.4), and control tumor growth (FASEB J IF 6, BBRC IF 3), and post-surgical adhesion (FASEB J IF 6). We identified plasmin and tPA as novel drugable pro-inflammatory molecules.

We also researched how the endothelial-derived growth factor Egfl7 controls stem cell fate. We identified a novel regulatory mechanism on how the angiogenic factor Egfl7 controls stem cell expansion that led to the initiation of a patent application through the University of Tokyo (international patent pending) and published that Egfl7 enhances T cell development (BBRC IF 3).

Research results obtained concerning the role of the angiogenic factor Egfl7 have not been published yet, and research progress is delayed. The interest of companies on the patent required experiments, which due to a lack of staff could not been done. More researchers (and not only a post-doc and myself) involved in the Egfl7-associated research projects and staff would have accelerated the research promotion. I am trying to improve the funding situation of the laboratory.

２）Education Activities

Over the period, 9 graduate students were instructed: 3 master students (Department of Medical Genome, CBMS) and 3 Ph.D. students from the Medical Genome/CBMS, and 1 Ph.D. student and 1 master student from the Graduate School of Medicine of the Tokyo University. 6 out of the 9 students were international students. In addition, I mentored a Ph.D. student from Juntendo University.

I was in charge of one class on the subject of stem cell biology for the Department of Medical Genome (CBMS).

３）Social Activities

I have given two lectures on the role of female scientists and foreign scientists at the Delegation of the European Union to Japan.

Research results on the cancer study were made public to the society with more than 8 different articles in newspapers in more than 4 countries, 2 different continents (Europe, Asia).

I have given a lecture at the Norwegian Embassy to enhance Norwegian-Japanese research efforts on the expansion of mesenchymal stem cell studies both in preclinical and clinical studies.

４）International Activities

In collaboration with Dr. Schmidt at the University of Mainz (Germany), we clarified the function of Egfl7 in hematopoietic stem cell biology.

In collaboration with the American-based company NapaJen, the laboratory concluded a preclinical study testing novel anti-GvHD drugs in murine acute Graft-versus-Host Disease models.

In collaboration with Dr. Raeder at the University of Bergen, we study the role of protease in pancreatic cell development.

I have organized various meetings with researchers from the University of Bergen (Norway) at the Institute of Medical Science, The University of Tokyo. Ultimately, these efforts led to the signing of a Memorandum of Understanding (MoU) of the University Bergen with the Institute of Medical Science, the University of Tokyo.

In collaboration with researchers from the AnNaJah University in Palestine, we examine the role of protease in stem cell biology.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

This Division has completed and closed as of March 31, 2019.

Division of Stem Cell Cellomics (-2019.5)

（１）Members

Project Associate Professor	Hiroshi Watarai
Others	3

（２）Research objectives

Centering around the field of immunology and stem cell biology, this division focused on elucidation of functions and modes of differentiation and development of iNKT cell as the research themes. In order to tackle new challenges, we participated in the ImPACT program “Creating new Scientific values through planed serendipity”. We also worked on the development of engineering and optical elemental technologies, aiming to introduce it as early as possible.

（３）Activity reports

１）Research activities

We newly achieved and reported creation of iNKT cell-deficient mice by establishing techniques for single-cell analysis and introducing the CRISPR method, as well as elucidation of the association of iNKT cells with obesity-induced inflammation and identification of neutrophil markers and iNKT cell markers.

２）Education Activities

To advance research activities, we accepted students mainly from the collaborative laboratories and gave them instruction. Eight students in the master’s course (including undergraduate students in 6th-year) graduated and took jobs with pharmaceutical and food companies.

３）Social Activities

Every year the member of our laboratory participated in the outreach activity “Men-eki Fushigi Mirai”, hosted by Japanese Society for Immunology as the chairperson, committee members, and supporters (students) of the project and had opportunities to pass on the interesting aspects and importance of immunity to the public.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and future prospects

This division concluded its term in May, 2019. As the term was limited, we could not recruit new students since we could not take responsibility for completing research instruction. And thus, some of the plans that should have been completed were delayed.

Division of Experimental Pathology

（１）Members

Professor	Yasuhiro Yamada
Assistant Professor	Sho Ohta
Postdocs	2
Graduate students	9
Technicians	3
Others	1

（２）Research objectives

Stem cells play an important role in homeostasis of organ function in multicellular organisms. They are responsible for tissue regeneration and their functional impairment causes various diseases in mammals. However, considering the complexity of multicellular organisms, it remains unclear how tissue microenvironment affects stem cell functions. We aim to elucidate the molecular basis for stem cell behavior in response to altered tissue microenvironments. The effort should eventually unveil the fundamental basis of how stem cells affect organismal functions in vivo and uncover the underlying mechanisms of tissue regeneration, various diseases and organismal aging. These findings may contribute to developing a feasible strategy to control the detrimental effects of stem cell dysfunction in diseases and aging.

（３）Activity Reports

１）Research Activities

Since its inception on April 2019, Division of Experimental Pathology has investigated the stem cell function in various biological aspects in multicellular organisms, including mammalian development and diseases. The following are major research achievements:

a) Pluripotent stem cell features drive pediatric cancer development

Atypical teratoid/rhabdoid tumor (AT/RT), which harbors SMARCB1 mutation and exhibits a characteristic histology of rhabdoid cells, has a poor prognosis. We established human SMARCB1-deficient pluripotent stem cells (hPSCs). SMARCB1-deficient hPSCs, but not neuronal progenitor cells, efficiently gave rise to AT/RT-like brain tumors in the mouse brain. We found that activation of an embryonic stem cell (ESC)-like signature confers a rhabdoid histology and causes a poor prognosis. SMARCB1-deficient hPSCs offer the human models for AT/RT, which uncover a therapeutic target of AT/RT. ***Cell Reports***. 26, 2608–2621, 2019.

b) Unveiling epigenetic instability in pluripotent stem cells

Pluripotent stem cells (PSCs), including ESCs and iPSCs hold promise as cell sources for regenerative medicine. However, the epigenetic stability of PSCs has not been fully understood. We conducted a comprehensive analysis of DNA methylation during somatic cell reprogramming. We found that several imprinted genes are often *de novo* methylated in reprogrammed PSCs. Mechanistically, ablation of *Dnmt3a* prevented PSCs from *de novo* DNA methylation. Notably, similar DNA hypermethylation pattern was observed in pediatric cancers. These results may have important implications in the pathogenesis of pediatric cancers and the application of PSCs. ***Stem Cell Reports***. 12(5):1113-1128, 2019.

２）Education Activities

Since April 2019, we accepted master course and PhD course students in Graduate School of Medicine and Graduate School of Frontier Sciences.

３）Social Activities

Prof. Yamada is a member of Science Council of Japan, a councilor of Japanese Cancer Association, The Japanese Society of Pathology, and The Japanese Society for Epigenetics.

４）International Activities

A joint project with Prof. Miguel Esteban at Chinese Academy of Sciences (CAS) is currently ongoing as a JSPS-CAS joint program (Project title: Molecular roadmap of in vivo reprogramming at the single-cell level). Our group is also collaborating with investigators at Harvard University, UCLA, and Max Plank Institute. Prof. Yamada is a member of publication committee of International Society for Stem Cell Research (ISSCR). Prof. Yamada co-organized Stem Cell Crossroads, a Cold Spring Harbor Asia (CSHA) meeting in 2018.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

We will investigate the stem cell function at the organismal level and reveal the role of stem cell dysfunction in the pathogenesis of age-related diseases. The ultimate goal of our research projects is to develop a novel therapeutic approach targeting the stem cell function to treat patients. Particularly, we will aim to rejuvenate the function of tissue stem cells to facilitate tissue regeneration.

Division of Stem Cell Biology

（1）Members

Project Associate Professor	Satoshi Yamazaki
Postdocs	2
Graduate students	3
Technicians	5
Others	1

（2）Research objectives

Our studies focus mainly on investigation of stem cell biology using the hematopoietic stem cell (HSC) as a research model. Recent identification of a variety of stem cell sources including embryonic and somatic (tissue-specific) stem cells has brought about substantial progress in the field of stem cell research.

（3）Activity Reports

1）Research Activities

Our studies focus mainly on investigation of stem cell biology using the hematopoietic stem cell (HSC) as a research model. Recent identification of a variety of stem cell sources including embryonic and somatic (tissue-specific) stem cells has brought about substantial progress in the field of stem cell research. The HSC represents the first stem cell for which identity and existence were determined. Studies on HSCs have provided us with some basic concepts applying to different types of stem cells, yet many of these concepts remain unverified. It therefore is very important to continue basic studies to answer many questions left unsolved and thus to permit contributions to the field of biological research and clinical medicine. HSCs are capable of continuous supply of all lineages of blood cells to each individual for his or her entire life. Both self-renewal and multilineage differentiation potentials enable this task. One major advantage in HSC research lies in that established assay systems allow clonal analysis of each individual stem cell. Using a defined assay system, we can test capabilities of self-renewal and multilineage differentiation at single cell levels using either in vitro or in vivo assays. We believe that HSC research will eventually make great contributions to the development of safe and efficacious regenerative medicine and gene therapy.

2）Education Activities

None.

3）Social Activities

None.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

In the future, through basic research on stem cells, we will lead to clinical research to treat diseases using stem cells.

International Research Center for Infectious Diseases

Director Yoshihiro Kawaoka

（１）Background (Missions and Features)

The COVID-19 pandemic continues to kill many people and affect economics and our daily lives, reminding us of what infectious diseases can do. To control infectious diseases, we need to understand pathogens and develop diagnostic tools and countermeasures such as drugs and vaccines. To this end, the International Research Center for Infectious Diseases was established in 2005 at the Institute of Medical Science, the University of Tokyo. Because the current governmental financial support for this center has been reduced by 75% compared to that in 2005, we now have only two research departments and the “Pathogenic Microbe Repository Unit”.

（２）Organization

Department of Special Pathogens

PI, Yoshihiro Kawaoka, DVM, PhD [concurrent appointment] [2005-to date]

PI, Chieko Kai, DVM, PhD [concurrent appointment] [2005-2018]

Department of Infectious Disease Control

PI, Yasushi Kawaguchi, DVM, PhD [concurrent appointment] [2005-to date]

Division of Viral Infection (PI, Takeshi Ichinohe, PhD [2012-to date])

Division of Bacteriology (PI, Hitomi Mimuro, PhD [2011-2018])

Division of Systems Virology (PI, Kei Sato, PhD [2018-to date])

Pathogenic Microbes Repository Unit

（３）Activity Reports

１）Research Activities

Researchers in our centers study herpes viruses, influenza viruses, Ebola viruses, HIV, Nipah virus, and *Helicobacter Pylori* and have made major contributions to the field and reported their finding in high profile journals, specifically: 1 in Nature (IF 43.070); 1 in Cell (IF 36.216); 1 in Nature Biotechnology (IF 31.864); 1 in Nature Immunology (IF 23.530); 1 in Cell & Host Microbe (IF 15.753); 5 in Nature Microbiology (IF 14.300); 6 in Nature Communications (IF 12.353); 4 in the Journal of Clinical Investigation (IF 12.282); and 1 in Nature Protocols (IF 11.334).

２）Education Activities

The number of students who received degrees is: 7 doctors and 4 masters in FY2016; 3 doctors and 5 masters in FY2017; 7 doctors and 3 masters in FY2018; and 6 doctors and 5 masters in

FY2019.

To help our students to be international researchers, we encourage them to give presentations at international conferences. The number of the students who presented at international conferences is: 6 in FY2016, 7 in FY 2017, 6 in FY 2018, and 5 in FY2019.

Graduate students and postdoctoral fellows received the following awards:

Feb 2017 The 45th Annual Meeting of the Japanese Society for Immunology, Best presentation award winner (Postdoc H.U.)

Mar 2017 IMSUT Outstanding student publication award FY 2016 (D3 S.N.)

Jun 2017 UT Graduate Program for Leaders and Life Innovation, General Meeting 2017, Best Poster Award (D2 M.S.)

Sep 2017 The Japanese Society of Veterinary Science, the 8th Vet. Microbiology Best presentation award winner (D3 M.W., D3 T.N, D2 K.T.)

Mar 2018 The 28th Molecular Immunology Forum Tokyo Research Incentive Award (D3 M.M.)

Mar 2018 IMSUT Outstanding Student Publication Award (D3 M.M.)

Apr 2018 Japanese Society for Immunology, Tadamitsu Kishimoto International travel award winner (Postdoc H.U.)

Sep 2018 The 27th Annual Meeting of the Bioimaging Society of Japan BIOIMAGING, Best imaging Carl Zeiss award winner (Postdoc H.U.)

Mar 2019 The 47th Annual Meeting of the Japanese Society for Immunology, Best presentation award winner (Postdoc H.U.)

Mar 2019 Most outstanding student publication award FY 2018 (D3 A.Y.)

Apr 2019 Best presentation award, General Meeting of Japanese Society of Bacteriology (D2 R.T.)

Mar 2020 Outstanding student publication award FY 2019 (D4 K.T.)

３）Social Activities

Every summer, we hold a public seminar "LOVE LABO" for high school and university students. In addition, we conduct the "LOVE LABO Laboratory Tour", which includes a laboratory tour and special lectures for high school students, and a one-day laboratory experience course for university students. Some of the students who participated in these activities later joined one of our labs as graduate students.

４）International Activities

We are conducting international joint research with 24 institutions in 7 countries. We have published the following international co-authored papers: FY2016, 11 papers; FY2017, 15 papers; FY2018, 20 papers; and FY2019: 20 papers.

In addition, we held the following international symposia:

06-09 Sep 2016: 15th Awaji International Forum on Infection and Immunity

05-08 Sep 2017: 16th Awaji International Forum on Infection and Immunity

04-07 Sep 2018: 17th Awaji International Forum on Infection and Immunity

19-20 Feb 2019: Influenza and Other Infections

10-13 Sep 2019: 18th Awaji International Forum on Infection and Immunity

５）Other matters to be noted

In the Pathogenic Microbes Repository Unit, we distributed pathogenic bacterial strains to universities, national public research institutes, nationwide sanitary laboratories, hospital laboratories, food laboratories, and corporate laboratories. We distributed 25 strains in FY2016, 14 strains in FY2017, 15 strains in FY2018, and 11 strains in FY2019. Thus, we contributed to infectious disease and medical microbiology education and research in Japan.

In addition, we held the following symposia:

17 Feb 2017: FY2016 Rising Stars in Cutting Edge Immunology Research

14 Mar 2018: Symposium on 4 Universities Infectious Diseases Collaborative Research Education Union

31 Jan 2019: FY2018 Rising Stars in Cutting Edge Immunology Research

27 Jan 2020: FY2019 Rising Stars in Cutting Edge Immunology Research

（４）Challenges and Future prospects

At the end of March 2019, Professor Kai (concurrent appointment) retired and Associate Professor Mimuro (concurrent post) moved due to Osaka University. Due to continued government budget cuts, we are unable to increase the number of faculty members in our center. The limited number of scientists in our center impedes our ability to respond to emerging pathogens such as SARS-CoV-2. We hope that the Japanese government will increase our budget in the future.

Division of Viral Infection

（１）Members

Associate Professor	Takeshi Ichinohe
Graduate students	1

（２）Research objectives

We focus on understanding how influenza virus is recognized by innate immune systems and how the innate recognition receptor controls the virus-specific adaptive immune responses. Our recent focus also includes the study of how microbiota regulates adaptive immune responses to influenza virus infection. Our ultimate goal is to utilize the knowledge we gain through these areas of research in the rational design of effective intranasal vaccines.

（３）Activity Reports

１）Research Activities

1. Recognition of influenza virus by cytosolic DNA sensors

Cytosolic mitochondrial DNA (mtDNA) activates cGAS-mediated antiviral immune responses, but the mechanism by which RNA viruses stimulate mtDNA release remains unknown. Here we show that viroporin activity of influenza virus M2 or encephalomyocarditis virus (EMCV) 2B protein triggers translocation of mtDNA into the cytosol in a MAVS-dependent manner. Although influenza virus-induced cytosolic mtDNA stimulates cGAS- and DDX41-dependent innate immune responses, the nonstructural protein 1 (NS1) of influenza virus associates with mtDNA to evade the STING-dependent antiviral immunity. The STING-dependent antiviral signaling is amplified in neighboring cells through gap junctions. In addition, we find that STING-dependent recognition of influenza virus is essential for limiting virus replication in vivo. Our results show a mechanism by which influenza virus stimulates mtDNA release and highlight the importance of DNA sensing pathway in limiting influenza virus replication (Moriyama et al. Nat Commun. 2019).

2. Effects of ambient temperature in the induction of antiviral immunity

Although half of the world's population could face severe food crisis as a result of global warming by the end of this century, the effects of environmental temperature and host nutritional status in host defense to viral infection in vivo are less clear. Here, we demonstrated that exposure of mice to the high ambient temperature of 36 °C reduced their food intake and impaired adaptive immune responses to influenza virus infection. In addition, we found that administration of glucose or dietary short-chain fatty acids restored influenza virus-specific adaptive immune responses in high heat-exposed mice. Our results imply possible public health problems and concerns that outside

temperature and host nutritional status may be critical determinants of viral pathogenesis or vaccine efficacy (Moriyama et al. Proc Natl Acad Sci U S A. 2019).

3. Pathogenesis of SARS-CoV

Nod-like receptor family, pyrin domain-containing 3 (NLRP3) regulates the secretion of proinflammatory cytokines interleukin 1 beta (IL-1β) and IL-18. We previously showed that influenza virus M2 or encephalomyocarditis virus (EMCV) 2B proteins stimulate IL-1β secretion following activation of the NLRP3 inflammasome. However, the mechanism by which severe acute respiratory syndrome coronavirus (SARS-CoV) activates the NLRP3 inflammasome remains unknown. Here, we provide direct evidence that SARS-CoV 3a protein activates the NLRP3 inflammasome in lipopolysaccharide-primed macrophages. SARS-CoV 3a was sufficient to cause the NLRP3 inflammasome activation. The ion channel activity of the 3a protein was essential for 3a-mediated IL-1β secretion. While cells uninfected or infected with a lentivirus expressing a 3a protein defective in ion channel activity expressed NLRP3 uniformly throughout the cytoplasm, NLRP3 was redistributed to the perinuclear space in cells infected with a lentivirus expressing the 3a protein. K+ efflux and mitochondrial reactive oxygen species were important for SARS-CoV 3a-induced NLRP3 inflammasome activation. These results highlight the importance of viroporins, transmembrane pore-forming viral proteins, in virus-induced NLRP3 inflammasome activation (Chen et al. Front Microbiol. 2019).

4. SFTS viral strategy that inhibits host antiviral immunity

Recognition of viruses by host innate immune systems plays a critical role not only in providing resistance to viral infection but also in the initiation of antigen-specific adaptive immune responses against viruses. Severe fever with thrombocytopenia syndrome (SFTS) is a newly emerging infectious disease caused by the SFTS phlebovirus (SFTSV), a highly pathogenic tick-borne phlebovirus. The 294-amino-acid nonstructural protein (NSs) of SFTSV associates with TANK-binding kinase 1 (TBK1), a key regulator of host innate antiviral immunity, to inhibit interferon beta (IFN-β) production and enhance viral replication. Here, we demonstrate that two conserved amino acids at positions 21 and 23 in the NSs of SFTSV and heartland virus, another tick-borne phlebovirus, are essential for association with TBK1 and suppression of IFN-β production. Our results provide important insight into the molecular mechanisms by which SFTSV NSs helps to counteract host antiviral strategies (Moriyama et al. J Virol. 2018).

２）Education Activities

A Ph.D. student published six papers as a first author in high impact factor journals including Nature Communications, PNAS, and Journal of Virology. After graduation, she got a postdoctoral

fellowships from Japanese government to extend her research in Fukuoka University. Recently, she started a new research project as a postdoctoral fellow in Yale School of Medicine (Prof. Akiko Iwasaki's laboratory).

３）Social Activities

I attended several outreach activities for high school and undergraduate students to introduce our recent findings. In addition, I hold a short-term training program for undergraduate students to teach them laboratory works.

４）International Activities

I continue international joint research with 3 institutes including Yale University, National Taiwan University, and Korea Advanced Institute of Science and Technology.

５）Other matters to be noted

2011 The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology, Japan: the Young Scientists' Prize (T.I.)
2014 Sugiura Incentive Award of the Japanese Society for Virology (T.I.)
2015 Research Incentive Award of the Kao Foundation for Arts and Sciences (T.I.)
2017 Takahashi Incentive Award of the Japanese Society for Vaccinology (T.I.)
2020 Research Incentive Award of the Intestinal Microbiology Society (T.I.)

（４）Challenges and Future prospects

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the infectious disease COVID-19. Despite the tremendous efforts to control the disease, COVID-19 has now spread to over 100 countries and caused a global pandemic. Therefore, there is an urgent and important public health need to develop effective vaccines against SARS-CoV-2. Thus, we will develop an intranasal vaccine that induce protective mucosal immune response at upper respiratory tract and protect against SARS-CoV-2 infection.

Division of Bacteriology (-2019.3)

（１）Members

Associate Professor	Hitomi Mimuro
Graduate students	1

（２）Research objectives

We are investigating the pathogenicity of gastrointestinal infection pathogenic bacteria. We will elucidate the dynamics of *Helicobacter pylori* (*H. pylori*) in the intestinal tract by 2018. By 2020, we aim to clarify the mechanisms of persistent infection of *H. pylori* based on bacterial genome sequence variation.

（３）Activity Reports

１）Research Activities

We have been conducting researches to elucidate the infection mechanisms of pathogenic gastrointestinal infectious pathogenic bacteria such as *H. pylori*, which is a causative agent of gastric diseases such as gastric cancer. Our goals from April 2016 to March 2019 were to elucidate the mechanisms of *H. pylori* infection in the intestinal tract and to elucidate genomic mutations in *H. pylori* that persistently infect the stomach.

When *H. pylori* invade the body along with foods and drinks during childhood, they adhere to gastric epithelial cells, establish long-term infection, and after decades, develop gastritis and gastric cancer. We have previously reported that the uptake of bacterial antigens at the immune system Peyer's patches in the intestinal tract is essential for the induction of *H. pylori*-induced gastritis. However, unlike the microaerobic environment in the stomach, bacterial dynamics in the anaerobic intestinal tract is unknown. In addition, it is considered that in the process of persistent infection, *H. pylori* enables to change the protein expression pattern by introducing mutations into its genome sequence under the environment, thereby enabling persistent infection. Graduate students in our laboratory successfully found that *H. pylori* change its morphology in an anaerobic environment such as the intestinal tract, and its growth decreases, but when it is returned to the optimum environment, the morphology and growth ability are restored. She reported this finding in a paper (Hirukawa et al., Microbial Immunol, 2018), and she received a degree. Besides, we constructed a rodent infection model of *H. pylori*, isolated colonized bacteria that established persistent infection from the stomachs and performed whole-genome analysis using a next-generation sequencer. As a result, we have found several specific mutations that changed the expression of multiple novel pathogenic genes that were acquired during host adaptation [Kinoshita-Daitoku et al., Biochem Biophys Res Commun (2020), Microbiol Resour Announc (2020)]. Among these novel genes, we

analyzed the effects of small RNA, which have particularly significant changes in the pathogenicity of bacteria (Kinoshita-Daitoku et al., bioRxiv, 2020). Based on these achievements, graduate students obtained his degree.

From these, it is considered that the results in our laboratory have been sufficiently achieved from the viewpoint of research execution. We will carry out additional experiments necessary for the revision in the future, and publish a paper as soon as possible.

２）Education Activities

The goal from April 2016 to March 2019 is to obtain a doctoral degree for four graduate students and one master's degree.

In fact, with regard to doctoral programs, a total of four people, two completed in March 2017, one completed in March 2018, and one ended in March 2019, received a degree. Also, one master's degree student received a degree in March 2018.

As a result, we were able to achieve the results in terms of educational activities and the number of students with a degree. Among the degree-obtained students, the first author's papers were accepted after graduation. Unpublished contents will be published as soon as possible.

３）Social Activities

None.

４）International Activities

None.

５）Other matters to be noted

2019 Best presentation award, General Meeting of Japanese Society of Bacteriology (D2 R.T.)

2018 Uehara *H. pylori* Award, The Japanese Society for Helicobacter Research (H.M.)

（４）Challenges and Future prospects

It is a problem in our laboratory that it takes time to publish a paper on research results. In the future, we aim to realize more prompt research presentations.

This Division has completed and closed as of March 31, 2019.

Division of Systems Virology

（１）Members

Associate Professor	Kei Sato
Postdocs	1
Graduate students	1
Technicians	3

（２）Research objectives

“Systems Virology” is a scientific field to understand “viruses” from multiple aspects in the combination of experimental virology and a variety of sciences such as bioinformatics, molecular evolution, phylogenetic, paleobiology, and mathematics. We consider the virus-host interaction and the events triggered by virus infections as a “mutualism” and “conflict” and aim to address these virological issues through multiple scientific approaches. Followings are our current projects:

1. Evolutionary episode of viruses and hosts
2. Mechanisms of viral cross-species transmission
3. Impact of endogenous viruses
4. Understanding of the viruses living with humans
5. Virus infections at “multi-omics” viewpoint

（３）Activity Reports

１）Research Activities

1. Evolutionary episode of viruses and hosts

2. Mechanisms of viral cross-species transmission

We revealed that mammalian APOBEC3 proteins can be species barriers to restrict lentiviral cross-species transmission, while lentiviral Vif protein antagonize the antiviral actions of host APOBEC3 proteins (Konno et al., ***J Gen. Virol.***, 2018 [IF 2.8] *corresponding author; Konno et al., ***Retrovirology***, 2019 [IF 3.7] *corresponding author). Also, we identified a novel anti-HIV-1 protein, N4BP1, that triggers viral genomic RNA degradation (Yamasoba et al., ***Nat. Microbiol.***, 2019 [IF 14.3]). Moreover, through comprehensive transcriptome analysis, we revealed the difference on interferon responses in a variety of HIV-1-targeting cells (Aso et al., ***Front. Microbiol.***, 2019 [IF 4.1] *corresponding author)

3. Impact of endogenous viruses

APOBEC3 genes are members of the AID/APOBEC gene family that are found exclusively in mammals. *APOBEC3* genes encode antiviral proteins that restrict the replication of retroviruses by

inducing G-to-A mutations in their genomes, and have undergone extensive amplification and diversification during mammalian evolution. Endogenous retroviruses (ERVs) are sequences derived from ancient retroviruses that are widespread mammalian genomes. In this study we characterize the A3 repertoire and use the ERV 'fossil record' to explore the long-term history of co-evolutionary interaction between A3s and retroviruses. We examined the genomes of 160 mammalian species and identify 1,420 AID/APOBEC-related genes, including representatives of previously uncharacterized lineages. We showed that *APOBEC3* genes have been amplified in mammals and that amplification is positively correlated with the extent of germline colonization by ERVs. Moreover, we demonstrate that the signatures of APOBEC3-mediated mutation can be detected in ERVs found throughout mammalian genomes, and show that in mammalian species with expanded APOBEC3 repertoires, ERVs are significantly enriched for G-to-A mutations. Finally, we show that APOBEC3 amplification occurred concurrently with prominent ERV invasions in primates. Our findings establish that conflict with retroviruses is a major driving force for the rapid evolution of mammalian A3 genes (Ito, Gifford and Sato, ***PNAS***, 2020 [IF 9.4] *corresponding author). We also revealed that endogenized human herpesvirus 6 may associate with immune activation (Kumata, Ito and Sato, ***Virus Genes***, 2020 [IF 1.6] *corresponding author).

4. Understanding of the viruses living with humans

Human-resident microbes can influence both health and disease. Investigating the microbiome using next-generation sequencing technology has revealed examples of mutualism and conflict between microbes and humans. Comparing to bacteria, the viral component of the microbiome (i.e. the "virome") is understudied. Somatic tissues of healthy individuals are usually inaccessible for the virome sampling, therefore, 1) which viruses infect which tissues in healthy individuals and 2) how virus infection associates with human gene expression and perturbs immunological homeostasis remains unclear. To characterize the human virome in a tissue-specific manner, here we performed meta-transcriptomic analysis using the RNA-sequencing dataset from the Genotype-Tissue Expression Project. We analyzed the 8,991 RNA-sequencing data obtained from 51 somatic tissues from 547 individuals and successfully detected 39 viral species in at least one tissue. We then investigated associations between virus infection and human gene expression and human disease onset. To our knowledge, this study is the first comprehensive investigation of the human virome in a variety of tissues in healthy individuals through meta-transcriptomic analysis (Kumata et al, ***BMC Biology***, 2020 [IF 6.7] *corresponding author).

5. Virus infections at "multi-omics" viewpoint

For eradication of HIV-1 infection, it is important to elucidate the detailed features and heterogeneity of HIV-1-infected cells *in vivo*. To reveal multiple characteristics of HIV-1-producing cells in vivo, we used a hematopoietic stem cell-transplanted humanized mouse model infected with GFP-encoding replication-competent HIV-1. We performed multiomics experiments using recently

developed technology to identify the features of HIV-1-infected cells. We described multiple characteristics of HIV-1-producing cells in vivo, which could provide clues for the development of an HIV-1 cure (Aso et al, ***Cell Rep.***, in press [IF 7.8] *corresponding author)

２）Education Activities

We have weekly progress meeting (on Thursday) and journal seminar (on Monday). We routinely have web meetings with the colleagues in the other laboratories via webcast.

３）Social Activities

As outreach activities, our laboratory joined "Lab-Labo", held in IMSUT in 2018 and 2019. The PI joined an outreach seminar "NEKKEN summer school" in NEKKEN, Nagasaki University, 2019.

４）International Activities

To proceed multi-disciplinary research projects, our laboratory have a variety of international collaborations with the scientists in University of Glasgow (UK; Drs. Robert Gifford, Sam Wilson, David Robertson, and Massimo Palmarini), Ulm University (Germany; Drs. Daniel Sauter and Frank Kirchhoff), University of Minnesota (USA; Dr. Reuben Harris), and University of Pennsylvania (USA; Dr. Kotaro Sasaki).

５）Other matters to be noted

Apr 2020　The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology, The Young Scientists' Award (Kei Sato)

（４）Challenges and Future prospects

In the last two years since the PI joined the IMSUT in April 2018, our laboratory published seven scientific papers with correspondence, indicating that our scientific activity is high and goes successfully. To expand our scientific activity, recruiting and educating graduate students would be essential. Also, to address more important and complicated issues in the field of virology, more sophisticated approaches and productive international collaborations would be required. Since April 2020, our laboratory has started projects focusing on SARS-CoV-2, the causative agent of COVID-19. This is one of the most important issues in the current world. We plan to elucidate the molecular mechanisms of COVID-19 pathogenesis and cross-species transmission of SARS-CoV-2 from bats to humans.

International Research and Development Center for Mucosal Vaccines

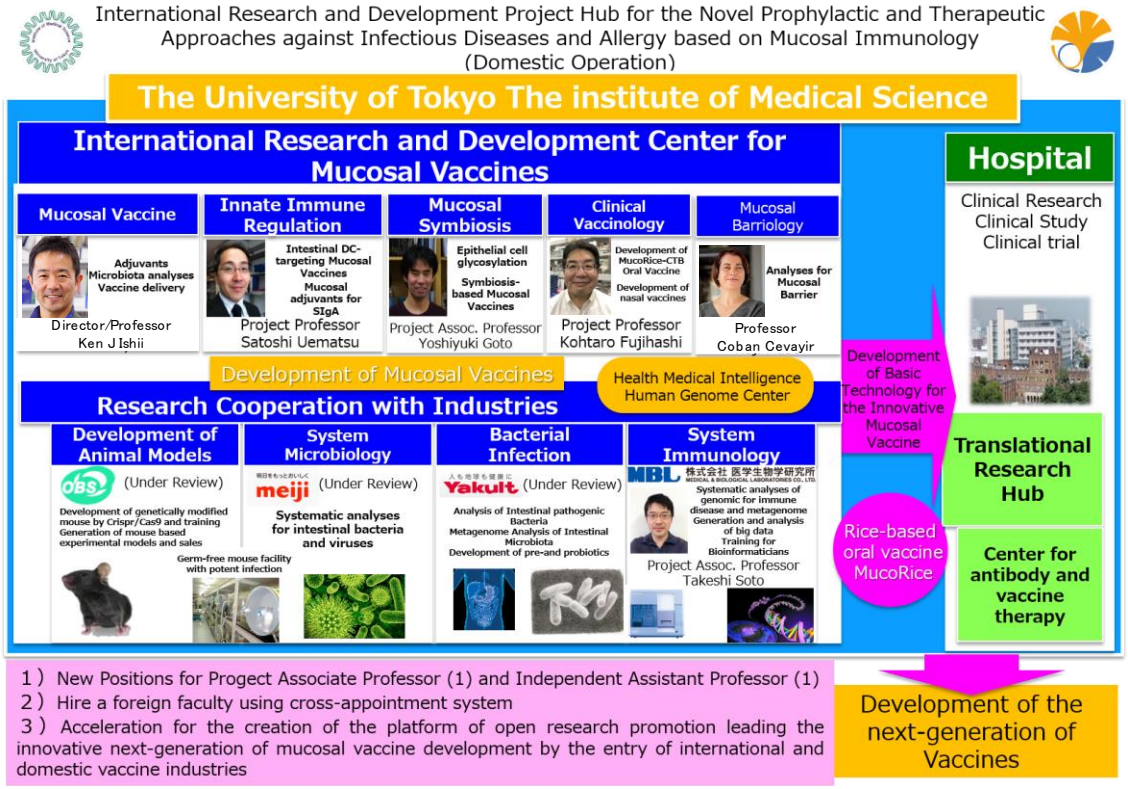
Director Hiroshi Kiyono (-2018)
Director Ken J. Ishii (2019-)

（1）Missions and Features

Humans have evolved together with a wide variety of microorganisms through life phenomenon "Symbiosis and Elimination". The immune system that serves as its foundation for harmonizing with beneficial microorganisms and attempting to eliminate it as harmful pathological microorganisms. The development of antibiotics and vaccines and the advancement of public health care systems have provided means to prevent and contain infectious diseases, thus contributing to the welfare of humanity and social progress in the 20th century. However, we are now facing new challenges including 1) The emergence of an entirely new range of problems including drug resistances, immunocompromised hosts, and hospital-acquired infections; 2) Serious problems in developing countries that repeat a vicious cycle of poverty and the spread of infectious diseases; and 3) The occurrence of emerging/reemerging infectious diseases such as AIDS, tuberculosis, and malaria. In advanced countries, the main serious problems include allergic diseases, such as pollen and food allergies, cancer, and severe infectious diseases including influenza and COVID-19. It is now known that a flexible but precise mucosal immune system exists and serves as an interface between in-and out-side environments. After infection, allergies and cancer often occur in mucosal tissues, such as the respiratory, digestive, and urogenital organs. Both basic investigations to clarify the role of the mucosal immune system from a physiological state to pathogenesis, and the development of fundamental technology to induce and modulate mucosal immunity artificially, are essential for the development of new preventative treatments and therapies.

In these circumstances, it is important to take the initiative in the development of ‘mucosal vaccines’ as a next-generation strategy for the prevention and treatment of illness in our country and the rest of worlds, which has taken the lead in the promotion of immunological research based on our understanding of “ Symbiosis and Elimination”. In 2011, The Institute of Medical Science at The University of Tokyo (IMSUT) initiated the establishment of an International Research and Development Center for Mucosal Vaccine (IMV), to promote cooperation between international researchers in integrating accumulated intellectual discovery and technology including immunology, microbiology, oncology, genome medical science, regenerative medicine and systems biology in a cross-disciplinary manner. The center will develop an innovative academic field, termed ‘Mucosal Vaccinology’, by promoting basic research on mucosal immunology and vaccinology for the development of the new generation of mucosal vaccines to form an international hub to foster next-generation researchers. Molecular and cellular bases of an integrated understanding of “Symbiosis

and Elimination" will lead to the opening of a new era for the development of next-generation of mucosal vaccines.



（2）Organization

Division of Mucosal Barriology

Division of Innate Immune Regulation

Division of Clinical Vaccinology

Division of Mucosal Vaccine

Division of Mucosal Symbiosis

（3）Activity Reports

1）Research Activities

Each division has its own task and goal for their research including publication, presentation at the meeting, and patent application. Please see the reports of individual divisions for the details described in the following pages.

2）Education Activities

Each division has its teaching activity for graduate students. Thus, faculty members of individual

divisions are involved in didactic and research mentorship education.

３）Social Activities

Each division has collaborative projects with companies. Please see the reports of individual divisions for the details described in the following pages.

４）International Activities

- The IMV has a research agreement with the Pasteur Institute in order to develop the joint research unit in each institute. Dr. James DiSanto agreed to serve as the director of the joint research unit at Pasteur Institute. As a part of this joint research project, we have been assessed microbiota of the nasal cavity of allergic patients.
- Dr. Kiyono possessed a position of Professor at The University of California, San Diego.
- Dr. Kiyono as the principal investigator obtained a new research grant from the AMED SATREPS program entitled “Surveillance and Laboratory Support for Emerging Pathogens of Public Health Importance.
- Dr. Ishii promoted international clinical study and got budget by GHIT fund.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

Since Dr. Kiyono (Director) has been retired, Dr. Ken J. Ishii took over the director’s position of IMV in April 2019. Dr. Ishii is currently planning a new organization of the center and preparing a new budget proposal for the renewal at 2021.

Division of Mucosal Barriology

（１）Members

Professors	Hiroshi Kiyono (2016-2018), Kensuke Miyake (2018-2019), Ken J. Ishii (2019), Cevayir Coban (2019-)
Visiting Professor	Koji Hase
Visiting Associate Professor	Shintaro Sato (2016-2019)
Project Associate Professors	Takako Negishi-Koga, Taketoshi Mizutani

（２）Research objectives

Division of Mucosal Barriology is conducting research on understanding homeostasis between the mucosal tissues and the immune barrier system. We will also focus on their pathological changes that occur during microbial infection and/or other immunological disorders, that novel intervention and prevention are needed. In addition, another goal of our research is to explore antigen uptake receptors on specialized epithelial M cells to identify potential targets for mucosal vaccine delivery. Thus, this division aims to develop novel mucosal vaccines by taking advantage of the conjugation of M-cell-receptor ligands with various vaccine antigens. To accomplish our goals, we are fully employing our evolutionally novel and fusion technics using molecular biology and bioengineering science.

（３）Activity Reports

１）Research Activities

- Visceral fat accumulation as observed in Crohn's disease and obesity is linked to chronic gut inflammation, suggesting that accumulation of gut adipocytes can trigger local inflammatory signaling. Thus, it is important to investigate direct interactions between intestinal epithelial cells (IECs) and adipocytes. We originally established intact, polarized, and cytokine responsive IEC monolayers from primary or induced pluripotent stem cell-derived intestinal organoids by simple and repeatable methods. When these physiological IECs were co-cultured with differentiated adipocytes in Transwell, pro-inflammatory genes were induced in both cell types, suggesting reciprocal inflammatory activation in the absence of immunocompetent cells. These inflammatory responses were blocked by NF-κB or signal transducer and activator of transcription 3 inhibition and by anti-tumor necrosis factor- or anti-IL-6-neutralizing antibodies. Our results highlight the utility of these monolayers for investigating IEC biology. Furthermore, this system recapitulates the intestinal epithelium–mesenteric fat signals that potentially trigger or worsen inflammatory disorders such as Crohn's disease and obesity-related enterocolitis.
- Gut epithelial organoids are routinely used to investigate intestinal biology; however, current

culture methods are not amenable to genetic manipulation, and it is difficult to generate sufficient numbers for high-throughput studies. Here, we present an improved culture system of human-induced pluripotent stem cell (iPSC)-derived intestinal organoids involving four methodological advances. We adopted a lentiviral vector to readily establish and optimize conditioned medium for human intestinal organoid culture. We obtained intestinal organoids from human iPSCs more efficiently by supplementing WNT3A and fibroblast growth factor 2 to induce differentiation into definitive endoderm. Using 2D culture, followed by the re-establishment of organoids, we achieved efficient transduction of exogenous genes in organoids. We investigated suspension organoid culture without scaffolds for easier harvesting and assays. These techniques enable us to develop, maintain, and expand intestinal organoids readily and quickly at low cost, facilitating the high-throughput screening of pathogenic factors and candidate treatments for gastrointestinal diseases.

- Worldwide, human norovirus (HuNoV) is a major cause of intestinal infectious gastroenteritis leading to morbidity and mortality in children and the elderly and thus having major social and economic influences. Neither an effective vaccine nor an effective treatment is currently available. One of the biggest reasons for the lack of an appropriate prevention or treatment strategy is the unavailability of methods for culturing HuNoV. Therefore, the recent development of a HuNoV replication system in human primary intestinal epithelial cells (IECs) has spawned advances in HuNoV characterization and opened up new strategies for HuNoV vaccine development. However, this technique currently requires human tissue cells and supplementation with bile, which contains unidentified components. Here, we report the replication of HuNoV in human induced pluripotent stem cell-derived IECs without bile. Furthermore, we provide evidence that vaccination with not only GII.4 but also GII.17 virus-like particles can induce neutralization antibodies against the predominant type of HuNoV, GII.4.
- During this reporting period (April 2016 to March 2019), we have published more than 50 peer-reviewed papers and 14 of which are closely related to the projects described above.
- We have filed one patent application: No. 2018- 152166, Shintaro Sato, Yoshikazu Yuki, Hiroshi Kiyono, “Human norovirus-like particles and the usages”, 2018/ 8/13

２）Education Activities

The members participate in the annual event, “Future of Immunology” organized by the Japanese Society of Immunology (JSI) to enlighten the immunology to the general public including children and students at The National Museum of Emerging Science and Innovation in every August.

３）Social Activities

None.

４）International Activities

The 10th Probiotics, Prebiotics and New foods, Nutraceuticals and Botanicals for Nutrition and Human and Microbiota Health /1st Science and Business Symposium, Rome, Italy

５）Other matters to be noted

None.

（４）Challenges and Future prospects

We have accomplished our primary goals during this period. Since the divisions of the International Research and Development Center for Mucosal Vaccines (IMV) have been re-organized in 2019, we will put our efforts to investigate the roles of the mucosal barrier system together with other divisions of the IMV including Mucosal Immunology, Mucosal Vaccine, and Clinical Vaccinology. To do this, we will continue to apply for outside funding, including the Grant-in aids for Scientific Research announced by Japan Society for the Promotion Science (JSPS), Japan Agency for Medical Research and Development (AMED) as well as others.

Division of Innate Immune Regulation

（１）Members

Project Professor	Satoshi Uematsu
Project Assistant Professor	Kosuke Fujimoto
Technician	1
Others	2

（２）Research objectives

1. Clinical application of our novel vaccine technology that can efficiently induce pathogen-specific sIgA on mucosal surface
2. Functional analysis of innate immune cells in the intestinal lamina propria
3. Development of new treatments for radiation-induced mucositis

（３）Activity Reports

１）Research Activities

The innate immune system senses the invasion of pathogens, induces an inflammatory response, and activates adaptive immunity. Since the innate immune system plays a role in initiating an immune response, it is thought that regulation of this mechanism enables control of various diseases related to the immune response. In particular, the innate immune system of the intestinal tract has a very unique function because it helps to ingests food safely and to coexist with commensal bacteria in itestine. In the division of innate immune regulation, we have established a technique to isolate innate immune cells from the lamina propria of the intestinal tract. Based on the findings obtained from the functional analysis of intestinal innate immune cells, we will develop new mucosal vaccines, treatment for various intestinal inflammation and the method to regulate intestinal bacteria.

1. Development of a new mucosal vaccine

There is a need for the development of a next-generation vaccine that induces systemic and potent pathogen-specific IgG and Th1 responses and high-titer pathogen-specific secretory IgA (sIgA) on the mucosa. Our division identified the unuque dendritic cells (DC) in the intestine, which induce IgA-producing B cells. We further found that the expression of retinoic acid synthase Raldh2 in DC was essential for IgA induction. As a result of the screening of microbe components, β1,3-glucan was found to induce Raldh2 in DC. By using CpG DNA and β1,3-glucan as mucosal adjuvants in intramuscular vaccination, we could induce antigen-specific IgG (in blood) and sIgA Induced (in feces). After the priming, high titer of antigen-specific sIgA was induced for a long period by boosting orally, respiratory tract, or vagina with only the antigen. Now, we are performing vaccine experiments in monkeys for clinical application.

2. Functional analysis of innate immune cells in the intestinal lamina propria

$CD11c^{int}CD11b^{int}$ MFs express CX3CR1. We are analyzing on the MFs about expression patterns of TLRs, cytokine production, regulatory function and roles in inflammation and infection. It is well known that large numbers of eosinophils reside in small intestinal lamina propira. However, the function of intestinal eosinophils is yet to be elucidated. We are analyzing on the eosinophils about the activation mechanism and roles in inflammation, parasite infection and food allergy.

3. Analysis of innate immunity in radiation syndrome

High-dose ionizing radiation induces severe DNA damage in the epithelial stem cells in small intestinal crypts and causes gastrointestinal syndrome (GIS). Although the tumour suppressor p53 is a primary factor inducing death of crypt cells with DNA damage, its essential role in maintaining genome stability means inhibiting p53 to prevent GIS is not a viable strategy. Here we show that the innate immune receptor Toll-like receptor 3 (TLR3) is critical for the pathogenesis of GIS. *Tlr3*−/− mice show substantial resistance to GIS owing to significantly reduced radiation-induced crypt cell death. Despite showing reduced crypt cell death, p53-dependent crypt cell death is not impaired in *Tlr3*−/− mice. p53-dependent crypt cell death causes leakage of cellular RNA, which induces extensive cell death via TLR3. An inhibitor of TLR3–RNA binding ameliorates GIS by reducing crypt cell death. Thus, we propose blocking TLR3 activation as a novel approach to treat GIS (Takemura N, et al. ***Nat Commun.*** 2014.). In addition, Radiation-induced intestinal fibrosis is a serious complication after abdominal radiation therapy for pelvic tumors or peritoneal metastases, causing significant fibrosis, especially in the submucosa of the small intestine. This condition was associated with excessive infiltration of activated eosinophils in the submucosa. After irradiation of the abdomen, chronic cell death was induced in the intestinal crypt, causing adenosine triphosphate (ATP) leakage outside the cell and activating myofibroblasts directly under the crypt. This activated myofibroblast was found to infiltrate and activate eosinophils under the mucous membrane. Activated eosinophils under the mucus membrane have been shown to stimulate collagen production from myofibroblasts through the production of TGF-β and induce significant fibrosis under the mucosa. In collaboration with Kyowa Hakko Kirin Co., Ltd., we have developed a new eosinophil-removing antibody targeting mouse interleukin (IL) -5 receptor (R) α. This antibody abolished intestinal eosinophil infiltration and markedly improved radiation-induced intestinal fibrosis. Based on the above, we were able to demonstrate a new treatment strategy for radiation-induced intestinal fibrosis by performing antibody treatment targeting eosinophils (Takemura N, et al. ***Sci Trans Med***. 2018.). We believe that administration of eosinophil-removing antibody can suppress fibrosis of the intestinal tract, prevent complications in patients after radiation therapy, and avoid a decrease in quality of life (QOL). We are now analyzing the mechanism of oral mucositis after radiation to develop a new therapy.

２）Education Activities

We accept 3 PhD students at the dual post.

３）Social Activities

We are collaborating with EA Pharma Co., Ltd and Meiji Co., Ltd.

４）International Activities

Our center has signed an agreement with the Pasteur Institute to create a joint unit for both parties. Prof. James Di Santo, the counterpart of the other party, made this joint research contract together with us. We are now conducting a joint research project to analyze the nasal microflora of allergic patients in France.

５）Other matters to be noted

We made a patent application for our developed immunization method as a new vaccination in 2016 (PCT / JP2016 / 67403). This was patented in 2019.

（４）Challenges and Future prospects

The granted patent has been licensed to Mitsubishi Tanabe Seiyaku Pharmaceutical Co., Ltd. and we are developing a pneumococcal vaccine and COVID-19 vaccine by using this method. The future prospect is to bring it into a formulation as a new mucosal vaccine.

Division of Clinical Vaccinology

（１）Members

Project Professor	Kohtaro Fujihashi
Project Associate Professor	Yosuke Kurashima
Technicians	1
Others	1

（２）Research objectives

To explore new avenues for mucosal vaccine development, investigators have begun to employ novel adjuvants and targeting mucosal tissues and immune cells for vaccine delivery. Despite recently advanced sciences, it still remains to develop effective mucosal vaccines for human use. To this end, our main task is to define the effectiveness and safety of novel mucosal vaccines including adjuvant- and delivery system-development and bring them from bench-top to practical applications. In order to accomplish our goals, we are fully employing evolutionally novel and fusion technics using agriculture and bioengineering science including botany and engineering knowledge.

（３）Activity Reports

１）Research Activities

In order to develop a new generation of oral vaccines which elicit mucosal immunity in the entire mucosal surfaces including respiratory and reproductive tracts, we have been studied to discover novel molecules which could use potential oral adjuvant for inducing global protective mucosal immunity by using single-cell mRNA sequencing approach. We have successfully established and analyzed several DNA libraries from nasopharyngeal associated lymphoid tissues and Peyer's patches of naïve mice as well as mice given the oral or nasal vaccine. We currently testing several candidate molecules for their ability to elicit antigen-specific immunity in the entire mucosal tissues.

We have studied to better define the cellular and molecular mechanisms of dendritic cell-targeting nasal adjuvant, i.e., plasmid encoding Flt3 ligand and CpG ODN for the induction of protective secretory IgA (SIgA) antibody responses against respiratory pathogens in aged mice. We are exploring the roles of Foxp1 and microRNA in the activation of naïve or memory $CD4^+$ T cells for the induction of mucosal immunity in the elderly. The successful outcome of our approaches would lead to facilitate the development of novel mucosal vaccines for the elderly.

During this reporting period (2018 to present), we have published 8 peer reviewed original papers and one review, and 5 of which are closely related to the projects described above. In addition, we have 3 papers in preparation.

２）Education Activities

None.

３）Social Activities

Collaborative research project with Astellas Pharmaceutical Inc to develop MucoRice-based new oral vaccines by using a novel oral adjuvant system.

We have been collaborative with Dr. Tomonori Nochi at Tohoku University to study the relationship between gut microbiota and Peyer's patch-dependent maternal IgA antibody responses. This study is supported by Joint Research Project of the Institute of Medical Science, The University of Tokyo (IMSUT).

４）International Activities

We have two international collaborative researches with Dr. Peter B. Ernst at the University of California San Diego (UCSD, Intratissue cohabitation of commensal bacteria for immunity and symbiosis) and Dr. Catherine Tsai at University of Auckland (Development of M2e-based intranasal universal influenza vaccine utilizing PilVax platform) supported by IMSUT International Joint Research Program.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

We will keep up our high performance in research in a comparable fashion to the last 2 years. In this regard, we will continue to study the projects showing above in order to understand the cellular and molecular regulation of mucosal immunosenecence and mucosal vaccines for the elderly by evolutionally novel and fusion technics using agriculture and bioengineering science including botany and engineering knowledge. The outcomes of studies will contribute to establish a healthy aging society and subsequently fill the gap between the actual life span and healthy life.

In order to maintain our research activities as well as to be involved and contribute to IMSUT, it will be essential to obtain new outside funding supports. We will continue to apply for outside funding, including the Grant-in aids for Scientific Research announced by Japan Society for the Promotion Science (JSPS), Japan Agency for Medical Research and Development (AMED) as well as others.

Division of Mucosal Vaccine

（１）Members

Professor	Ken J. Ishii
Visiting Professor	Jun Kunisawa
Visiting Associate Professor	Tomonori Nochi
Project Assistant Professor	Rika Nakahashi
Postdocs	3
Technicians	8
Others	2

（２）Research objectives

Division of Mucosal Vaccine is conducting research and development for mucosal vaccines. The mucosal vaccine is a prospective strategy for vaccine development against pathogens invading through mucosal tissues. We have examined the immunological functions of commensal and pathogenic microorganisms as well as diets and applied them to the development of adjuvants and antigen delivery for the efficient immune responses against mucosal vaccines. These findings also could be extended to the development of mucosal immunotherapy against cancer, allergic, inflammatory, and infectious diseases. To accomplish our goal, we are fully employing our evolutionally novel and fusion technics using the agriculture and bioengineering science including botany and engineering knowledge.

（３）Activity Reports

１）Research Activities

Food poisonings caused by *Clostridium perfringens*, Shiga toxin (Stx)-producing Escherichia coli (STEC), and cholera occur frequently worldwide; however, no vaccine is currently available. Therefore, we aimed to develop a bivalent vaccine against *C. perfringens*, STEC, or cholera infections. The fusion of the C-terminal region of C. perfringens enterotoxin (C-CPE) with Stx2 B subunit (Stx2B) or cholera toxin B subunit (CTB) induced T cell-mediated high levels of C-CPE-, Stx2B- or CTB-specific neutralizing IgG antibody responses which were sufficient for protective immunity. These findings collectively indicate that C-CPE-based fusion protein could be efficient against *C. perfringens*, STEC, and cholera infections.

We have developed cationic types of cholesteryl group-containing pullulan (cCHP) nanogels as a novel drug delivery system that adhere to the epithelial layer of the nasal cavity after nasal immunization and elicit the effective immunity by sustained antigen release. Using the cCHP nanogel system, we are currently developing a universal nasal vaccine for all serotypes of pneumococcal infection. Based on the findings, we plan to conduct a double-blind, randomized,

placebo-controlled phase I study to evaluate the safety, tolerability, and efficacy of the cCHP nanogel nasal vaccine. Further, we have been testing the effectiveness of cCHP nanogel-based nasal vaccines for human papillomavirus and RSV in murine experimental models.

MucoRice-CTB (line 51A) has been developed as a rice-based oral vaccine against diarrheal diseases. Line 51A was self-pollinated for five generations to fix the transgenes, and the seeds of the sixth generation produced by T5 plants were defined as the master seed bank (MSB). T6 plants were grown from part of the MSB seeds and were self-pollinated to produce T7 seeds (next seed bank; NSB), and were compared to the whole genomes and proteomes of MSB and NSB samples. Our results showed that NSB is essentially identical to MSB in terms of the genetic, protein contents, and their functionality.

During this reporting period (April 2016 to present), we have published more than 50 peer-reviewed papers which are closely related to the projects described above. In addition, we have published 15 review papers. Further, 5 manuscripts were submitted for the publication and 4 of them are currently under the revision process.

２）Education Activities

None.

３）Social Activities

None.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

We will keep up our high performance in research in a comparable fashion to last 5 years. In this regard, we will continue to study the projects showing above in order to understand the cellular and molecular regulation of mucosal immunology and mucosal vaccine by evolutionally novel and fusion technics using the agriculture and bioengineering science including botany and engineering knowledge.

In order to maintain our research activities as well as to be involved and contribute to IMSUT, it will be essential to obtain new outside funding supports. We will continue to apply for outside funding, including the Grant-in aids for Scientific Research announced by Japan Society for the Promotion Science (JSPS), Japan Agency for Medical Research and Development (AMED) as well as others.

Division of Mucosal Symbiosis

（１）Members

Project Professor	Tetsuro Matano
Project Associate Professor	Yoshiyuki Goto

（２）Research objectives

In the division of Mucosal Symbiosis, the following goals are set every year.

1. Publish at least 2 international journals

2, Submit at least 1 patent application

We will also investigate and clarify the scientific objectives as described below.

3. Elucidate the interplay between gut resident microorganisms and host epithelium and immune cells.

4. Isolate and identify intestinal microorganisms that contribute to boost host immunity and regulate host diseases.

5. Clarify the mechanism of immune activation by intestinal microorganisms and develop novel therapeutic technology to optimize the effect of vaccine.

6. Elucidate induction and regulation mechanism of α1,2-fucose of intestinal epithelial cells.

（３）Activity Reports

１）Research Activities

In our laboratory, we aim to develop new prophylactic, therapeutic, and diagnostic methods for infectious diseases and other host diseases by conducting the research using immunological and biological techniques. In particular, we isolate and identify useful gut microorganisms for human and propose novel therapeutic approaches against various host diseases. Our research aim from January 2018 to March 2019 was to publish at least two international original articles and to apply for at least one related patent. In fact, we published 6 original papers in international journals, including 3 papers that are IF>10 in this period, and one more original article was accepted. We also submitted one patent related to detecting gut inflammation. From these results, the progress of research of Mucosal Symbiosis is satisfactory in this period.

２）Education Activities

None.

３）Social Activities

None.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

We will continue to carry out the research stated in the above goals. As a potential problem, it is necessary to develop research that is associated with clinical research on human diseases in addition to the basic research using experimental animals. We plan to promote research directly linked to control human disease by accelerating the corroboration with clinical researchers and promoting the analysis and isolation of microorganisms in feces and tissue samples from patients with specific conditions. In addition, we will continue the isolation, identification, and management of microorganisms that regulate human diseases and create a biological bank of disease-related microorganisms in the future. At the same time, we aim to apply various patent by establishing a method for creating a microorganism cocktail that contributes to the regulate multiple diseases. We will create a cooperative system in our laboratory for an accomplishment of early acceptance of papers that were submitted or ready to submit.

Health Intelligence Center

Director Seiya Imoto

（１）Missions and Features

Health Intelligence Center aims to promote data science and personalized genomic medicine for predicting and preventing diseases and maintaining health by using supercomputers to analyze big data combined with genome-related data, health and medical data.

（２）Organization

Division of Health Medical Data Science

Division of Health Medical Computational Science

（３）Activity Reports

１）Research Activities

We have developed statistical data analysis technologies for prediction and prevention of diseases and maintenance of health by analyzing whole genome, transcriptome, epigenome, and commensal microbial metagenome data (e.g., intestinal and oral microbiome) together with big data on health and medical care such as health insurance claims and specific health checkup information.

In April 2020, Health Intelligence Center was merged to Human Genome Center in order to increase its research activity and promote new dimension genomic medicine. This integration provided a stronger research center with genomic and health medical big data analysis researches.

２）Education Activities

The OJT (On the Job Training) utilizing supercomputer SHIROAKNE is provided to not only students of computer science department, but also experimental laboratories' students in IMSUT and young researchers such as postdocs. We also provide guidance to undergraduate students who wish to become a data scientist in health medical researches.

３）Social Activities

Science Café (The Takeda Foundation), Education Course (lectures about AI in medical researches) at the Japanese Society of Rheumatology and the Japanese Medical AI Society.

４）International Activities

We participated and contributed to the International Cancer Genome Consortium and TCGC/TCGA PanCancer Analysis of Whole Genomes.

５）Other matters to be noted

Together with members of Human Genome Center, we managed SHIROKANE supercomputer at Human Genome Center and improved its service. The number of users, which had been hovering around 500 in the past, has exceeded 1,500. We analyzed over 10,000 whole genome sequencing data through collaborative research with other universities and other organizations. over 10,000 We created an information infrastructure that enables us to analyze the sequence data of human whole genome, intestinal microbiota and oral flora with health check-up data and medical records.

（４）Challenges and Future prospects

By the integration of Health Intelligence Center into Human Genome Center, reorganization of the center that enables to create personalized medicine in the Society 5.0 era ahead of the world is the primary issue. Based on this integration and renewal, we will address the following four areas.

(1) The challenge of addressing important issues in cancer genomics, such as the unveiling mechanisms of generating cancer heterogeneity, and the development of fundamental infrastructure for genomic data and data sharing.

(2) Promoting artificial intelligence research for clinical translation of new dimensional genomic information (integrated genomic information from human genome, commensal bacteria and virus genomes).

(3) Proceeding medical informatics research, which organizes, analyzes, and interprets new dimensional genomic, medical, and health-related information and training researchers and physicians who translate it for personalized medicine.

(4) ELSI research addressing a variety of issues, which arise at the contact point between medical research such as advanced medicine including new dimensional genomic medicine and society.

Division of Health Medical Data Science

（１）Members

Professor	Seiya Imoto
Assistant Professor	Takanori Hasegawa
Graduate students	3

（２）Research objectives

By integrating human genome-derived data such as whole genome sequencing (WGS) data and transcriptome data to medical data like blood tests and time-series health-related data from wearable devices using IoT, we develop big data analysis technologies and create an information infrastructure for the analysis using supercomputer. Furthermore, using the analysis results of big data and personal data, we aim to establish an informatics method that enables us to provide health-medical action plans that improve personal health condition and realize personalized precision medical care.

（３）Activity Reports

１）Research Activities

As the datasets of whole genome sequencing, we collected 3,000 samples from BioBank Japan (BBJ), about 6,000 samples of normal and tumor from ICGC/TCGA PanCancer, and about 1,500 samples from Hirosaki University Center-of-Innovation Program and analyzed them integrating with RNA-sequencing data. We also started a collaborative research with researchers of Monash University to develop a method for the integrative analysis of pathological image data and genomic sequencing data. We use TCGA data of multiple types of cancers for this purpose. We have received 15 years of health checkup data (approximately 30,000 records, WGS, intestinal and oral flora, health checkup information, lifestyle habits, etc.) from Hirosaki University, and we are developing a risk prediction model for lifestyle-related diseases. In addition, in an effort to return analysis results to individuals, we are working with a company that conducts direct-to-consumer genetic testing to analyze SNP information from approximately 100,000 users. In order to analyze such big data and personal data and apply them to health/medical care, we have been working on a project in collaboration with IMSUT Hospital, Advanced Clinical Research Center and Human Genome Center to realize WGS-based cancer genomic medicine for hematological and gastrointestinal cancers. In this context, we were one of the pioneer groups in the world to implement an artificial intelligence system to clinically interpret genomic mutations of cancer genomes, proceeding the learning and developing new AI, which now allows us to complete the process of receiving consent for genomic analysis from patients and returning the results to the physician in charge in about five days.

２）Education Activities

Accepting graduate students from Department of Computer Science (2 in 2019 and 3 in 2018); and we provide research guidance related to bioinformatics. We also provide training to motivated graduate students who want to study bioinformatics in experimental laboratories (several students each year). We provided several bioinformatics related lectures to graduate and undergraduate students in the University of Tokyo. Undergraduate students at the University of Tokyo who are interested in data science are asked to visit the laboratory on a regular basis for guidance. Lecturer for the 2019 Japan Rheumatology Society's "Medical Education Project to Foster the Interface between AI Technology and Rheumatology held in Tokyo, Osaka and Fukuoka. We also provide the Japanese Society of Internal Medicine's Educational Lecture Series for 2020.

３）Social Activities

- The Takeda Foundation, Science Café “Changing medicine and health care by genomic information” (All 6 sessions in the series)
- Host of JST Sakura Science Program (Central Asian countries for 2019, Chinese Academy of Sciences for 2018, governmental officers of China (ministry of health) for 2017, Rajiv Gandhi Centre for Biotechnology, India for 2016)

４）International Activities

- ICGC/TCGA PanCancer Analysis of Whole Genomes (PCAWG)
- Collaborative research with Center for Research and Advanced Studies, Mexico (Prof. Martha Espinosa-Cantellano) was accepted and supported by the IMSUT International Joint Research Center’s project (2019 and 2020)
- Collaborative research with China Medical University, Taiwan Genome Project (Dr. Ro-Ting Lin) was accepted and supported by the IMSUT International Joint Research Center’s project (2020)
- ollaborative research with Monash University (Assc. Prof. Jiangning Song) for Image and Genome Analysis was started.

５）Other matters to be noted

- Presentation and Panel Discussion at Tokyo Forum 2019’s session “Healthy Aging Society”
- Press Releases
  - with Riken about the Nature paper of PanCancer project in Feb 2020
  - with Fujitsu Laboratory about AI for genomic medicine in Nov 2019

- with Kao about microbiome research in Nov 2019
- with BrightPath Bio about the launch of joint research in Dec 2018

- Prof. Imoto was served as a member of committee "Studying a vision of how doctors, nurses and other professionals work based on a new way of medical care" Ministry of Health, Labour and Welfare in 2016. Research on "Survey of Physicians' Working Conditions and Work Style" (a survey of 100,000 physicians) was conducted as the principal investigator. This is the largest survey for physicians' working style in Japan. The result was published in the Press Office of the Ministry of Health on April 6, 2017. It was covered by various media such as newspapers, TV and the web.

（4）Challenges and Future prospects

Recent studies have shown that our commensal microbes are linked to our health and disease. It is not only limited to bowel disease, but also affects mental illnesses such as depression and even neurodegenerative diseases. It's called "alter ego". Integrating the microbe information is essential for the future of genomic medicine. We will promote the development of information analysis techniques and artificial intelligence for this purpose.

Center for Gene and Cell Therapy

Director Keiya Ozawa (-FY2017)
Director Arinobu Tojo (FY2018-FY2019)
Director Takashi Okada (FY2019-)

<Members>

Professors	Arinobu Tojo, Tomoki Todo, Toshio Kitamura, Fumitaka Nagamura
Invited Professor	Koji Tamada
Project Professor	Hideaki Tahara
Visiting Professor	Shin-ichi Muramatsu
Associate Professors	Satoshi Takahashi, Tokiko Nagamura-Inoue
Project Associate Professor	Hiroaki Uchida

（１）Missions and Features

IMSUT hospital has been playing a crucial role in clinical gene therapy and stem cell transplantation in Japan. In order to reinforce this clinical development even further, IMSUT established the Center for Gene & Cell Therapy (CGCT) in 2014. CGCT particularly focuses on the development of gene therapy and cell therapy for intractable cancer and chronic diseases, such as oncolytic virus therapy, engineered T cell therapy, gene therapy for neurological disorders using AAV vectors, T cell therapy for post-transplant viral infections, and cell therapy using mesenchymal stem cells.

（２）Organization

Division of Molecular and Medical Genetics

（３）Activity Reports

１）Research Activities

CGCT has promoted the development and trial of oncolytic virus therapy, engineered T cell therapy, gene therapy for neurological disorders using AAV vectors, T cell therapy for post-transplant viral infections, and cell therapy using mesenchymal stem cells. With the aim of mass-producing high-quality GMP/GCTP-compliant gene therapy products that are needed to promote further trials, CGCT is working with domestic companies to conduct development research for manufacturing processes. In addition, CGCT has conducted collaborative research on gene therapy and related technologies with various facilities in Japan and abroad. The research results are published in journals such as *Science, Nat Biotechnol, Nature, J Immunol, J Exp Med, Stem Cells, J Virol, Cancer Res, Sci Rep, J Biol Chem, Circulation, Proc Natl Acad USA, J Clin Invest, Mol*

Ther, EMBO Rep, Leukemia, Blood, and *Nat Commun.* The followings are the total numbers of the original papers published in the peer reviewed international journals in each fiscal year: 79 in 2016, 95 in 2017, 106 in 2018, 70 in 2019, and 16 in 2020.

２）Education Activities

In the process of our research, we have educational programs for graduate students interested in pursuing a career in the field of gene and cell therapy. The faculties of various divisions teach a wide range of courses in graduate school of medicine and graduate school of frontier sciences. Through graduate seminar series, researchers from various academic backgrounds domestically and internationally, interact with one another making interdisciplinary research which provide an ideal educational environment. Between 2016 and 2018, more than 10 graduate students received degrees, some were accepted as JSPS Research Fellowship for Young Scientists and some were to study abroad. There were also graduate students who started their professional careers at major pharmaceutical companies.

３）Social Activities

There are high expectations for the development of gene therapy products. However, the construction and operation system of domestic GMP/GCTP compliant manufacturing facilities are not sufficient. In fiscal year 2018, proposals from IMSUT-CGCT for AMED's Program to Develop Fundamental Technologies for Industrialization of Regenerative Medicine and Genetic Treatment were accepted. We expect that the domestic academia will be organized and have at its center on IMSUT, Jichi Medical University, and Osaka University.

４）International Activities

A CGCT Seminar was held on Apr. 8, 2016. We invited R. Michael Linden, Ph.D. (Vice President, Gene Therapy Head, Genetic Medicine Institute Pfizer Inc.) as the senior lecturer to give a talk on “Open innovation for development of therapeutic agents against intractable diseases and its future directions.” Taking the situation in the United States as an example, we exchanged views on regulatory compliance and development strategy schemes.

５）Other matters to be noted

The 3rd IMSUT-CGCT Symposium was held on Mar. 13, 2017, the 4th on Jun. 27, 2017 and the 5th on Jan. 30, 2018. Well-known researchers in the field of gene therapy not only from Japan but from various countries and regions were invited to have lively discussions.

（４）Challenges and Future prospects

As a nationwide inter-university research hospital, the Institute of Medical Science is characterized by accepting seeds from outside the university, and is widely used as a place to promote clinical development of excellent projects in Japan. With regard to gene and cell therapy, clinical development toward commercialization is activating in Japan due to the marketization in Europe and the United States, and TR promotion at IMSUT-CGCT is required as a base for gene and cell therapy in Japan. In the future, in order to actively promote gene and cell therapy research and clinical trials for intractable cancers and hereditary diseases, it is required to build a cooperative system with TR supporting sections such as IMSUT Hospital Center for Translational Research, Department of Cell Processing and Transfusion, Therapeutic Vector Development Center, and Department of Biopharmaceutical Safety Inspection.

Division of Molecular and Medical Genetics

（１）Members

Professor	Takashi Okada
Postdocs	6
Technicians	1
Others	2

（２）Research objectives

Division of Molecular and Medical Genetics has been continuously carrying out research into the development of fundamental gene therapy techniques with the adeno-associated virus vectors and cell therapeutic modalities. The main research theme is the development as well as clinical application of gene and cell therapies using viral vectors and MSCs for the treatment of diseases where fundamental therapies are still difficult, such as various neuromuscular diseases. We promote international contribution by developing the world's most advanced technology and industrial power by gathering academia and companies with original technology.

（３）Activity Reports

１）Research Activities

Since the division opened in July 2019, we have been continuously carrying out research into the development of fundamental gene therapy techniques. Our main research theme is the development and clinical application of gene and cell therapies using viral vectors as well as mesenchymal stromal cells for the treatment of illnesses where fundamental therapies are still difficult, such as muscular dystrophy, stroke, and cancer. The research achievements are published in journals such as *Hum Gene Ther Methods, Glia., Mol Pain, Calcif Tissue Int, Int J Lab Hematol, Exp Anim., Mol Ther Methods Clin Dev., Mol Ther Methods Clin Dev., Glycobiology.* The total numbers of the original papers published in the peer reviewed international journals in each fiscal year are 4 in 2019, and 7 in 2020.

Overall findings of the research were also presented at the scientific symposiums including International Gene & Cell Therapy Symposium, The 25th Annual Meeting of Japan Society of Gene and Cell Therapy, The 61st Annual Meeting of Japanese Association of Oral Biology, The 64th Annual Meeting of the Japan Society of Human Genetics, and the Gunma Univ Initiative for Advanced Research Viral Vector Core Start-up Symposium.

We also presented our findings at the academic conferences held by American Society of Gene and Cell Therapy, Japan Society of Gene and Cell Therapy, Japan Neuroscience Society, Japanese Society for Neurochemistry, Japan Muscle Society, Japanese Pharmacological Society, Molecular

Biology Society of Japan, and Japanese Pharmacological Society.

Research grant proposals for Ministry of Education, Culture, Sports, Science and Technology (MEXT) and Japan Agency for Medical Research and Development (AMED) were accepted such as Grant-in-Aid for Scientific Research (B), Program to Develop Fundamental Technologies for Industrialization of Regenerative Medicine and Genetic Treatment, Acceleration Transformative Research for Medical Innovation, Translational Research Grant (B, preB).

２）Education Activities

We develop global human resources who will play a leading role in the next generation with diverse academic backgrounds. With the opening of the postgraduate course, we started recruiting graduate students at the Graduate School of Medicine. We also gave lectures at the School of Medicine and research guidance for graduate students at Nippon Medical School.

Educational lectures were provided through the programs prepared by Manufacturing Technology Association of Biologics and Japan Biological Informatics Consortium.

３）Social Activities

In cooperation with the AMED and the Manufacturing Technology Association of Biologics, we would like to contribute to the elimination of trade deficits and economic growth in the domestic medical field, whereas fostering the gene and cell therapy as an academic discipline.

Various cooperative research programs toward social implementation have been actively conducted with academia and companies such as National Center of Neurology and Psychiatry, Osaka University, and Nippon Medical School.

４）International Activities

We are seeking for the way to establish the next generation vector manufacturing process technology and reform import-dependent medical structure. In addition to publicizing research activities at the international conferences, such as annual meetings of the American Society of Gene & Cell Therapy as well as the Bioprocessing Summit, we have routinely exchanged opinions among international communities toward future advances. Furthermore, we gave a course lecture of Introduction to Medical Science at the International Course, the School of Advanced Science and Engineering, Waseda University.

５）Other matters to be noted

As a member of the Center for Gene and Cell Therapy, we are establishing a major international medical research center that will lead the world in this field by establishing advanced technologies and fields by using the background and unique achievements of gene and cell therapy. Our unique

research activity was introduced in the media.

（４）Challenges and Future prospects

We would like to continue the research carried out to present into fundamental vector techniques, stromal cell techniques, molecular pathology analysis, and the gene therapies that make use of these. Additionally, so that these results can make it to clinical use, we would like to guide the standardization of gene and cell therapies for the treatment of neuromuscular disorders and cancer.

Laboratory Animal Research Center

Director Chieko Kai (-FY2018)
Director Tomoji Mashimo (FY2019-)

（１）Missions and Features

Laboratory Animal Research Center (LARC) was founded in 1965 as the first modern animal facility in Japan. Mice and rats are strictly maintained in the SPF condition for many scientific experiments. We also provide several services for mouse embryo manipulation and generating genetically modified animals with genome editing technologies.

In addition, we are developing novel genome editing tools such as CRISPR-Cas3 and (Combi-CRISPR) knock-in strategies in mice and rats, which can be widely applied in laboratory rodents. We are also focusing on generating "humanized animals" or "immunodeficient animals". These valuable animal models can be used for xenotransplantation of human cells/tissues including human iPS cells.

（２）Organization

Laboratory Animal Research Center (Kai Laboratory) (-FY2018)
Division of Animal Genetics
Animal Center

（３）Activity Reports

１）Research Activities

Genome engineering technologies achieve a "revolution" in life science and medical science. These techniques allow us to manipulate genes of interest for multiple purposes. Using those technologies, we have developed many useful strains in mice and rats. We are now focusing on generating and optimizing "humanized animals" or "immunodeficient animals" for xenotransplantation of various human cells/tissues including human iPS cells. We are also developing therapeutic strategies such as cell therapy and gene therapy with genome editing tools.

２）Education Activities

We have an annual training course for all researchers and technical staffs who use our animal facility.

３）Social Activities

None.

４）International Activities

By utilizing our efficient genome editing technologies, we generate immunocompromised transgenic rats with the suicide gene to induce apoptosis of rat hepatocytes. We are collaborating with the University of Pittsburgh in the USA to develop in vivo proliferation strategy of human hepatocytes for clinical application.

５）Other matters to be noted

Nowadays, the technologies of genome editing enable us to generate various animal model. Different from mice, the laboratory rats have larger size and more relevance to human diseases and attract more attention in many fields, such as Pharmacology and Toxicology. Among numerous rat models, the immunodeficient rats have large applicability and potential in multiple researches including cancers, stem cells, organ transplantation, etc. As a participant of NBPR-RAT project, we breed SCID rats and provide them to worldwide institutes.

（４）Challenges and Future prospects

We will continue devoting to improve the breeding space and experimental environment to meet the needs of more researchers. As the experiments related to the tumor transplantation and infection are increased in these years, we will expand the special space for the increasing requirement. We will also continue the support of making SPF mice, embryos preservation and generation of advanced animal models. In addition, we are also developing novel diagnosis strategy and more clinical application by using CRISPR-Cas3 technology.

Laboratory Animal Research Center (Kai Laboratory) (-2019.3)

（１）Members

Professor	Chieko Kai
Associate Professor	Misako Yoneda
Project Senior Assistant Professor	Hiroki Sato
Assistant Professors	Tomoko Fujiyuki, Shotaro Uchida
Project Assistant Professor	Akihiro Sugai
Postdocs	3
Graduate students	1
Technicians	1
Others	10

（２）Research objectives

Goals as of April 2016;

１）To advance the preclinical study for the novel measles virus for cancer therapy that we have been developing for the past three years to completion by the end of FY 2019, leading to clinical studies from FY 2020.

２）To conduct a collaborative study toward practical application of the candidate of the recombinant vaccine against Nipah virus that we have developed.

３）To identify factors associated with growth of Morbillivirus in the study to elucidate its mechanism of pathogenesis.

４）To identify factors associated with growth of Nipah virus in the study to elucidate its mechanism of pathogenesis.

（３）Activity reports

１）Research activities

1. The preclinical study was supported by AMED for the second time in FY 2017, and was successfully continued. We conducted 4 animal safety tests, and applied for face-to-face advice on safety tests with the PMDA. The production of GMP-compliant viruses for clinical studies was completed using the GMP-compliant cells for virus replication that had already been generated, and quality assurance testing was completed. We started individual consultations for face-to-face advice with the PMDA on pharmaceutical product manufacturing. Applicability testing also revealed new efficacy of the novel measles virus for cancer therapy in the other four carcinoma cell lines. A number of other preclinical study procedures are going smoothly, and thus the goal of completing the preclinical study by the end of FY2019 will be achieved.

2. We started a collaborative research with countries where Nipah virus is epidemic. We made various attempts to obtain the substantial amount of research funds required to conduct translational research leading to clinical study. As the international organization CEPI was established in January 2017 to support grants dedicated to the development of vaccines against emerging infectious diseases, we have set up a consortium for international collaboration with the institutions from EU, the US and Bangladesh. We applied to the CEPI's first public offering and accepted first from Japan in February 2019. We are now promoting developmental research to reach a phase II clinical trial in the next 5 years with the aim of putting it to practical use, and we have reached and significantly exceeded our goals.
3. In the study to elucidate the mechanism of pathogenesis of Morbillivirus, we showed that gene expression dynamics in various organs interact with each other by viral infection as a factor associated with its growth.
4. In the study to elucidate the mechanism of pathogenesis of Nipah virus, we identified two factors associated with its growth. We identified two of the mechanisms involved with them.

２）Education Activities

We provided lectures and practical training in the Department of Computational Biology and Medical Sciences of the Graduate School of Frontier Sciences, and the Department of Pathology, Immunology and Microbiology of the Graduate School of Medicine.

３）Social Activities

None.

４）International Activities

To develop the vaccine against Nipah virus infection described above, we have set up an international consortium with the institutions of EU, the US and Bangladesh, and are promoting a large developmental study to achieve the practical use of the vaccine.

５）Other matters to be noted

None.

（４）Challenges and future prospects

We believe that we have reached and significantly exceeded our goals, which can be evaluated. Although the two large projects are still on the way, the activities in this laboratory were terminated in IMSUT because of the mandatory retirement of the professor. These projects are going to be continued in another institute.

Division of Animal Genetics

（1）Members

Professor	Tomoji Mashimo
Senior Assistant Professor	Kazuto Yoshimi
Project Assistant Professor	Tomoaki Fujii
Postdocs	1
Technicians	2
Others	1

（2）Research objectives

Genome engineering technologies achieve a "revolution" in life science and medical science. These techniques allow us to manipulate genes of interest for multiple purposes. Using those technologies, we have developed many useful strains in mice and rats. We are now focusing on generating and optimizing "humanized animals" or "immunodeficient animals" for xenotransplantation of various human cells/tissues including human iPS cells. We are also developing therapeutic strategies such as cell therapy and gene therapy with genome editing tools.

（3）Activity Reports

1）Research Activities

We have established several useful animal mice and rats by genome editing tools. Especially, we generated a Severe Combined. Immunodeficiency (SCID) rat model, which carry homozygous mutation in both *Il2rg* and *Rag2* gene. The immunodeficiency animals are valuable experimental models, not only in the studies of immunodeficiency related diseases, they also have good performances in the application of grafting various tissues. We also established photoactivatable-Cre(PA-Cre) knock-in mice at safe harbor locus for the spatial and temporal regulation of Cre recombinase activity. The PA-Cre knock-in mice can facilitate spatiotemporal control of genetic engineering and promise a useful resource to elucidate gene function in vivo with Cre-loxP.

2）Education Activities

None.

3）Social Activities

None.

4）International Activities

By utilizing our efficient genome editing technologies, we generate immunocompromised transgenic rats with the suicide gene to induce apoptosis of rat hepatocytes. We are collaborating with the University of Pittsburgh in the USA to develop in vivo proliferation strategy of human hepatocytes for clinical application.

５）Other matters to be noted

Nowadays, the technologies of genome editing enable us to generate various animal model. Different from mice, the laboratory rats have larger size and more relevance to human diseases and attract more attention in many fields, such as Pharmacology and Toxicology. Among numerous rat models, the immunodeficient rats have large applicability and potential in multiple researches including cancers, stem cells, organ transplantation, etc. As a participant of NBPR-RAT project, we breed SCID rats and provide them to worldwide institutes.

（４）Challenges and Future prospects

To generate humanized rat models, we will modify other genes in these SCID rats, to improve the efficiency of xenograft and alleviate acute xenogeneic graft-versus-host disease (GVHD) in the recipient SCID rats. These valuable animals can be used for xenotransplantation of human cells/tissues including human iPS cells. We are also developing the efficient genome editing strategies with genome editing tools in mice and rats to generated humanized animals.

Animal Center (-FY2018)

（１）Members

Professor	Chieko Kai
Technicians	5
Others	9

（２）Mission and features

We provide technical assistance for research using laboratory animals in IMSUT; husbandry and housing of laboratory animals; maintenance of cleanliness and cleaning in contaminated rooms; monitoring; freezing, cryopreservation and thawing of embryos and sperm; embryo manipulation in genetically modified animals; maintenance and provision of genetically engineered mice and their biological genetic resource bank. We house animal species including mice, rats, rabbits and hamsters, all of which are SPF animals. About 30,000 mice are being raised at any given time, accounting for the highest percentage of the animals in the center. The numbers of mice used in FY 2016, 2017, and 2018 were 26,061, 29,192, and 17,599. We have P2 and P3 animal infection laboratories, which are provided to researchers who wish to use them for experiments of infection and tumor transplantation by lending them for each experiment term. We are also equipped with analytical instruments including MRI and IVIS, to contribute to various animal experiments performed in the institute. This center was used by 36 laboratories, had 346 researchers registered on average and around 22,000–30,000 users in total annually.

Microbial monitoring is conducted each month in the SPF animal breeding areas, and no viral or significant bacterial infections have occurred in the last three years. Although about 2 cases of minor contamination per year occurred in the past, SPF cleanliness has been kept by killing all infected animals followed by cleanup of the contaminated rooms and a cleaning support system in which clean SPF animals are produced from embryos or sperm. The biological genetic resource bank contributes to preservation of biological resources by opening itself to both Japan and other countries to share its information, and collecting and providing mice. The number of strains deposited in the biological genetic resource bank is 184 at present.

（３）Activity reports

１）Research activities

None.

２）Education Activities

None.

３） Social Activities

The animal center has established a biological resource bank to respond to the international need for preservation and provision of biological genetic resources.

４） International Activities

None.

５） Other matters to be noted

None.

（４） Challenges and future prospects

Animal experiments are essential for research in the field of medical science, and thus the animal center is highly significant as it maintains a high level of cleanliness and addresses the diverse needs of researchers in IMSUT. The animal center is highly rated because it has and maintains excellent functions as a center for supporting animal experiments in medical science studies; for example, it has an embryo manipulation room and cleaning methods that can be implemented immediately so that it has experienced no serious contamination by infectious diseases in the last 20 years, and it is equipped with laboratories for infection and tumor transplantation and analytic instruments including MRI and IVIS for laboratory animals. The IMSUT biological genetic resource bank was established to meet the needs of the institute to preserve and share biological resources and to support long-term preservation and provision of genetically modified animal embryos, responding to international needs. Although there still remain issues to be improved, the animal center should be maintained and improved further for its high user-friendliness.

Animal Center (FY2019-)

（１）Members

Professor	Tomoji Mashimo
Senior Assistant Professor	Kazuto Yoshimi
Technicians	4
Others	1

（２）Research objectives

The Laboratory Animal Research Center (LARC) was founded in 1965 as the first modern animal facility in Japan. Currently about 30,000 mice are housed for different researches in IMSUT, and strictly maintained in the SPF condition. The Animal Center building of LARC was improved in 1998 to perform genome engineering in animals, make infectious experiments (P2A, P3A), and house bigger animals, such as rats and rabbits. Techniques of mouse embryo manipulation and generating genetically modified mice, including genome editing technologies, have been introduced into the LARC.

（３）Activity Reports

１）Research Activities

The Animal Center building is a centralized facility designed, constructed and maintained to meet regulatory standards required for the operation of research animal facilities. The barrier housing rooms to support the production and use of genetically-engineered mice, biohazardous experiments area and equipment room which has X-ray Irradiator, MRI and IVIS imaging system were provided in this facility.

Our Barrie housing rooms are strictly maintained in the SPF condition, therefore, we provide IVF mouse derivation service for all mice shipped to LARC from other institutions or non-approved vendors to keep mice in SPF grade. We make frozen embryo for reducing number of using animals and laboratory space. In addition, it is useful for making back up of the strains

２）Education Activities

We have an annual training course for all research and technical staffs who use our animal facility.

３）Social Activities

None.

４）International Activities

None.

5）Other matters to be noted

None.

（4）Challenges and Future prospects

We will continue devoting to improve the breeding space and experimental environment to meet the needs of more researchers. As the experiments related to the tumor transplantation and infection are increased in these years, we will expand the special space for the increasing requirement. We will also continue the support of making SPF mice, embryos preservation and generation of advanced animal models.

Amami Laboratory of Injurious Animals (-FY2018)

Director Chieko Kai

（1）Members

Professor	Chieko Kai
Assistant Professor	Shinichi Yokota
Postdocs	1
Technicians	2

（2）Mission and features

Amami Laboratory of Injurious Animals was originally established as Oshima branch laboratory to study endemic tropical diseases in 1902, at the time of the National Institute for Infectious Diseases when Dr. Shibasaburo Kitasato was the director. It was taken over the Medical Science Institute of the University of Tokyo, and yielded excellent results, including from the studies that formed the basis for the eradication of filariasis in Japan and from those on bites by the venomous Habu snake, which made a great contribution to the study of tropical diseases. From 2005, as a base for primate experiments, the laboratory was equipped to be a rare facility where infection experiments can be carried out using primates for national universities in Japan. Now, as a base for collaborative studies, it has many users in the field of basic medicine not only with laboratories in IMSUT but also with a number of other universities, national institutes and other research institutes. It also houses and breeds precious biological resources, squirrel monkeys and owl monkeys, which are useful primates for experiment but cannot be purchased in Japan at present, and also conducts studies to preserve those biological resources.

（3）Activity reports

1）Research activities

Collaborative studies were conducted with 8 institutes in FY2016, 8 in FY2017, and 8 in FY2018 except laboratories in IMSUT. We worked on projects including studies in variation of Habu venom by islands and Habu venom inhibitor in serum, morphogenesis of Habu’s pit organ, development of methods of controlling vivax malaria using owl monkeys, analysis of pathogenesis of measles virus, safety analysis of measles virus vector vaccine, elucidation of biological characteristics of New World monkeys, analysis of pathogenesis of novel animal pathogens in primates, and wound healing using autologous cells of squirrel monkeys and cynomolgus monkeys.

2）Education Activities

We held public seminars and provided hands-on experience on the activities in IMSUT and Amami Laboratory of Injurious Animals.

３）Social Activities

None.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and future prospects

There are only two other experimental facilities affiliated with universities under the Ministry of Education, Culture, Sports, Science and Technology that are allowed to use primates for experiments. Further, the pathogens they are allowed to use are limited. Amami Laboratory of Injurious Animals is the only facility affiliated with the university where P2 and P3 infection experiments with primates can be carried out without limitation on the pathogens. This laboratory is open to institutes and universities in Japan, serving as the Joint Usage/Research Center affiliated an institute of the university, and thus its maintenance as a valuable facility is significant.

Amami Laboratory of Injurious Animals (FY2019-)

Director Tomoji Mashimo

（１）Members

Professor	Tomoji Mashimo
Project Assistant Professor	Shin-Ichi Yokota
Technicians	3

（２）Research objectives

Amami Laboratory of Injurious Animals is the unique International Joint Usage and Research Center capable of infection experiment using non-human primates. We are maintaining the colonies of New World monkeys and providing them for medical research in non-human primates to assess the pathogenicity of various pathogens, including viruses, bacteria, and protozoa, together with various domestic and foreign research institutions. In addition, research such as regenerative medicine, reproductive engineering, etc., in which our monkeys become suitable experimental models are also conducting at our laboratory.

（３）Activity Reports

１）Research Activities

As FY2020 adopted IMSUT Joint Research Project, we are conducting research related to the development of a malaria vaccine using squirrel monkeys with external research institutes such as Kyoto University, Nagasaki University, National Institute of Infectious Diseases, etc.

２）Education Activities

None.

３）Social Activities

None.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

This facility is the only university-affiliated research institute capable of primate infection experiments up to BSL3 without limiting the kind of pathogens. It is extremely important to continue to open this facility to universities and other institutions and maintain it as a Joint Usage and Research Center. Also it is important to keep colonies of squirrel monkeys and owl monkeys, whose trading is severely restricted by the CITES, from the viewpoint of biological resource conservation in Japan.

Medical Proteomics Laboratory

Acting Director Yuji Yamanashi

（1）Members

Professors	Yuji Yamanashi, Kouhei Tsumoto
Project Professor	Koichi Tanaka
Associate Professors	Masaaki Oyama
	Makoto Nakakido (Graduate School of Engineering)
Project Assistant Professor	Hiroshi Sagara
Technicians	3
Graduate students	20
Others	17

（2）Research objectives

The mission of our laboratory is to develop advanced technologies for antibody engineering, small molecule screening, mass spectrometry and electron microscopy to perform an integrative proteomic analysis of disease-related protein-protein interaction networks from a physicochemical, structural, and bioinformatical point of view.

Our main goal regarding research activities is to publish more than 20 research papers in international journals each year. We also encourage graduate students to make presentations at academic conferences to be awarded at least 3 prizes annually. For industry-academia collaboration activities, we aim to set up a corporate sponsored research program in cooperation with domestic and foreign companies.

In addition, our laboratory is widely involved in many collaborative research projects to facilitate the utilization of these medical proteomics technologies inside and outside the institute. In our mass spectrometry/electron microscopy facilities, we plan to establish an integrative platform for mass spectrometry-based comprehensive identification and quantification of multiple protein modifications and easy section-preparation methodology for serial ultrathin section scanning electron microscopy.

（3）Activity Reports

1）Research Activities

We published 20 (FY2016), 31 (FY2017), 26 (FY2018), and 25 (FY2019) research papers in international journals based on a wide range of advanced technologies as noted above. Regarding antibody engineering and small molecule screening platform, Dr. Tsumoto’s group have developed a variety of novel biophysical based strategies for antibody engineering and compound screening to

modulate protein-protein interactions. For the mass spectrometry facility, Dr. Oyama's group established a highly sensitive proteomic workflow for integrative analysis of protein phosphorylation, ubiquitination, acetylation and methylation. For the electron microscopy facility, Dr. Sagara's group developed a widely available technology for serial preparation of ultrathin sections and is now involved in methodological sophistication for picking up these sections.

２）Education Activities

The young researchers in Dr. Tsumoto's group received 3 (FY2016), 6 (FY2017), 6 (FY2018), and 7 (FY2019) awards at various academic conferences. Dr. Oyama's group conducted 13 (FY2016), 8 (FY2017), 11 (FY2018), and 12 (FY2019) outreach scientific programs for junior and senior high school students.

３）Social Activities

Dr. Tsumoto's group has started a project division of advanced biopharmaceutical science with Tosoh Corporation since 2017.

４）International Activities

Dr. Oyama's group has initiated a clinical proteomics project with Abbott Laboratories under IMSUT-Abbott strategic research collaboration agreement since 2017.

５）Other matters to be noted

Dr. Tsumoto's group published 3 press releases regarding the outstanding research achievements.

（４）Challenges and Future prospects

Continuous and cumulative improvement of mass spectrometry-based analytical workflow for sample preparation, comprehensive measurement, and subsequent bioinformatic analysis, is crucial as technological advancement at each step is very rapid. We will forward establishment of a next-generation analytical and computational platform based on proteomic big data-oriented drug discovery and disease diagnosis. For the electron microscopy facility, we consider that a novel device to automatically pick up ultrathin sections is needed for constantly applicable sample preparation. Based on the draft by Dr. Sagara's group, a prototype model is under development to be introduced in our facility within a few years.

Research Center for Asian Infectious Diseases

（１）Members

Professors	Yasushi Kawaguchi, Yoshihiro Kawaoka
Project Professor	Mitsue Hayashi
Project Associate Professors	Seiya Yamayoshi, Jin Gohda
Project Senior Assistant Professor	Mizuki Yamamoto
Assistant professors	Akihisa Kato, Naoto Koyanagi, Yuhei Maruzuru

（２）Research objectives

The Research Center for Asian Infectious Diseases, in addition to establishing and operating an overseas base in the People's Republic of China, the country that recorded the first cases of Severe Acute Respiratory Syndrome (SARS) and avian influenza, and facilitating in recent years numerous personnel interactions of great significance for advancing efforts to control infectious diseases in Japan, is currently conducting research on emerging and reemerging infectious diseases in collaboration with the Institute of Medical Science, the University of Tokyo. With the support of the Japan Agency for Medical Research and Development (AMED) the Center advanced its "China-Japan Research Collaboration on Defense against Emerging and Reemerging Infections" project from April 2016 to March 2019. In addition, in collaboration with the National Institute of Infectious Diseases, the Center conducted research projects targeting the Middle East Respiratory Syndrome (MERS) coronavirus strain, HIV-1, flavivirus, influenza virus, drug-resistant viruses, and infectious diarrhea virus, published the results in various papers (more than 20 reports per year), and obtained related patents. Through these Japan-China joint research activities, we will cultivate the next generation of infectious disease researchers and contribute to amicable relations between Japan and China.

（３）Activity Reports

１）Research activities

Through the support of the Ministry of Education, Culture, Sports, Science and Technology's (MEXT) "Program on Founding Research Centers for Emerging and Reemerging Infectious Diseases" as well as the "Japan Initiative for Global Research Network on Infectious Diseases" (J-GRID), the Research Center for Asian Infectious Diseases has established and currently operates laboratories at the Institutes of Biophysics and Microbiology at the Chinese Academy of Sciences in Beijing, China's most advanced research institution, in which Japanese researchers are assigned to permanent positions. This support has also allowed the Center to establish a joint research program with the Harbin Veterinary Institute of the Chinese Academy of Agricultural Sciences (CAAS). Additionally, from April 2016 to March 2019, the Center conducted in cooperation with

Japanese medical research institutes: ① basic and applied research on the control of envelope virus infection, ② research on dormant HIV-1 infections to develop curative treatment, ③ basic research and epidemiological studies on influenza virus, and ④ activities to establish a collection system for epidemiological information related to drug-resistant bacteria. The major achievements of these activities are detailed below.

① Basic and applied research on the control of envelope virus infection

A cell-based quantitative method capable of high-throughput screening of candidate inhibitors against MERS coronavirus, HIV-1, Dengue virus, and Zika virus not requiring use of infectious virus samples was established as a result of collaboration between the Institute of Biophysics at the Chinese Academy of Sciences in Beijing and Japanese institutions. In addition, Nafamostat was identified from a library of drugs for clinical use as a specific inhibitor of the MERS coronavirus, and various other agents acting to inhibit Dengue and Zika viral activity were also found. Nafamostat also strongly inhibited the fusion activity of SRAS-CoV-2, which is a causative virus of coronavirus disease 19 (COVID-19). Further, a parallel search of compound libraries yielded multiple agents capable of inhibiting the membrane fusion activity of HIV-1, MERS coronavirus, and Dengue virus.

② Research on dormant HIV-1 infections to develop curative treatment

At the Institute of Microbiology in Beijing, an HIV-1 dormant infection model cell line was established, after which two compounds each with the ability to reactivate dormant viral infections were identified. Three compounds able to act synergistically with existing reactivation inducers were also identified. These drug candidates are thought to be effective in inducing activation of dormant HIV-1 as part of a treatment strategy designed to cure HIV-1 infections known as “Shock and Kill”.

③ Basic research and epidemiological studies on influenza virus

Through its collaborative efforts with the China CDC, Taiwan CDC, and the National Institute of Infectious Diseases, the Center was able to produce monoclonal antibodies targeting H7N9 influenza virus isolated from humans in China and develop a rapid diagnostic kit for H7 subtype influenza virus in collaboration with CAAS-Harbin Veterinary Institute and Japanese facilities. In addition, between late-2016 and 2017, we obtained two strains of highly pathogenic H7N9 virus, which were transmitted to mammals through droplets, indicating that infections originating from exposure to even a small amount of virus can become severe, highlighting the need for caution. Our results also showed that a mutation in the H7N9 viral polymerase could enhance polymerase activity and contribute to pathogenicity.

The H5N1 virus was determined to be enzootic in Indonesia in 2016, whereas the H7N9 virus was not isolated. Three of nine isolates of the H5N1 virus that was enzootic in Egypt from 2014

to 2015 transmitted via respiratory droplets in ferrets with one fatality. No droplet transmission was observed during three follow-up experiments. Nonetheless, our data suggest that these viruses have pandemic potential.

To date, a database maintained by Hokkaido University has catalogued 4 highly pathogenic strains of H5N1 avian influenza virus isolated from Vietnamese birds, 9 highly pathogenic H5N1 avian influenza strains isolated from Egyptian birds between 2014 and 2015, and 6 strains of seasonal influenza virus isolated from Japanese patients (3 hCK cell isolates, MDCK cell isolates, and AX4 cell isolates). This not only enables comparisons with virus strains isolated in other countries, but also allows for sharing of information on nucleotide sequence mutations that differ for each cell line used for virus isolation; it is therefore expected to be useful for future epidemiological research.

④ Establishment of a collection system for epidemiological information related to drug-resistant bacteria

With the participation of researchers from the Department of Bacteriology II and Antimicrobial Resistance Research Center of the National Institute of Infectious Diseases, the Center conducted a survey to gather epidemiological information concerning drug-resistant bacteria in China. In China, the National Health and Family Planning Commission (equivalent to Japan's Ministry of Health, Labour and Welfare) operates the China Antimicrobial Resistance Surveillance System (CARSS) which monitors over 1,000 hospitals, and maintains oversight over the management of this system by researchers at Peking University. We exchanged information with these researchers and conducted a comparative study with Japan. As a result, it was determined that the rate of development of drug resistance in many bacterial species tends to be higher in China compared to Japan. Moreover, with particular regard to the issue of nosocomial infections caused by *K. pneumoniae*, although in Japan this species has a <1% rate of resistance to carbapenem, the current "trump card" of antibiotic drugs, the rate has been rapidly rising in China in recent years. In a 2018 study examining bacteria isolated from target hospitals, 10.1% of all samples were resistant, and 21.9% of samples taken from ICUs were resistant.. Although it can be said that the prevalence of drug-resistant bacteria in Japan at present is relatively low, there is a high possibility that these resistant strains could spread to Japan via importation. Accordingly, continued surveillance and care as well as taking sufficient precautions is believed to be necessary.

The above research results were published in various journals (29 reports in 2016, 23 reports in 2017, 31 reports in 2018, 28 reports in 2019), patent applications were filed (2 claims in 2016, 3 claims in 2019), and we believe overall that the Center has been successful in achieving its goals related to information dissemination and acquisition of intellectual property.

２） Education Activities

Our staff actively contribute to activities to educate young people interested in infectious disease research by giving regular laboratory tours (1 in 2016, 1 in 2017, 1 in 2018, 2 in 2019) and lectures geared towards high school students and teachers (2 in 2016, 2 in 2017, 1 in 2018, 1 in 2019).

３） Social Activities

Our staff have contributed to initiatives to raise awareness of infectious disease activities by giving public talks at various venues in Japan (1 in 2016, 1 in 2018, 2 in 2019) as well as presentations at the Japanese Embassy in China (2 in 2017).

４） International Activities

In addition to the above collaborative research activities, the IMSUT-CAS Workshops on Infectious Diseases was held at the Institute of Biophysics at the Chinese Academy of Sciences on April 17, 2017, at the Institute of Medical Science, the University of Tokyo on October 9, 2018 and at the Institute of Microbiology Chinese Academy of Sciences on December 17, 2019. These events served as a platform for presentation of the latest research results as well as constructive interaction between researchers in Japan and China.

５） Other matters to be noted

We are continuing our efforts to nurture young Chinese researchers in the field of infectious diseases by locally hiring a total of 9 dispatch researchers, with 2-3 people at each of the Japan-China collaborative laboratories at our Beijing bases (Institutes of Biophysics and Microbiology). We continue to cultivate the next generation of researchers at Japanese sites as well, and during this period two specially-appointed professors were promoted to succeeding Assistant Professors, we have had three postdoctoral students dispatched overseas, one Special Assistant Professor was promoted to Special Associate Professor, and two staff members accepted more senior positions at other institutions.

（４） Challenges and Future prospects

With the recent revisions to Chinese Japanese laws, it has become more difficult for foreign nationals to obtain epidemiological information as a result of protections placed on genetic and epidemiological information related to pathogens. In order to facilitate epidemiological research in China in the future, we will further strengthen our cooperative initiatives with infectious disease specialists and epidemiological researchers in China. Supporting the development of the next generation of human resources in China through programs such as those supporting students in Beijing

has been difficult based on research funded by AMED alone. To solve this problem, we will utilize the international joint use and joint research center program launched in fiscal 2019, invite human resources including students from China to Japan, and promote joint research activities in infectious diseases and other fields.

In addition to frequent interactions between Japan and China-based researchers, the Center regularly holds a Japan-China steering committee meeting each year through our Beijing office to review the operation of our China base as well as maintain productive and amicable relations with the relevant research institutes and our two countries. In the future, we plan to continue to encourage young researchers to participate in this project as we work to cultivate the next generation of researchers.

Laboratory of Molecular Genetics (-FY2016)

（１）Members

Professor	Izumu Saito
Assistant Professor	Saki Kondo
Assistant Professor	Tomoko Nakanishi
Postdocs	1
Graduate students	1
Technicians	2
Others	3

（２）Research objectives

The research aims of our laboratory are to develop adenovirus vectors and provide powerful tools for biomedical research including gene therapy, to promote pathophysiological research on hepatitis B virus, and to support gene-recombination experiments and biohazard experiments in IMSUT as a consultation counter.

（３）Activity Reports

１）Research Activities

In this laboratory, we developed useful adenoviral vectors and support biomedical research both within and outside Japan under at least five collaboration s in a year. The results have been published in several peer reviewed international journals. In 2016, we developed a novel single-type adenoviral vector with which more than two independent shRNAs are simultaneously and effectively expressed. This vector could be utilized in a therapy for hepatitis B virus. Hepatitis B virus genome contains both pregenomic RNA and covalently-closed circular DNA. Using an above adenoviral vector, we could reduce the level of pregenomic RNA in an infected liver through simultaneous expression of three distinct shRNAs for the hepatitis B genome. However, the reduction of covalently-closed circular DNA was not apparent. In future, we will try to overcome this problem.

In order to eradicate hepatitis B, the hepatitis B genome has to be completely destroyed. In this respect, CRISPR-Cas9 genome editing technology can digest and destroy the intrinsic hepatitis B genome. However, constitutive expression of Cas9 might undergo a harmful consequence through off-target digestion of the host genome. Therefore, its transient expression or activation is desired. For this purpose, in 2016, we developed an adenoviral system with a circular DNA in which the expression of Cas6 could be regulated by Cre recombinase.

These research achievements had been published in 3 peer reviewed international journals and

thus we believe that we achieved our research missions. In addition, we collaborated with more than ten research subjects in a year.

２）Education Activities

In 2016, one PhD student received their PhD from Graduate School of Medicine, University of Tokyo.

３）Social Activities

Many of the adenoviral vectors we developed have been supplied to many laboratories within and outside Japan and have led to substantial contribution to advances in medical sciences as well as other basic biology.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

Expanding our research by integrating all members in our laboratory as well as materials, equipments, and technologies.

Laboratory of Molecular Genetics (Frontier Research Unit)

（１）Members

Acting Director, Professor	Yuji Yamanashi
Associate Professor	Kazuo Tatebayashi

（２）Research objectives

The aim of this unit is to address how cells appropriately respond to various environmental stresses such as high osmolarity. Our research focuses on the stress-sensing mechanisms as well as the regulatory mechanisms of stress-activated MAP kinase (MAPK) signaling pathways. Our final goal is to understand the molecular bases of cellular stress responses, for developing the technology to confer environmental stress resistance to animals and plants to survive in severe environmental conditions caused by global warming, and also for developing methods of treating human diseases such as cancer and autoimmune diseases caused by dysregulation of the stress response machinery.

（３）Activity Reports

１）Research Activities

Since 2017, this unit has conducted researches to elucidate the mechanisms of how cells respond appropriately to extracellular stress stimuli including high-osmolarity stress using budding yeast with cell biological, biochemical, and molecular genetic approaches. We have focused on two issues of the osmoregulatory Hog1 MAPK pathway of *Saccharomyces cerevisiae*: 1) the sensing mechanism of high osmolarity by osmo-sensors, 2) the regulatory mechanisms of intracellular signaling. Our research achievements of these three years are as follows. First, we identified the interaction sites of the transmembrane osmo-sensors Sho1 and Opy2 in the Hog1 MAPK pathway by biochemical and genetic analyses, and found that the interaction between the transmembrane domains of Sho1 and Opy2 enhances the signaling efficiency of the Hog1 MAPK cascade. This study was published in PLOS ONE (Takayama et al. 2019). Next, we found that osmostress enhances activating phosphorylation of Hog1 MAP kinase by mono-phosphorylated Pbs2 MAP2K. The lack of the osmotic enhancement of the Pbs2-Hog1 reaction suppresses Hog1 activation by basal MAP3K activities and prevents pheromone-to-Hog1 crosstalk in the absence of osmostress. This study was published in The EMBO Journal with an impact factor of 11.2 (Tatebayashi et al 2020). These findings highly contributed to our research goal: the understanding of the full picture of how cells appropriately respond to environmental stresses.

The unit member got research funding from JSPS Grants-in-Aid for Scientific Research (B) (2016-2019), The Salt Science Research Foundation (2017), and the Japan Foundation for Applied Enzymology (2017).

The unit member organized a symposium at Annual meeting of the Japanese Biochemical Society in 2019, and presented the achievements at the symposiums (Annual meeting of the Japanese Biochemical Society (2019), Kyushu Regional Meeting of the Japan Transporter Research Association (2019)). These activities contributed to the academic societies.

Based on the research accomplishments described above, the goal of this unit has been largely achieved.

２）Education Activities

The aim of this unit for education is to train talented personnel who will play active roles as future leaders in the field of life sciences. The unit member contributed to the education of graduate students at the graduate school of Science, the University of Tokyo by giving the lectures of molecular and cellular biology (especially on cellular stress response and signal transduction), and also by serving as a member of the evaluation committees for the assessment of PhD or MA theses and dissertations every year. In addition, the unit member has been engaged in health and safety education for the students of this institute as a manager of the health and safety office.

３）Social Activities

None.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

Our recent research contributed to an understanding of the mechanisms for cellular adaptation to environmental stresses. Especially, the newly discovered regulatory mechanism of the MAP kinase pathway will be useful in human diseases, because many are caused by excessive or deficient activities of MAP kinase pathways. Therefore, we can anticipate development of treatments and therapeutics for human diseases such as cancer and autoimmune diseases in the future. To achieve this goal, it will be necessary to promote interdisciplinary collaborations for application of our findings to biomedical area.

IMSUT Hospital

Director Keiya Ozawa (-FY2017)
Director Arinobu Tojo (FY2018-)

（１）Missions and Features

IMSUT Hospital is the only one hospital affiliated with a national university research institute in Japan and has 122 beds including a unique ward organized for translational research and early clinical trials such as a F-I-M study, an outpatient clinic, and operating rooms. Currently, IMSUT Hospital focuses diseases such as hematological malignancies, solid tumors, infectious diseases, and autoimmune disorders and is conducting research on their pathophysiology and promoting translational research (TR), such as gene, viral, and cell therapy of cancers as well as novel vaccine treatment. IMSUT Hospital aims to be a core facility for clinical application of excellent outcomes by domestic and international collaborative research, especially in close association with Advanced Clinical Research Center and other centers/departments in IMSUT. IMSUT hospital is still setting up its infrastructure for better clinical practice.

（２） Organization

Medical Care Unit
- Department of Hematology/Oncology
- Department of Infectious Diseases and Applied Immunology
- Department of Rheumatology and Allergy
- Department of General Medicine
- Department of Applied Genomics
- Department of Radiology
- Department of Palliative Medicine
- Department of Diagnostic Pathology
- Department of Surgery
- Department of Anesthesia
- Department of Joint Surgery
- Department of Surgical Neuro-Oncology

Care Support Unit
- Department of Medical Informatics
- Department of Radiological Technology
- Department of Cell Processing and Transfusion
- Surgical Center

Department of Medical Supply Center
Department of Laboratory Medicine
Department of Pathology
Department of Clinical Genomics
Department of Clinical Nutrition
Radiation Control Office
Regional Medical Liaison Office
Clinical Safety and Infection Control Unit
Center for Clinical Safety and Infection Control
Clinical Research Support Unit
Center for Translational Research
Center for Antibody and Vaccine Therapy
Therapeutic Vector Development Center
IMSUT CORD
Department of Nursing
Department of Pharmacy
Department of AIDS Vaccine Development

（3）Activity Reports

1）Medical Activities

Medical activities in FY 2016 - 2018 has remained lower compared to preceding years mainly due to gradual decrease in the number of inpatients. Actually, over the past three years, inpatient occupancy rates have revealed a worsening trend, as shown in the table below. This trend is mainly attributed to temporary closure of one ward for renovation and human factors including lack of young resident doctors and retirement of experienced doctors.

	2016	2017	2018
Average daily number of inpatients	62.5	52.0	46.2
Average daily number of outpatients	114.4	98.9	98.5
Average length of hospital stay	11.4	11.1	11.7
%Ratio of nursing needs	41.6	43.7	39.9
%Ratio of medical care	66.2	68.6	72.1

2）Research Activities

Five distinct physician-initiated or company-based early clinical trials including herpes virus therapy of brain tumors, peptide vaccine therapy against solid tumors, and rice-based oral cholera vaccine were conducted in 2016. Clinical study of viral therapy of mesothelioma were approved by

IRB in 2017. Two physician-initiated clinical trials, WT1-expressing artificial adjuvant vector cell (aAVC-WT1) therapy for AML and cord-derived MSC therapy for refractory GVHD were started, and a physician-initiated clinical trial for melanoma using another recombinant herpes virus was approved by IRB in 2018.

３）Education Activities

Since there are no undergraduate students and few residents in IMSUT Hospital, educational activities for physician are very limited. However, we have over 15 years' experiences of hospital internship program for non-MD master's and doctoral students (Graduate School of Frontier Sciences) and undergraduate students of Bunkyo University. This program is designed to provide students with lessons on ethical considerations and practical training in translational research. More than 50 people participate in the curriculum every year. There appears a favorable impact on their reaffirmation of the dignity of life, motivation for medical research, and post-graduate career selection.

４）Social Activities

Based on a partnership agreement with Minato City, we bimonthly hold an open medical seminar for citizens, which provide useful medical information to help them stay healthy and prevent diseases. Around one hundred people attend each seminar from inside and outside of Minato City, and the total number of participants in 2016 was 522, 384 in 2017 and 566 in 2018.

５）International Activities

None.

６）Other matters to be noted

In order to realize genomic medicine, we are promoting clinical research termed as AI medicine in which artificial intelligence (AI) is applied to interpret enormous data from NGS analysis of cancer genome and to find therapeutic options deduced from driver mutations. Our trial for AI medicine was introduced by various media including newspapers and TV program with a significant impact.

（４）Challenges and future prospects

Within FY2018, the 5th floor ward was restarted after renovation. This ward is specified to be used for translational research and early clinical trials, and also to accept VIP and patients from overseas for medical check-up and/or care. Therefore, this ward is mainly consisted of private rooms and equipped with ICU-mimetic rooms. To revitalize outpatient clinic, second opinion clinic and travel

clinic with vaccination were open in 2017 and 2018, respectively. Furthermore, the main laboratory room was relocated to B1F of the Building 1 East and simultaneously, several laboratory testing machines were updated in 2018.

In order to recruit young doctors, we made partnership agreements between more than 10 general hospitals and at the same time, we are making efforts to appeal our unique training program via our website and other media. In 2019, we plan to expand both rehabilitation room and outpatient chemotherapy unit.

Department of Hematology/ Oncology

（１）Members

Professor	Arinobu Tojo
Associate Professors	Yoichi Imai, Satoshi Takahashi, Tokiko Nagamura-Inoue
Project Associate Professor	Hiroshi Yasui
Assistant Professors	Tomohusa Fukuyama, Seiko Kato, Takaaki Konuma, Toyotaka Kawamata, Kazuaki Yokoyama, Aki Sato, Muneyoshi Futami, Masamichi Isobe

（２）Research objectives

We are challenging to cure intractable hematological disorders such as leukemia and lymphoma with the aid of hematopoietic stem cell transplantation (HSCT). Our major stem cell source for recipients without suitable family donors is unrelated cord blood, with which no less than 20 adult patients receive cord blood transplantation (CBT) annually. Since 1998, we have performed around 360 cases of CBT, which appears a distinguished experience in the world. Recent advances in identification of tumor-specific therapeutic targets resulted in a series of rationally designed therapeutic agents. In the field of hematological malignancies, we have already experienced remarkable clinical efficacies of molecular targeted drugs including tyrosine kinase inhibitors for Philadelphia-chromosome positive leukemia, monoclonal antibodies (MAb) for $CD20^+$ B cell lymphoma and $CCR4^+$ adult T cell leukemia/lymphoma (ATL), and proteasome inhibitors, immunomodulatory drugs for multiple myeloma (MM), respectively. Additionally, novel therapeutic modalities including anti-CD319 and anti-CD38 MAb are available for MM. We extensively apply these molecular targeted therapies for in- and out-patients. Furthermore, our department is one of the hub facilities in Japan for clinical practice and clinical research in ATL and Langerhans cell histiocytosis (LCH), both of which are rare and intractable tumors.

（３）Activity reports

１）Medical Activities

Outpatient clinic is staffed by physicians above the rank of assistant professor on weekdays. The annual number of new patients has been varying around 120, most of which are those with leukemia, lymphoma, and myeloma. Hospitalized patients in our department are mainly held in a clean ward on the seventh floor of the hospital building, which include an average of 20-25 patients per day. Since the mid 1980s, our department has been a core facility of allogeneic stem cell transplantation

(SCT) in Japan, and in recent years, we have performed around 25 allogeneic SCT per year. More than 90% of stem cell source are unrelated cord blood, and their clinical outcomes are among the best in the world. Our unique projects of clinical practice include specialized outpatient clinic for patients with HTLV-1 infection/adult T cell leukemia (ATL) as well as patients with adult Langerhans cell histiocytosis (LCH). We are also conducting a number of physician-initiative or company-based early clinical trials, which include various types of cell therapies using mesenchymal stem cells (MSC) for therapy-resistant GVHD, WT1-expressing artificial antigen-presenting cells (aAVC-WT1) for relapsed/refractory AML, and CD19-targeted CAR-T cells for intractable B-ALL.

２）Research Activities

We have been conducting two types of physician-initiated phase I clinical trials; (1) aAVC-WT1 therapy for relapsed/refractory AML (started in 2017) and (2) cord-derived (MSC) therapy for steroid-resistant acute GVHD (started in 2018). In addition, many peer-reviewed articles were published according to well-organized clinical database for allogeneic cord blood transplantation (CBT). In the field of HTLV-1 infection and ATL, we developed a HAS-Flow method to analyze dynamics and malignant progression of HTLV-1-infected cells by flow cytometry. Moreover, we are promoting AI-guided precision medicine approach to hematological malignancies through clinical sequencing of patients' samples and actually analyzed about 180 cases between 2015 and 2018. We have also demonstrated the significance of circulating tumor DNA (liquid biopsy) in clinical outcome after allogeneic SCT in AML/MDS. We published a number of peer-reviewed original articles every year; 2 papers in FY2016, 8 in FY2017, and 10 in FY2018.

３）Education Activities

In clinical departments, education and instruction to residents is achieved as On-the-Job-Training (OJT). We supervised 4 senior residents in 2016, 3 in 2017, and 2 in 2018 according to the clinical hematology program. All these residents were qualified to be board certified hematologists of Japanese Society Hematology (JSH).

４）Social Activities

Several physicians in our department regularly cope with consultations and/or give a lecture at patient meetings.

５）International Activities

None.

６）Other matters to be noted

In order to realize genomic medicine, we are promoting clinical research termed as AI medicine in which artificial intelligence (AI) is applied to interpret enormous data from NGS analysis of cancer genome and to find therapeutic options deduced from driver mutations. Our trial for AI medicine was introduced by various media including newspapers and TV program with a significant impact.

（４）Challenges and future prospects

Human resources are important in the field of clinical hematology, especially in SCT. Since IMSUT hospital is small-sized and has a limited number of departments, junior residents have been not available so far, and we cannot accept senior residents under the novel specialist system which started in 2018. Lack of young physicians is a critical obstacle to maintain clinical activity. We need iminent personnel exchange through inter-hospital network.

Department of Infectious Diseases and Applied Immunology

（１）Members

Professor	Hiroshi Yotsuyanagi
Associate Professor	Takeya Tsutsumi
Assistant Professors	Eisuke Adachi, Michiko Koga, Makoto Saito
Technicians	2
Others	5

（２）Research objectives

- We will carry out clinical research while inheriting and developing the tradition of HIV treatment / international infectious disease treatment, which is our tradition.
- A travel outpatient department is opened to facilitate medical care for international infectious diseases.
- We will develop an environment for conducting research, including translational research, in cooperation with researchers within the institute.
- We will actively provide hepatitis virus treatment in cooperation with general medical departments.

（３）Activity Reports

１）Medical Activities

- HIV medical care

  IMSUT hospital, the Institute of Medical Science is a medical institution with the longest history of HIV treatment in Japan and is closely related to the AIDS Research center, National Center for Global Health and Medical Research. (1) Observing the long-term progress of infected people by making use of this characteristic, (2) constructing a database, making necessary ethical applications, preparing research seeds, and (3) actively reporting cases. The target was set when the classroom was established (July 2016).
- Regarding (1), most patients continue to visit our hospital, and there are 20-30 new visits annually, achieving the target.
- Regarding (2), the target has been achieved.
- Regarding (3), we were able to prepare four case reports. I was also able to report a paper on the construction of a Care Cascade for HIV-infected persons, which has been ongoing since my predecessor.
- International infectious disease medical care
  - The outpatient clinic started in May 2018 with the full cooperation of hospital staff. We also

prepared imported vaccines and prepared a system to deal with consultations before traveling abroad and health problems after traveling abroad. Currently, there are 30-40 medical examinations per month. In the future, we are considering improving the research system in addition to the summary of medical records.

- Medical care for viral hepatitis
  - While taking over the patient who was being treated in the general medical department, he is actively accepting patients from other medical institutions. Consideration is being given to medical treatment so that patients can continue to go to the hospital, and it has been doing well so far.

２）Research activity

Wet research is carried out in the field of infectious diseases, and research in the field of infectious immunology aims to report the experience in cases as described above and link it to further research. As described above, four case reports have been made. Of these, cases of HIV/HBV co-infection have led to current research in the field of infectious diseases.

３）Education Activities

Every year, about 2 early trainees and 2 late trainees are accepted.

In May 2018, we held a May festival emergency plan for university students-to protect young people from sexually transmitted diseases-and provided information and discussion centered on the outbreak of syphilis infection.

４）Social Activities

None.

５）International Activities

None.

６）Other matters to be noted

As activities of the Department of Internal Medicine for Infectious Immunology, we held public lectures, a social gathering for medical cooperation, and a medical seminar at the Institute of Medical Research, the University of Tokyo Hospital, to raise awareness about overseas travel. We also opened a travel outpatient department.

（４）Challenges and prospects

For the two and a half years until March 2019, the emphasis was placed on the establishment of a

travel outpatient facility that also served as a hospital. I am thinking that the outpatient will go on track and carry out research based on the outpatient.

Department of Rheumatology and Allergy

（１）Members

Professor	Hirotoshi Tanaka
Project Associate Professor	Motohisa Yamamoto
Senior Assistant Professor	Noritada Yoshikawa
Assistant Professor	Hiroki Yamazaki
Postdocs	1
Others	3

（２）Research objectives

Our department is founded in 2001 to tackle systemic autoimmune inflammatory diseases including rheumatoid arthritis, systemic lupus erythematosus, vasculitic syndromes and IgG4-related disease. We provide patients personalized and evidence-based medical service. Moreover, we challenge cutting edge science of autoimmune, rheumatic and allergic diseases and novel treatments for patients with these disorders.

Our specific aims are

- Developing a novel therapy preventing glucocorticoid-induced muscle atrophy in patients with rheumatic diseases
- Developing a novel therapy to improve abnormal fat distribution in patients taking GC therapy
- Development of novel therapeutic modalities against metabolic syndrome targeting the skeletal muscle-liver-fat signalling axis
- Clarification of functional crosstalk between GR and sex hormone receptors for body composition and metabolic regulation
- Clarification of the effect of ageing for regulation of energy storage in skeletal muscle and adipose tissues
- Translational Research and Clinical Trial of Division of Rheumatology

（３）Activity reports

１）Medical Activities

We vigorously conducted patient management at outpatient clinic (4 days per week) and ward (over 100 patients).

Rheumatologic services offered at IMSUT Hospital include:

- Outpatient consultations
- Outpatient specialty care for patients with chronic rheumatic diseases
- Hospital consultations

- Diagnostic and therapeutic intra-articular and soft tissue injections and aspirations
- Diagnostic ultrasonography
- Education on rheumatologic diseases and treatments
- Clinical trials

２）Research Activities

We published 9 original research papers in peer-review journals, and reported 39 research papers in various academic meetings from 2017 to 2018.

３）Education Activities

We took charge of 4 lectures for graduate students every year.

４）Social Activities

We published 7 review articles in Japanese medical journals from 2017 to 2018. We performed one collaboration with Japanese pharmaceutical company (3-year contruct).

５）International Activities

We are promoting international collaborative research for IgG4-relared disease with Wuhan University Medical Center in China.

６）Other matters to be noted

None.

（４）Challenges and future prospects

We will develop novel therapeutic approach for intractable diseases in the field of rheumatology and allergy. Currently, we are heavily involved in clinical research for IgG4-related disease and rheumatoid arthritis. Moreover, we, through our longstanding basic research, are working to renovate glucocorticoid therapy.

Department of General Medicine

（１）Members

Professor	Hiroshi Yotsuyanagi
Project Professors	Kenzaburo Tani, Takayuki Morisaki
Associate Professors	Takeya Tsutsumi, Yoshihiro Hirata
Senior Assistant Professor	Yasuo Matsubara
Project Senior Assistant Professor	Yasuki Hijikata
Project Assistant Professor	Koichi Kimura

（２）Research objectives

- Perform general medical examinations for gastrointestinal disorders, including endoscopy for general consumers. The target number of endoscopic examinations by the local government is 150 cases a year, and the number of new cases including referrals for outpatients of *Helicobacter pylori* is 40 cases a year.
- In addition to standard treatment for patients with solid tumors, advanced treatment is performed in collaboration with various departments within the institute.
- Provide medical treatment as one of the centers for diseases such as Marfan syndrome and muscular dystrophy.
- Actively provide viral hepatitis treatment in collaboration with Department of Infectious Disease and Applied Immunology.

（３）Activity reports

１）Medical Activities

- Medical treatment of digestive diseases

Helicobacter infection is one of the main targets of medical treatment for digestive organs. Regarding gastrointestinal tract diseases in our hospital, inflammatory bowel disease is more common than other medical institutions. Department of general medicine focuses on the treatment of these diseases. The number of endoscopic examinations in the upper digestive tract is 60 to 70 per month, and the number is increasing gradually. Considering the number of hospital beds, the number is quite large.

- Treatment of solid tumors

We accept patients who are considered to have only Best Supportive Care at other medical institutions, and offer the possibility of treatment based on histopathological findings and gene analysis. Some patients are receiving treatment out of insurance coverage.

- Cardiovascular disease medical treatment

In addition to supporting cardiovascular medical treatment for patients who are hospitalized, we also provide medical treatment support for rare disease patients from all over the country.

２）Research Activities

Taking advantage of the characteristics that rare diseases are often dealt with, a summary of the pathophysiology and clinical aspects of various diseases, genetic analysis and biomarker search are being conducted.

３）Education Activities

None.

４）Social Activities

None.

５）International Activities

None.

６）Other matters to be noted

We deal with rare diseases, and conducted awareness-raising activities through a public medical conference on tumors.

（４）Challenges and future prospects

We deal with rare diseases, and cooperation with other facilities is important, and it is necessary to improve the system.

Department of Applied Genomics

（１）Members

Professor	Yoichi Furukawa
Associate Professor	Tsuneo Ikenoue
Technicians	1
Others	1

（２）Research objectives

Our department has been working on the application of human genome information in clinics. As a clinical service, we provide genetic counseling, genetic tests for human malignancies such as leukemia and cancer, and a surveillance program for patients with hereditary colorectal cancer. In addition, we have been carrying out two research projects; 1) determination of genetic alterations in human tumors, and elucidation of the mechanisms underlying their development, and 2) clinical sequence for the implementation of genomic medicine

（３）Activity reports

１）Medical Activities

As a part of clinical service, we have been performing genetic analysis of human neoplasms such as leukemia and colorectal cancer. In 2019, a total of 539 genetic analyses were performed in our department. The results were utilized for the precise classification of neoplasms, evaluation of disease status, selection of therapeutic drugs, and evaluation of the response to treatment.

Additionally, we provided genetic counseling and genetic tests to clients who visited our counseling clinic. In 2019, we had a total of 42 counseling cases including hereditary breast and ovarian cancer, familial adenomatous polyposis, Lynch syndrome, Li-Fraumeni syndrome, tuberous sclerosis, adrenoleukodystrophy, hemophilia A, spinal and bulbar muscular atrophy, spinocerebellar degeneration, Huntington’s disease, developmental disorders, and achondroplasia. In the counseling, we provided appropriate information about hereditary diseases and took psychological care of the clients in collaboration with a clinical psychologist. Genetic testing was performed in five cases with informed consent after thoughtful discussion about its merit and demerit.

Systematic surveillance programs are provided for the clients susceptible for hereditary tumors. Patients with familial polyposis visited our hospital to undergo clinical checkup and endoscopic colonoscopy.

２）Research Activities

For the implementation of precision medicine for patients with rare or intractable cancer, we have

carried out whole exome sequencing/whole genome sequencing of cancer genome and analyzed the sequencing data using IBM Watson for Genomics (WfG). Patients with colorectal, breast, uterine, gallbladder, pancreatic cancer, lymphoma, prostate cancer, liposarcoma, glioblastoma, and hepatoblastoma were enrolled in the study after written informed consent was obtained. WfG selected driver mutations from the somatic mutations in the tumors and suggested actionable drugs. These data were discussed in the Tumor Board meetings every two weeks.

３）Education Activities

As a training hospital authorized by Japanese Board of Medical Genomics and Clinical Genetics, we provide a practice and seminars course of genetic counseling in the hospital. In 2019, six medical doctors participated in this course.

４）Social Activities

None.

５）International Activities

None.

６）Other matters to be noted

None.

（４）Challenges and future prospects

To develop better medical service, we would like to promote the precision medicine project in collaboration with clinical departments in our hospital and other domestic hospitals.

Department of Radiology

（1）Members

Director/Associate Professor	Akira Kunimatsu
Senior Assistant Professor	Hiroyuki Akai
Assistant Professor	Koichiro Yasaka

（2）Research objectives

- To hold the eligibility to claim the reimbursement for managing the quality of diagnostic imaging
- To publish three articles in international journals every year

（3）Activity reports

1） Medical Activities

Our department offers a radiology service at the IMSUT hospital. We conduct radiological examinations and report the results of the exams. Computed tomography (CT), magnetic resonance imaging (MRI), and radioisotope scans are available at our department. We made 9,480 reports from 2016 to 2018. The local bureau of health and welfare has authorized the high quality of our service.

2）Research Activities

Using CT and MRI, we sought novel imaging findings of disease and performed statistical machine learning on imaging features. We also performed basic research using mouse models on a small animal MRI and reported the pharmacokinetics of MRI contrast agents. From 2016 to 2018, we published 52 articles in international peer-reviewed journals.

3）Educationl Activities

Medical school: a lecture for the radiology section of systematic lectures in medicine (A.K.)

Post-graduate: a lecture for clinical radiology in the master course in bioscience (A.K.), a hospital visit program (H.A.)

The residency program at the IMSUT hospital: short clinical lectures in diagnostic imaging (A.K. and H.A.)

4）Social Activities

None.

5）International Activities

None.

６） Other matters to be noted

We would be honored to accept requests for radiological examinations from family medicine doctors in the neighborhood. More than 300 patients visited our department from 2016 to 2018.

（４） Challenges and future prospects

- Medical image analyses using statistical machine learning
- Basic research using the small animal MRI
- A rise in profit for radiology service through business cooperation with the University of Tokyo Hospital

Department of Palliative Medicine

（1）Members

Professor	Arinobu Tojo
Project Senior Assistant Professor	Yasumoto Hijikata
Others	2

（2）Research objectives

The Department of Palliative Medicine is committed to providing evidence-based treatment, and research to create evidence for palliative medicine with multidisciplinary collaboration. Through domestic and international activities, we promote palliative medicine.

（3）Activity reports

1）Medical Activities

Consultation activities: (1st Apr.2017-31st May 2019): 728cases (33 patients)

2）Research Activities

Aug 2018 Shimada, Fujiwara	Comprehensive exploration of monoclonal autoantibodies against tumor cells from lymphocytes of cancer patients
June 2017 Shimada, Fujiwara	Exploratory research on determinants of place of death by a large scale of cohort study: the JPHC study
July 2018 Shimada, Fujiwara	Development of precision palliative medicine based on genetic polymorphisms
2018 Fujiwara	Association between the degree of supporting patients' decision-making and nurses' perception of the degree of importance of their role in supporting patients' decision-making of whether to participate in cancer clinical trials
2018 Fujiwara	A prospective observational study to evaluate the effect of rehabilitation for cancer patients in palliative care units in Japan: a pilot-feasibility study
2018 Fujiwara	The efficacy of specialized rehabilitation using the Op-reha Guide for cancer patients in palliative care units: protocol of a multicenter, randomized controlled trial
2018-2020 Fujiwara	Development of a practice guide to support clinical nurses in patient decision-making in cancer clinical trials.

【Publications】

1. Ishiki H, Kinkawa J, Watanabe A, Watanabe C, Chiba T, Yasui H, Shimada N, Ariyoshi K, Nojima M, Iwase S, Tojo A, Imai K. Prevalence of myofascial pain syndrome in patients with incurable cancer. ***J. Bodyw Mov Ther***. 22(2):328-32, **2018**
2. Shimada N, Ohno N, Tanosaki R, Yuji K, Uchimaru K, Tojo A. Therapy-related acute myeloid leukemia after the long-term administration of low-dose etoposide for chronic-type adult T-cell leukemia/lymphoma: A case report and literature review. ***Intern Med.*** 56(14):1879-84, **2017**
3. Shimada N, Ishiki H, Iwase S, Chiba T, Fujiwara N, Watanabe A, Kinkawa J, Nojima M, Tojo A, Imai K. Cancer transitional care for terminally ill cancer patients can reduce the number of emergency admissions and emergency department visits. ***Am J Hosp Palliat Care***. 34:831-7, **2017**
4. Noriko F, Ryota O, Yuki S, Yuko S, Fumitaka N, Satoru I, Keiko K, Qualitative analysis of clinical research coordinators' role in phase I cancer clinical trials. ***Contemporary Clin Trials Commun.*** 8 :156–61, **2017**
5. Iwase, S Ishiki H, Watanabe A, Shimada N, Chiba T, Kinkawa J, Tojo A. Mapisal versus urea cream as prophylaxis for capecitabine-associated hand-foot syndrome. ***J Clin Oncol***, 34(4):391, **2016**

【Invited speaker】

1. Fujiwara.N. Palliative Care; Japanese experience, 17th Binenial meeting of the International Gynecologic cancer Society. Kyoto, Japan Nov14-16.2018
2. Fujiwara.N.UK study visit;Manchester. Panel Discussion: International Research Exchange-Perspectives from a UK Study Visit Experience.10th Annual meeting of International Association of clinical research Nurses. 2018.10.16. Arlington, VA, USA
3. Fujiwara.N.. Belinda Fazekas. The Clinical Trial Life Cycle. Australia-Japan Palliative Care Trials Project, 20171119, Tokyo, Japan
4. Fujiwara.N.. What is Clinical Research Nursing? Australia-Japan Palliative Care Trials Project, 20171119, Tokyo, Japan
5. Fujiwara.N. Research Ethics and Good Clinical Practice, at The Global Academic Program conference at the university of Texas, MD Anderson Cancer Center.May.9.2017, Houston, TX, USA

3） Education Activities

Shimada Fujiwara	Lecture for Graduate students of Graduate School of Frontier Sciences, The University of Tokyo.

Fujiwara	Lecture for nurses regarding narcotic and psychotropic drugs Supervise for research nurse working group Supervise for nurses to conduct research A part‐time instructor: Kawasaki University of Medical Welfare, Okayama, Japan A part‐time instructor: Tokyo Medical and Dental University, Tokyo, Japan

４）Social Activities

Collaboration with UI KEA MINATO in Minato-city, Tokyo, Japan

５）International Activities

Collaboration with Palliative Care Clinical Studies Collaborative (Australia research group) to held research forum, Tokyo, Japan

６）Other matters to be noted

None.

（４）Challenges and future prospects

While continuing international collaboration and research, treatment, and education activities with a multidisciplinary team approach, we will promote cooperation between the University of Tokyo Hospital and the IMSUT Hospital, to provide palliative care for patients with terminal cancer.

Department of Diagnostic Pathology/Department of Pathology

（１）Members

Project Associate Professor	Yasunori Ota
Clinical Laboratory Technologist	Yukihisa Tanaka
Others	1

（２）Research objectives

To publish 10 articles in English scientific journals every year to report study findings of our department.

To “improve quality” of diagnosis. To prepare “beautiful” specimens.

To write reports that clinicians can understand easily.

To develop diagnosis into research. To acquire new technologies and apply them to diagnosis.

To develop medical doctor and technicians who will become leaders of the next generation.

（３）Activity reports

１）Medical Activities

In 2016, 1,594 cases of histological examination, 216 cases of cytology, 14 cases of autopsy, and 12 cases treated in the Pathology Core Laboratory

In 2017, 1,493 cases of histological examination, 200 cases of cytology, 4 cases of intra-operative histology, 2 cases of intra-operative cytology, 11 cases of autopsy, and 16 cases treated in the Pathology Core Laboratory

In 2018, 1,255 cases of histological examination, 127 cases of cytology, 5 cases of intra-operative histology, 8 cases of autopsy, and 41 cases treated in the Pathology Core Laboratory

In 2019, 1,199 cases of histological examination, 141 cases of cytology, 5 cases of intra-operative histology, 4 cases of intra-operative cytology, 5 cases of autopsy, and 25 cases treated in the Pathology Core Laboratory

２）Research activities

Original articles published in international journals written in English;

9 articles in 2016, 19 in 2017, 9 in 2018, and 9 in 2019

３）Education Activities

1. Lectures for undergraduate students

One lecture period of systemic pathology for 4th year students in the Faculty of Medicine of the University of Tokyo

One lecture period of systemic pathology for 2nd year students in the Faculty of Medicine of Akita University

2. Lectures and exercises for graduate students

One lecture period in the Graduate School of the University of Tokyo

４） Social Activities

None.

５） International Activities

Cooperation in tasks of pathological diagnosis with the Moscow Regional Research Clinical Institute named after M. F. Vladimirsky

６） Other matters to be noted

None.

（４） Challenges and future prospects

To keep trying to achieve our goals with respect to publication of our research results in English scientific journals.

To accelerate writing reports of pathological diagnosis. We aim to reduce turnaround time of 95% of the cases to within 4 days.

Department of Surgery

（１）Members

Professor (Directors/Concurrent Posts)	Arinobu Tojo
Associate Professors	Masaru Shinozaki
Lecturer (Deputy Director)	Giichiro Tsurita
Assistant Prof. / Hospital Lecturer	Kentaro Yazawa
Assistant Prof.	Tomohiro Kurokawa
Others	3

（２）Research Objectives

Our goal in medical practice is to perform 200 cases of surgery (including 130 cases of major abdominal surgery) yearly, and to see an average of 25 hospitalized patients daily. For research, under normal circumstances, our goal is, to participate in more than one clinical trial and to prepare five English papers yearly. As for education, our goal is to educate new graduate students and clinical doctors.

（３）Activity Reports

１）Medical Activities

Our department mainly conducts surgical treatment for malignant gastrointestinal tumors, such as colorectal cancer and gastric cancer. The goal of our department between April 2016 and March 2020 was to carry out 100 colorectal and gastric cancer procedures yearly. However, we were only able to perform around 60 every year and did not achieve our goal. Except for a few select institutions, the number of colorectal/gastric cancer surgeries being performed in hospitals throughout Tokyo has decreased across the board; this outcome was therefore somewhat unavoidable. Nevertheless, we continue to aim for our target number of cases and hope to achieve it through close clinical collaborations and united, teamwork-oriented participation in medical care from all members. We also plan to proactively expand the indications for laparoscopic surgery and to introduce robotic surgery accordingly.

In addition, our department provides endoscopic treatment for inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn's disease, as well as anal disease, and colon polyps. From April 2016 to March 2020, one of our goals in this field was to perform surgeries on 30 cases of IBD and 30 cases of anal disease, which we were largely able to achieve. We were also largely able to achieve our goals of 500 colonoscopies and 300 polypectomies yearly. Nevertheless, we continue to strive to increase the number of these cases that we are able to treat.

In terms of the number of hospitalized individuals seen, our goal was an average of 25 per day.

In reality, our average was around 18. We believe this is the primary reason we were unable to meet our surgery caseload goals.

２）Research Activities

Our department also strives to carry out clinical research alongside our medical activities. From 2013 to 2016, our department participated in the following joint physician-led clinical trial initiative with Sapporo Medical University and the Kanagawa Prefectural Cancer Center: “A multi-center double-blind parallel-group placebo-control Phase II study on the efficacy of survivin-2B peptide vaccine therapy for patients with advanced or recurrent pancreatic cancer, and for which there is no effective treatment.” From April 2016 to March 2020, the goal of this department was the analysis and reporting of the results of this trial. In reality, we completed the analysis of our results and held a general meeting in March 2017, followed by a review meeting of autopsy casers in January 2018. In June 2019, we published two English papers publicizing our results. In terms of our activities outside of clinical trials, we also aimed to publish 10 case reports between April 2016 and March 2020 detailing medical procedures performed in our department. In reality, we only published 4 such case reports, because our participation in clinical trials and work on case reports is carried out alongside our daily medical practice; we believe these results are somewhat substantial in this context. However, following the completion of the aforementioned clinical trial, we did not initiate any new clinical trial, and we were also unable to achieve our goal in publication of case reports. In the future, we hope for all members to work together to acquire the necessary elements to achieve our goals from both within and outside our department, enabling us to initiate new clinical trials and engage in other clinical research, such as the publication of case reports.

３）Education Activities

A doctoral student entered our department in April 2014, and in collaboration with the Department of Surgical Neuro-Oncology at the IMSUT Hospital, carried out research on viral therapy for biliary tract cancers. This doctoral student was enrolled in our department from April 2016 to March 2017 and conducted the research herein. Since then, however, there are no graduate students enrolled in our department. In the future, we aim to organize our research environment to enable us to accept new graduate students.

In terms of clinical education, between April 2016 and March 2017, we aimed to provide specialist resident training to at least one full-time physician at all times. In reality, although their employment periods varied from 6 to 15 months, we were able to train a total of 4 physicians, with 1-2 being present in our department at all times, achieving our original goal. One of these physicians was certified as a surgical specialist, while the other was certified as a digestive system surgical specialist. The other two were able to publish English case reports while enrolled in our department.

There is a shortage of young surgeons throughout Japan, and while we predict that our educational goals will be difficult to achieve in the future, we plan to work together to educate the young surgeons of the future.

４）Social Activities

None.

５）International Activities

In July 2017, one full-time physician in our hospital began studying abroad in Boston, at Massachusetts General Hospital, and carried out joint research with our department on new treatments for pancreatic cancer (CAR-T).

６）Other matters to be noted

None.

（４）Challenges and future prospects

The primary challenge in our medical practice is to increase the number of surgery cases we perform. We will work to do so by increasing the number of laparoscopic surgeries and introducing robotic surgeries. In terms of research, we will proactively participate in new clinical trials and accelerate our efforts to carry out case reports and other types of clinical research. Finally, in terms of education, we will recruit young physicians and promote the education of specialists. We hope that by parallel engagement in all these efforts, we will continue to remain an active medical department.

Department of Anesthesia

（１）Members

Director/Associate Professor	Ryo Orii
Assistant Professor	Miho Asahara
Graduate students	1
Others	3

（２）Research objectives

We strive to perform perioperative anesthetic management carefully in cooperation with medical staff. We provide safe, high-quality health care and services to all patients without causing medical accidents. We participate and cooperate in facilitating the planned implementation of robotic surgery. In addition, we strive to promote the ongoing clinical research and target to publish research results in English journals.

（３）Activity reports

１）Medical Activities

As the system of our department, three anesthesiologists, an associate professor Orii, an assistant professor Asahara, and a graduate student in the Department of Anesthesiology, School of Medicine, The University of Tokyo, are in charge of anesthesia management.

Operations of four departments; neurosurgery, surgery, joint surgery, and hematology are performed. We strive to maintain safe and careful anesthetic management. We conduct preoperative visit of all surgical patients and explain them about the perioperative risk. In addition, postoperative rounds are routinely performed. Our managed cases are recorded in the the anesthesia ledger system (JSA-PIMS from Japanese Society of Anesthesiologists).

The number of general anesthesia management was 149 cases in 2016. There were 135 cases of general anesthesia management, and 23 cases of local anesthesia management in 2017. There were 132 general anesthesia management cases in 2018. Over the past four years, three incidents were reported to the Japanese Society of Anesthesiologists; one in cardiac arrest, one in severe hypotension, and one in the neurological accident associated with surgical invasion. We immediately reported to the Medical Safety Management Committee about the incidents and all patients were well discharged.

We are involved in respiratory management not only in perioperative patients but also in severe cases of internal medicine by endotracheal intubation or non-invasive ventilation (3 cases in 2016, 5 cases in 2017, 6 cases in 2018, 2 cases in 2019).

２） Research Activities

Clinical research about “Postoperative deep vein thrombosis in hemophilia patients undergoing total knee arthroplasty” (approval number: 26-23) and “Anesthesia management of hemophilia patients” (approval number: 29-48) are in progress. Since hemophilia patients undergoing arthropathy surgery gather from all over the country and at risk of perioperative bleeding, coagulopathy and thrombosis, we carefully perform anesthetic management. We published on anesthetic experience of a hemophilia patients in Masui, the Japanese Journal of Anesthesiology, and peer-reviewed English journal (Anesthesia management of arthroscopic ankle artherosis for a hemophilia patient after living-donor liver transplantation, Intractable Rare Dis Res. 2019) We also participated in clinical trials for hemophilia patients conducted by department of joint surgery (Evaluation of the efficacy and safety of NC-0129-0000-1003 in hemophilia A and hemophilia B in the perioperative period).

In addition, as other clinical researches, such as "Comparison of position- related changes in respiratory status by oxygen administration via a nasal cannula during general anesthesia" (approval number: 29-34), and " Comparison of central, nasopharynx, and tympanic temperature during abdominal surgery using TENPLE TOUCH PRO” (approval number: 30-16) are ongoing.

We conducted a clinical research on cardiac output was undertaken at the University of Tokyo Hospital and published a paper in a peer-reviewed English journal (Reliability of cardiac measurements using LiDCOrapid and FloTrac/Vigileo across broad band ranges of cardiac output values. , J Clin Monit Comput. 2017).

Since the systemic and respiratory management is one of our research themes. We have assessed impaired controlled ventilation in the anesthetic machine due to poor control of PEEP valve mechanism and submited a paper in English journal (Unexpected deposits in the anesthetic circuit: a possible cause of PEEP/Pmax valve malfunction, BMC Journal) .

As a retrospective study, we confirmed that a large number of perioperative blood coagulation disorders occurred in the patients undergoing a liver donation surgery and reported at the annual meeting of the American Society of Anesthesiologists. A graduate student is currently preparing a doctoral dissertation for this research now. We are planning to proceed with clinical research about evaluation of the effect of new anesthetic drugs on perioperative liver function , as a joint research with Department of Surgery, University of Tokyo Hospital.

３）Education Activities

As an education for students of the Graduate School of Frontier Sciences, The University of Tokyo,

we provide hospital training in order to learn about the environment and outline for surgery in the operating room and give lectures about anesthesia (5 times a year). Similarly, we conduct

hospital training and lectures for psychology students in response to the requests from Bunkyo University every year. In addition, the anesthesiology lecture "Postoperative complications" held at the Hongo campus for M2 students of the Graduate School of Medicine, the University of Tokyo is our charge. We are in charge of lectures about anesthesia for senior residents belonging to IMSUT hospital.

As an education about clinical anesthesia, one doctor of a graduate student of anesthesiology department at the University of Tokyo Hospital was dispatched to our hospital on the scheduled surgery day, and provide clinical training while implementing anesthesia management.

As a medical device safety manager, I teamed up with clinical engineers and conducted in-hospital education. Specifically, we planned and conducted training programs for nurses (six times a year), training sessions for mechanical ventilator, new medical equipment briefing sessions, medical equipment training, joint staff training.

４）Social Activities

None.

５）International Activities

None.

６）Other matters to be noted

The restart the 5th floor ward was decided in 2019, and construction of two ICU beds are planned. In mid-2018, The 5th floor ward started in May. In addition, a special project for strengthening hospital functions, which is one of the tasks of the University of Tokyo General Project Organization, will start operation from 2020. Since September 2018, the director has instructed us to formulate the Da Vinci surgical system and prepare the environment of the operating room for the introduction of robotic surgery. We set up working groups and hold meetings, visits and hear opinions from other hospitals, prepares and submits plans for medical devices and equipment.

（４）Challenges and future prospects

As a general principle of anesthesiology, it is important to protect the safety of patients and to adjust the homeostasis of patients due to surgical invasion, to provide appropriate pain management and high-quality health care services. We will continue to carefully manage perioperative management in cooperation with surgeons and medical staffs to provide safe and high-quality medical care to prevent medical accidents.

As for research activities, I am working on the contents of multiple themes mentioned above. In particular, I am planning to submit a paper on “Perioperative management of female hemophilia”

during this year. In addition, we will proceed with the publication of "Consideration of the inability to control the PEEP valve of anesthesia machine" during the next fiscal year to be published in the magazine within the next year.

This year, a special hospital strengthening project led by the university started to operate, and it was planned to introduce robot surgery to our hospital. Aiming to improve the operating rate of hospitals and increase income, assuming the addition of medical departments and securing doctors. The expansion of surgery contents by introducing robotic surgery is premised on securing sufficient numbers of surgical doctors, anesthesiologists, and clinical engineering technicians, and educating operating room nursing staff. I will continue to participate in the operation room management as an anesthesiologist in the future.

Department of Joint Surgery

（１）Members

Senior Assistant Professor	Hideyuki Takedani (chief of department),
Assistant Professor	Kumino Ono
Others	3

（２）Research objectives

Our department was established in 2006 to treat hemophilic arthropathy surgically. There are three major missions, the clinical research of safety surgical and hemostatic management for hemophilic arthropathy, the development of imaging and functional evaluation methods of hemophilic arthropathy, and development of treatment to keep and improvement of joint function and daily activities for people with hemophilia.

As for clinical research, A) Clinical investigation of influence of viral infection such as HIV, HCV on joint surgeries for patients with hemophilia, B) Development of safety hemostatic management during peri-operative period of surgical treatments, C) Clinical trial participation of new concentrates, especially surgical matter.

As for development of evaluation methods, A) planning and implement of national investigation of QOL in people with hemophilia using questionnaire, and B) gait analysis using depth sensing camera.

As for development of treatments, A) evaluation of rehabilitation efforts with and without surgical treatments, and B) basic research of regenerative treatment using mesenchymal stem cell.

（３）Activity reports

１）Medical Activities

From 2006, we have performed over 200 surgeries for patients with hemophilia and other coagulation diseases such as VWD, FVII deficiency. Many patients with joint dysfunction caused hemophilia and other coagulation diseases are arrival at our institutes as outpatients from all over Japan and from 15 to 20 surgeries are undergone annually.

２）Research Activities

For people with hemophilia, total and conventional functional evaluation system is need because they have many affected joints. Therefore, we are developing gait analysis system using game gadget with depth sensing camera.

Basic pathological research for hemophilic arthropathy and regenerative research using mesenchymal stem cell are going, collaborated with department of orthopeadic surgery in the university of Tokyo.

３）Education Activities

A couple times in a year, we speech about hemophilic arthropathy to people and family with hemophilia

４）Social Activities

None.

５）International Activities

None.

６）Other matters to be noted

None.

（４）Challenges and future prospects

Development conventional gait analysis system helps to evaluate their daily functional and emotional variation at home and to detect infinitesimal joint bled (micro bleeding) for people with hemophilia.

There are two major surgical methods which are synovectomy and total joint arthropathy (TJA) for hemophilic arthropathy. Usually synovectomy for early staged arthropathy and TJA for end staged arthropathy are performed. Development of regenerative treatment using mesenchymal stem cell help for patients with hemophilia who have arthropathy from early to progressive staged.

Department of Surgical Neuro-Oncology

（１）Members

Professor	Tomoki Todo
Project Associate Professor	Minoru Tanaka
Assistant Professors	Seisaku Kanayama, Hirotaka Ito
Postdocs	2
Graduate students	2
Technicians	5
Others	2

（２）Research objectives

Our department focuses on malignant tumors of the brain, such as gliomas or metastatic brain tumors. We are developing recombinant herpes simplex virus type I (HSV-1). Clinical trials using a third-generation, triple-mutated oncolytic HSV-1, G47Δ, is ongoing in patients with olfactory neuroblastoma or malignant pleural mesothelioma. Recently we have started a new investigator-initiated clinical trial using T-hIL12 for malignant melanoma.

（３）Activity reports

１）Medical Activities

Department of Surgical Neuro-Oncology was established in 2011. Our department started treating out-patients in October 2011 and in-patients in April 2012. Glioblastoma is refractory to conventional therapies and has a poor prognosis with a 5-year survival rate of less than 5%. Therefore, we should consider refined and personalized treatment approaches for selected patients: high dose radiation therapy of 80Gy for newly diagnosed glioblastoma or extended field stereotactic radiosurgery for recurrent gliomas. Four neurosurgeons treat patients with brain tumors. Standard craniotomies, image-guided stereotactic biopsies of deep-seated lesions, and high-tech brain tumor resections have been performed. The high-tech equipment regularly used in brain tumor resection surgeries includes an operative microscope, a 3-D neuro-navigation system, intraoperative monitoring with motor and sensory-evoked potential (MEP and SEP) recording, intraoperative ultrasonography and an ultrasonic surgical aspirator.

Patients with newly diagnosed malignant glioma have been treated with high dose or standard-dose radiation therapy and concomitant chemotherapy. Temozolomide was given to glioma patients during radiation therapy and repeated every 28 days for as long as possible. The overall survival of patients with glioblastoma was 30.3 months (95% confidence interval, 24.5-36.1 months. The five-year overall survival rate was 26.5%.

Recurrent malignant glioma patients are treated with innovative non-standard therapies whenever possible. Recurrent glioma patients who have small lesions, receive extended field stereotactic radiosurgery. To enhance the efficacy of stereotactic radiosurgery (SRS), we extended the irradiation field with the intent to include as many tumor cells as invasive to the surrounding tissue as possible. We demonstrated 93% local control in patients who received 20 Gy to a 0.5-1.0 cm extended field SRS compared to 47% of patients who were treated with 20 Gy to the gadolinium-enhancing margin only.

２）Research Activities

We are developing recombinant herpes simplex virus type I (HSV-1), which has genetic modifications in the viral genome so that the viruses replicate selectively in cancer cells while giving rise to an immune response against tumor-associated proteins.

We conducted a phase II clinical trial of G47Δ in patients with glioblastoma. The planned interim analysis showed that the one-year survival rate of the 13 patients who completed the one-year follow-up assessment was 92.3%. The independent data monitoring committee (IDMC) recommended terminating the trial because the one-year survival rate was tremendously higher than the set control value based on the meta-analysis of historical data. Daiichi Sankyo Company will submit a Marketing Authorization Application for G47Δ to the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). Clinical trials using a third-generation, triple-mutated oncolytic HSV-1, G47Δ, is ongoing in patients with olfactory neuroblastoma or malignant pleural mesothelioma.

Recently we have started a phase 1/2 clinical trial of T-hIL12 in patients with advanced malignant melanoma. T-hIL12 is a recombinant herpes simplex type I with IL-12 expression. This IL-12-mediated antitumor immunity could be T-cell-mediated. T-hIL12 will be administered into the tumor of skin or lymph node metastases in patients with the advanced stage of malignant melanoma. The assigned dose will be repeatedly inoculated into the metastases 2 or 4 times, with an interval of 14 (14 -28) days. The primary endpoint in phase 1 is safety, whereas, in phase 2, it is the response rate (RECIST 1.1).

３）Education Activities

We offer various opportunities for graduate students to be involved in research activities. We also give lectures associated with clinical issues for nurses.

４）Social Activities

We continue to educate the public about brain tumors and oncolytic virotherapy through public lectures.

５） International Activities

We frequently exchange information through international conferences.

６） Other matters to be noted

Primary central nervous system lymphoma patients will first undergo biopsy for pathological diagnosis. In addition to the standard therapy regimen using high-dose methotrexate followed by radiotherapy, an advanced treatment regimen utilizing rituximab, methotrexate, procarbazine, and vincristine (R-MPV) therapy followed by consolidation whole-brain radiation therapy and high dose cytarabine has been used as a treatment option.

（４） Challenges and future prospects

To date, immunotherapy, such as immune checkpoint inhibitors, has been shown to have the most significant impact on immunogenic cancers such as malignant melanoma and renal cell cancer. However, many immunotherapies that succeeded in immunogenic cancers have failed for glioblastoma because the tumor microenvironment of glioblastoma is extremely immunosuppressive. G47Δ not only selectively replicates in and kills solid tumor cells without harming healthy tissue, but also induces antitumor immune responses. Further clinical studies are needed to understand whether G47Δ, combined with an immune checkpoint inhibitor, can break the immune tolerance in a highly immunosuppressive tumor microenvironment.

Department of Medical Informatics

（1）Members

Director/Associate Professor	Akira Kunimatsu
Senior Assistant Professor	Hiroyuki Akai
Assistant Professor	Koichiro Yasaka
Radiologic Technologist	Nobukiyo Yoshida
Chief Clerk	Toru Sano
Others	2

（2）Research objectives

- To operate and manage the electronic medical record system and network at the IMSUT hospital
- To renew an old ordering system and implement the latest electronic medical record system

（3）Activity reports

1）Clinical activities

The IMSUT hospital started to use a new electronic medical record system in October 2017. On renewing the system, our department took the initiative, coordinating hospital members and the system vendor. We responded 1104 calls for system disruptions and how-to questions in 2016, 1406 in 2017 (611 before the renewal, 795 after the renewal), and 1334 in 2018. These figures suggest that we could satisfactorily control the initial system disruptions.

2）Research activities

The IMSUT hospital is a member of the nation-wide backup program for the electronic medical record system (the GEMINI project). Our department participated in trial runs in uploading data from our hospital to a designated data center and downloading stored data from the center.

3）Educational activities

For newcomers to our hospital, we held a how-to-use seminar of the electronic medical record system every year.

4）Social activities: nothing in particular

None.

5）International joint activities: nothing in particular

None.

6） Other matters to be noted: nothing in particular

None.

（4） Challenges and future prospetcs

- To evaluate the current IT-Business Continuity Plan (BCP) at the IMSUT hospital
- To implement a system upgrade periodically and improve IT-BCP when a problem is identified

Department of Radiological Technology

（1）Members

Director/Associate Professor	Akira Kunimatsu
Chief Radiologic Technologist	Tomio Inoshita
Radiologic Technologists (RT)	6
Technical assistants	1

（2）Research objectives

- To provide safe and high-quality medical care
- To assist technologists who present their work
- To encourage young technologists to improve their skills and knowledge
- To encourage active participation in conferences and research groups
- To assist technologists who attend post-graduate courses

（3）Activity reports

1）Medical Activities

- Revision of operating manuals
  - MRI
  - Infection control manual for the department
  - Emergency operation manual for the department
  - Operating manual for emergency CT
- Maintenance of radiation protectors and protecting clothes (every year)
- Attendance to seminars held by the Society of Radiological Technology
  - 2 RTs (2016), 5 RTs (2017), and 1 RT (2018)
- Emergency CT and MRI (cases on average per month)
  - CT 20.5, MRI 4.5 (2017)
  - CT 18.6, MRI 3.8 (2018)
- Preparing for and responding to annual audits by the Tokyo metropolitan government

2）Research Activities

- Publication: co-author 1
- Presentation at Meetings
  - Domestic: 1st author 2, co-author 3
  - International: co-author 6

３）Educational Activities

- Radiological technologist exchange program with the University of Tokyo Hospital: 6RTs from 2016 to 2018 (fiscal year)
- Completion of the master program: 1 RT
- Attendance to conferences, study groups, and workshops (in total number)
  - 17 RTs (2016), 18 RTs (2017), 9 RTs (2018)

４）Social Activities: nothing in particular

None.

５）International Activities: nothing in particular

None.

６）Others matters to be noted: nothing in particular

None.

（４）Challenges and future prospects

- A rise in the number of CT and MRI examinations
- Continuous improvement in healthcare safety and personal skills
- Improving the work environment to achieve balanced work and research activities

Department of Cell Processing and Transfusion

（1）Members

Associate Professor	Tokiko Nagamura-Inoue
Assistant Professors	Kazuaki Yokoyama, Toyotaka Kawamata
Postdocs	1
Graduate students	1
Technicians	8
Others	7

（2）Research objectives

The aim of our department is to support and manage the safe and appropriate use of transfusion medicine. We also perform cell processing for cell therapy not only for clinical use but also for translational research. This department consists of a division of blood transfusion medicine, division of cell processing, and a cell resource center (IMSUT-CRC).

（3）Activity reports

1）Medical Activities

(A) Division of blood transfusion medicine: We continuously tested for blood type and performed cross-match and irregular antibody tests. To eliminate abnormal blood products, including bacterial contamination, we established visual test methods for the identification of platelet products by placing samples under bright lights for 10 minutes. Since September 2019, regulations regarding radioisotopes have become stricter, and we have strengthened the monitoring of our radiation instruments as well as have limited access to trained users.

(B) Division of cell processing: We collected peripheral blood stem cells (PBSC) and processed and cryopreserved the collected cells for patients with multiple myeloma and malignant lymphoma. CD34+ cells were counted by flow cytometry and the patients with sufficient CD34+ cells received PBSCT. In addition, beginning in 2018, apheresis was conducted to collect mononuclear cells for clinical trials of CAR-T cell therapy initiated by Takara Bio Inc. We also collected mononuclear cells for a clinical trial of dendritic cell therapy.

(C) IMSUT-CRC: We maintained a clean room and sterile instruments to be able to adjust the environmental standards/criteria and quality tests for cell processing. We have supported several translational projects including aAVC-WT-1 immunotherapy, dendritic cell therapy, and the cord blood/umbilical cord bank (IMSUT CORD).

2）Research Activities

Our recent projects include the IMSUT serum bank, the Research Cord Blood Bank (RCBB), the National BioResource Project (NBRP) supported by AMED (MEXT) and CB, and the umbilical cord-derived mesenchymal stromal cell (UC-MSC) bank for clinical use supported by AMED (MHLW). We began an investigator-initiated clinical trial in 2018 for the administration of umbilical cord-derived MSCs in treatment-resistant severe acute graft-versus-host disease. We also studied the immunological properties of umbilical cord-derived MSCs (UC-MSCs) for clinical applications in graft-versus-host disease (GVHD), Hemophagocytic lymphohistiocytosis (HLH), and regenerative medicine for neonatal encephalopathy, cleft palate, and hemophilia arthropathy.

The main publications related to this work are listed below:

- Mukai T, Tojo A, Nagamura-Inoue T. Mesenchymal stromal cells as a potential therapeutic for neurological disorders. Regen Ther. 2018, 9:32-37. (Review)
- Mukai T, Tojo A, Nagamura-Inoue T. Umbilical cord-derived mesenchymal stromal cells contribute to neuroprotection in neonatal cortical neurons damaged by oxygen-glucose deprivation, Front Neurol. 2018, 9:466.
- Nakamura S, Yokoyama K, Yusa N, Ogawa M, Takei T, Kobayashi A, Ito M, Shimizu E, Kasajima R, Wada Y, Yamaguchi R, Imoto S, Nagamura-Inoue T, Miyano S, Tojo A. Circulating tumor DNA dynamically predicts response and/or relapse in patients with hematological malignancies. Int J Hematol. 2018,108:402-410.
- Ikeda K, Ohto H, Okuyama Y, Yamada-Fujiwara M, Kanamori H, Fujiwara SI, Muroi K, Mori T, Kasama K, Iseki T, Nagamura-Inoue T, Fujii N, Ashida T, Kameda K, Kanda J, Hirose A, Takahashi T, Nagai K, Minakawa K, Tanosaki R. Adverse events associated with infusion of hematopoietic stem cell products: A prospective and multicenter surveillance study. Transfus Med Rev. 2018, 32:186-194.
- Tanaka E, Ogawa Y, Mukai T, Sato Y, Hamazaki T, Nagamura-Inoue T, Harada-Shiba M, Shintaku H, Tsuji M. Dose-dependent effect of intravenous administration of human umbilical cord-derived mesenchymal stem cells in neonatal stroke mice. Front Neurol. 2018, 9:133-14.
- Shintaku H, Nabetani M, Hamazaki T, Kusuda S, Tamura M, Watabe S, Hayakawa M, Sato Y, Tsuji M, Taguchi A, Ichiba H, Oka A, Mori R, Taki A, Mukai T, Nagamura-Inoue T. Regenerative therapy for cerebral palsy: Transplantation of umbilical cord blood stem cells and umbilical cord mesenchymal stromal cells. J Hell Stud. 2017, 26:71.
- Isobe M, Konuma T, Abe-Wada Y, Hirata K, Ogami K, Kato S, Oiwa-Monna M, Tanoue S, Nagamura-Inoue T, Takahashi S, Tojo A. Alloimmune hemolysis due to major RhE incompatibility after unrelated cord blood transplantation. Leuk Lymphoma. 2018, 59:1000-1003.
- Kondo T, Nagamura-Inoue T, Tojo A, Nagamura F, Uchida N, Nakamae H, Fukuda T, Mori

T, Yano S, Kurokawa M, Ueno H, Kanamori H, Hashimoto H, Onizuka M, Takanashi M, Ichinohe T, Atsuta Y, Ohashi K. Clinical impact of pretransplant use of multiple tyrosine kinase inhibitors on the outcome of allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia. Am J Hematol. 2017, 92:902-908.

- Mukai, T., Mori, Y., Shimazu, T., Takahashi, A., Tsunoda, H., Yamaguchi, S., Kiryu, S., Tojo, A., and Nagamura-Inoue, T. Intravenous injection of umbilical cord derived mesenchymal stromal cells attenuates reactive gliosis and hypomyelination in a neonatal intraventricular hemorrhage model. Neuroscience. 2017, 355:175-187.

３）Education Activities

We have four cell therapy specialists in our hospital. Dr. Nagamura is the chairperson of the steering committee of Cell Therapy specialist in the education/certification system, which allows the growth and certification for the individuals working in the clinical field of cell processing in Japan. Our facility (IMSUT-CRC) was the first certified educational and training facility to host educational lectures and examinations for examinees.

４）Social Activities

Our department conducted joint research studies with the companies Tsubakimoto Chain Co., Ltd. (2013 – present), Rohto Pharmaceutical Co., Ltd. (2014-2018), Human Life Cord Inc. Stem Cell Institute Inc. (2017-present), NIPRO Corp. (2020-), PharmaBio Inc.(2018), Kaneka (2019-present), and Tess Inc. (2017-present). These studies were mainly focused on the research and development of mesenchymal cells for clinical use.

５）International Activities

We collaborated with the Chinese researcher He H.M.D., Ph.D., from the Department of Hematology of Kunming University of Science and Technology/Yunnan Province First People's Clinic, which was supported by the Sasagawa scholarship grant, the National Natural Science Foundation of China (NSFC-81760028), the Yunnan Provincial Basic Research (Kunming Medical Joint Project-2018FE001-129) in 2018, and the IMSUT International Joint Research Project (2019 – present) for the immunological study of UC-MSCs. Furthermore, we collaborated in an international research study with Dr. Coq at the France National Science Center and Dr. Tsuji at the Kyoto Women's University supported by the MEXT grant from 2018-2019 and the IMSUT International Joint Research Project (2020) for the study of the efficacy and mechanisms of UC-MSCs for brain developmental disorders in intrauterine fetal hypoplasia.

６）Other matters to be noted

Please visit our website for further information: http://www.ims.u-tokyo.ac.jp/dcpt/english/

（４）Challenges and future prospects

In our department, we deal with biological resources for clinical use. We prioritize safe and qualified blood and cell products. In near furure, because of the deterioration of the present cell processing facility (IMSUT-CRC), we are planning to establish a new facility to serve and support cell processing and product management.

Surgical Center

（1）Members

Professor	Tomoki Todo
Project Associate Professor	Minoru Tanaka

（2）Research objectives

The IMSUT hospital gives seamless support for translational research. Our mission is the management and operation of the surgical center to achieve a safe and organized environment where surgical procedures can be performed in high quality. By next year we will introduce the da Vinci surgical system, which is a robotic technology that allows surgeons to perform minimally invasive procedures.

（3）Activity reports

1）Medical Activities

The IMSUT hospital gives seamless support for translational research. The aim is to apply knowledge gained from the basic sciences to clinical and community health-care settings. Our activities include the management of clean areas, the establishment of protocols for infection control, maintenance of equipment such as astral lamps, surgical microscopes, and fiberscopes, and organizing of daily and weekly operations. Three of four operating room is maintained at a NASA class 1,000 clean level and specifically designed for neurosurgery and joint surgery. The others are maintained at a NASA class 10,000 clean level. For prompt and sustained supply of sterilized materials, we keep the surgical tools for each department in sets of designated purposes.

2）Research Activities

i) Equipment in the surgical center

The center is equipped with C-arm x-ray, TV systems, surgical microscopes, ultrasonic aspirators, image guided navigation systems, intraoperative ultrasound imaging systems, intraoperative nerve simulation monitoring systems, etc. The endoscopic procedure rooms is located separately but adjacent to the surgical center.

ii) TV monitoring system

Each operating room is equipped with a TV camera, so that the rooms can be monitored in the control center as well as by pad devices carried by managing anesthesiologists.

iii) Induction of electronic ordering system

We are accelerating the induction of an electronic ordering system for the surgical center that allows a real time ordering by clinical departments and computerized management of operation

schedules.

３）Education Activities

None.

４）Social Activities

None.

５）International Activities

None.

６）Other matters to be noted

Facts in the fiscal year 2018

Total number of operations	161
Planned operations	149
Emergency operations	12
General anesthesia	132
Spinal	1
Epidural	0
Local	28
Others	0

（４）Challenges and future prospects

The da Vinci system enables surgeons to perform the most complex and delicate procedures through very small incisions. The da Vinci Surgical System is often being used for prostatectomy and other urologic procedures. This minimally invasive approach is ideal for delicate urologic surgery. Using this system, surgeons have a better tool to spare surrounding nerves, which may enhance clinical outcomes.

Department of Medical Supply Center

（1）Members

Professor	Tomoki Todo
Others	3

（2）Research objectives

We manage the process of medical device distribution in the IMSUT Hospital to offer safe and high-efficient medical service. Medical devices directly or indirectly affect the human body and have potential risks; therefore, quality control is especially important at all stages of the process.

The Central Sterile Supply Department provides complex services including the preparation of sterile medical supplies for the surgery rooms and all other stations and centers of the IMSUT Hospital. The main aim is to guarantee a high quality and level of sterilization for all medical supplies.

（3）Activity reports

1）Medical Activities

The Central Sterile Supply Department is responsible for preparing medical-surgical supplies and equipment so that they are sterile and ready for use. Medical supplies are packed into special single-use or reusable sterile packs. The machine-controlled washing is carried out in a closed system and uses thermal-chemical or thermal disinfection. Both chemical and biological indicators rigidly monitor all sterilization processes. Medical devices, equipment, and surgical materials are divided into three general categories: (1) critical items, (2) Semi-critical items, and (3) Non-critical items, based on the potential risk of infection. Most surgical instruments are sterilized using a high-pressure steam sterilizer/low-temperature hydrogen peroxide gas plasma sterilization system. Commonly used sterilization processes have a variety of advantages and disadvantages. For example, the high-pressure steam sterilizer is an effective sterilization process, but its high temperature and moisture make it unusable for many of today's devices. Instead, hydrogen peroxide gas plasma is used worldwide for the terminal sterilization of medical equipment. Sterilization occurs in a low-moisture environment at a temperature of less than 50°C. It is suited for sterilizing heat-and moisture-sensitive items, delicate instruments, and instruments with sharp edges. The hydrogen peroxide gas plasma sterilization system can safely and effectively sterilize most surgical instruments, except for powders, liquids, devices with long, narrow lumens, linens, and other cellulosic materials.

２）Research Activities

None.

３）Education Activities

None.

４）Social Activities

None.

５）International Activities

None.

６）Other matters to be noted

A Sterile Processing Technician who completed the skill training course for operations chief of use of class -1 pressure vessel works to prepare, sterilize, install, assemble, or clean all laboratory or healthcare equipment required for surgeries, examinations, and medical procedures.

（４）Challenges and future prospects

The IMSUT Hospital will introduce the da Vinci surgical system. Before use in the operating room, the system needs to be properly draped and the instruments and accessories sterilized. This is comprised of the following: (1) surgeon console with an integrated 3-D display stereo viewer, (2) the InSite vision system, and (3) surgical cart with one camera arm, and two instrument arms. There are a wide range of expensive and sophisticated accessories and instruments that come along with the da Vinci surgical system, that need special care and attention.

Department of Laboratory Medicine

（１）Members

Professor	Tokiko Nagamura-Inoue
Assistant Professor	Tomohiro Ishigaki
Head Clinical Technologist	Hiroyuki Shingyochi
Clinical Technologists	13

（２）Research objectives

The department of Laboratory Medicine consists of seven divisions: clinical hematology, biochemistry/serology, microscopy, pathology, bacteriology, physiology, and TR verification laboratory.

Clinical laboratory tests are necessary for all the steps of clinical practice, including diagnosis of diseases, evaluation of stages, determination of treatments, and assessment after therapy. Our department engages in most of the clinical laboratory examinations in our hospital under stringent quality control and provides investigational laboratory analysis in collaboration with many other departments.

Our clinical and research objective is to facilitate translational research projects in this research hospital from the point of view of the clinical laboratory. For the purpose, we had established a special division named TR verification laboratory, and this division has been contributing to evaluating the safety of experimental therapeutic approaches and biopharmaceutical products for clinical trials.

As a central medical department, we are also taking part in many clinical trials and supporting researches conducted in our hospital.

（３）Activity reports

１）Medical Activities

Our department is engaged in almost all the clinical laboratory tests except blood transfusion screening and radiological ones in this hospital. As this institute is one of the central institutes for translational researches in Japan, many clinical trials and investigational studies have been conducted in this hospital. To support such medical activities, we have been making efforts to report laboratory results swiftly with high precision and high accuracy. Clinical laboratory tests in our hospital should be managed under stringent quality control. Although this hospital is not large, we are now participating in many external quality control tests. In addition to major tests conducted by Japan Medical Association and Japanese Association of Medical Technologists (JAMT), we are also participating in the survey of American Society of Clinical Pathologists (CAP Survey), which is the world's largest comprehensive proficiency testing program, to ensure the accuracy of the tests.

２）Research Activities

As presented above, we have supported many clinical trials and researches conducted by other departments in this hospital: eight main projects and more. Faculty doctors have also performed our own basic and clinical researches about hematological malignancies (leukemia and lymphoma). Our researches about adult T-cell leukemia / lymphoma have recently been awarded by four academic societies: the Japanese Society of Laboratory Medicine (JSLM), the Japanese Society of Hematology, the Japanese Society for Amino Acid Science, and the Japanese Society of HTLV-1 and Associated Diseases. Moreover, we have also developed a new laboratory management system from scratch and applied it to the TR verification laboratory, which is picked up as one of the recommended presentations by the chairman of the 66th annual meeting of JSLM.

３）Education Activities

Although there are no graduate school courses such as clinical laboratory medicine courses attached to our department, we accept students from our university and other colleges. We regularly conduct educational activities to teach them the importance of clinical laboratory examinations. In addition to lectures about the role of clinical laboratory testing in clinical practice, we make the students see the actual scene of the clinical laboratory to deepen the understanding of the clinical laboratory department.

４）Social Activities

None.

５）International Activities

None.

６）Other matters to be noted

None.

（４）Challenges and future prospects

As a laboratory department of the only hospital attached to research institutes in Japan, we will keep on supporting translational researches from the points of view of clinical laboratory medicine. More active participation of clinical technologists to researches is one of the challenges for the future. It is necessary to create an environment and work system that will make clinical technologists be more interested in research activities and contribute more to clinical laboratory researches.

Regional Medical Liaison Office

（1）Members

Professor	Hiroshi Yotsuyanagi
Others	6

（2）Research objectives

As a hospital information desk, we work closely with local medical institutions so that patients can receive optimal medical care smoothly. Further we announce the latest medical information at our hospital. Social workers and nurses who support the discharge of patients support the use of the social welfare system necessary for patients to receive medical care with peace of mind.

（3）Activity Reports

1）Medical Activities

We help with the patients introduced to the IMSUT hospital and support introduction to other hospitals or medical facilities. Furthermore, we support patients who need social and/or financial help.

2）Research Activities

None.

3）Education Activities

None.

4）Social Activities

(a) Cooperation with regional medical institutions

- After accepting referral from a local medical institution, we communicate with doctors and arrange the appointment schedule.
- After seeing referred patients, the reply letter from the doctor in charge is sent via the community medical cooperation room.
- “IMSUT Hospital News” is sent to the medical institutions in communication with our hospital four times a year.
- In the fall, we invite nearby medical institutions and those who have a referral record to our hospital to have a medical cooperation round-table conference.
- We still have shortcomings in contact with regional medical institution, which are to be improved.

(b) Patient support

- We introduce available social welfare services to patients and their families.
- We support patient transfer, facility admission.
- We introduce the social security system and medical cost subsidy to patients with financial problems.

５） International Activities

None.

６） Other matters to be noted

None.

（４） Challenges and future prospects

As mentioned in the “Social activities” section above, insufficient attention is paid to confirm whether all the patients referred from other medical institutions are recognized, whether the visits of the referred patients are notified to the institutions, and whether response letters are sent to the institutions, all of which require further improvement. If those issues are resolved, an increase of referred patients can be expected.

Center for Clinical Safety and Infection Control

（１）Members

Director of Center/Professor	Hiroshi Yotsuyanagi
Head of Medical safety Management Division/Associate Professor	Yoichi Imai
Head Nurse/General Risk Manager	Hatsuko Narita
Pharmaceutical department manager/General Risk Manager	Seiichiro Kuroda
Associate Professor /Medical safety Management Division	Ayako Kamisato
Head of Infection Control Division	Hiroshi Yotsuyanagi
Assistant Professor /Infection Control Division	Eisuke Adachi
Head Nurse/Infection Control Division	Mika Kogayu
Pharmacist/Infection Control Division	Mika Yamamura
Clinical Technologist/Infection Control Division	Hiroko Shibata
Others	1

（２）Research objectives

The Medical Safety Management Division consisting of doctors and nurses and pharmacists was founded in July 2001 and is responsible for carrying out medical safety in order to prevent incidents and accidents beforehand and deliver safe medical care to patients. Especially at our hospital, we mainly focus on hematological malignancies, infectious diseases, immune diseases, refractory malignant solid tumors etc, and are performing many kinds of therapies including transplantation. So, we are keeping in mind that we can adequately respond to the things those will happen in these kinds of medical activities.

ICT（Infection Control Team）has a key role to play in educating staff and ensuring appropriate systems to encourage infection prevention and control as part of routine practice are in place. The ICT consists of infection control doctors, infection control nurses, pharmacists, clinical laboratory technicians and administrative staff.

（３）Activity reports

１）Medical Activities

① Reports of incident and accident in our hospital are collected and analyzed using electronic medical record system. Based on the analysis, we are taking preventive measures for such incident and accident.

② Monthly in-hospital inspection is performed to prevent occurrence of incident and accident

③ We perform monthly report of incident and accident at the committee of Medical Safety Management and have launched several guidelines for medical safety management in our

hospital.

④ We hold meeting of field representative for medical safety management ten times per year to secure the medical safety management in our hospital.

⑤ We have held emergency meeting for serious incident and accident to take measures for such problems (6 times in 2017, ten times in 2018, and once in 2019).

２）Research Activities

Hatsuko Narita, Annual meeting of Japan Society of Clinical Safety, March 2020, Tokyo

３）Education Activities

Hiroshi Yotsuyanagi, Seminar for Medical Safety Education, September 2019, Tokyo

４）Social Activities

Yoichi Imai, Hatsuko Narita, and Seiichiro Kuroda, the meeting for medical safety management in National University Hospitals, twice per year

５）International Activities

None.

６）Other matters to be noted

None.

（４）Challenges and future prospects

While trying to resolve the nation-wide problems concerning lacks of checking reports of CT and pathological findings, we will continue to ensure and promote clinical safety in our hospital.

Center for Translational Research

（１）Members

Professor	Fumitaka Nagamura
Associate Professor	Masanori Nojima
Project Associate Professor	Hiroshi Yasui
Technicians	11
Others	6

（２）Research objectives

Center for TR is the management and support section for both pharmaceutical company initiated and sponsor-investigator clinical trials and non-IND clinical studies like clinical trial support organization of other hospitals. Translational Research (TR) is the clinical application of the results of basic research. One of the major missions of IMSUT is to promote TR. Our center is the core organization to support the conduct of TR from patent application to sponsor-investigator clinical trial. University of Tokyo has been designated as a Translational Research Core Center by Japan Agency for Medical Research and Development. As an Academic Research Organization, Translational Research Core Centers should support the conduct of TR in both own university and other institutes. For the support of TR, our center consists of clinical research coordinator (CRC) section, secretariat section, data management/biostatistics section and project management section. Occupations of our center include CRC, patent attorney, project manager, study manager, data manager, monitor, biostatistician, pharmaceutical expert, and secretary. By securing these occupations, we support patent application, regulatory compliance, preclinical studies, manufacturing, data management, biostatistical analysis, and conduct of clinical trials. Conducting sponsor-investigator clinical trials, especially for First-in-Human (FIH) clinical trials, with new modality products still accompanies with many difficulties. Our goal is to support an average of one first-in-human clinical trial based on academia seeds per year.

（３）Activity reports

１）Medical Activities

We support industry-sponsored clinical trials, however, the main role of our center is to support the conduct of TR, especially for FIH clinical trials. Following are FIH sponsor-investigator clinical trials we supported:

- Phase I study of WT1-expressing human artificial adjuvant vector cells (aAVC-WT1) for patients with relapsed or refractory acute leukemia. (2016)
- Phase I clinical trial with umbilical cord-derived mesenchymal stromal cells (IMSUT-CORD)

for treatment-resistant severe acute graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation. (2017)

- A phase 1/2 clinical trial of a recombinant herpes simplex type 1 with IL-12 expression in patients with malignant melanoma. (2018)
- Investigator-initiated phase 1 study of nucleic acid medicine targeting PRDM14 in patients with breast cancer. (2019)

Followings are FIH clinical study under Clinical Trials Act (non-Investigational New Drug application)

- A clinical study of a replication-competent, recombinant herpes simplex virus type 1 (G47delta) in patients with progressive malignant pleural mesothelioma. (2018)
- Phase I clinical study on safety and efficacy of Ebola vaccine iEvac-Z. (2019)

All test products were entirely new modality ones. As an ARO in Japan, this achievement is considered remarkable.

２）Research Activities

Researches as clinical research coordinator (CRC) on how to properly support TR, especially for First-in-Human studies and those on efficient TR related administration and regulatory compliance as secretariats have been conducted. We made two presentations at domestic conferences in 2016, one in 2017 and 2018, and two in 2019. The contents of the research presented at conferences were: role of CRC in the review of study protocol of first-in-human clinical trials, reduction of time required for the beginning of clinical trials by reviewing documents processing, and so on. Research activities of professor and associate professor are described in “Division of Advanced Medicine Promotion”.

３）Education Activities

Education for hospital staff and investigators is indispensable. We have encouraged to participate in graduate school lectures described in “Division of Advanced Medicine Promotion”. We have held a seminar on clinical trials and provided the e-learning developed by University Hospital Clinical Trial Alliance (IMSUT Hospital is one of the members), and attendance and taking e-learning are obligations as investigators and study collaborators.

４）Social Activities

As a public relation activity, we present a glossary of TR, information on ongoing clinical trials, that of Institutional Review Board, and so on.

５）International Activities

We have been involved in the Nipa Vaccine development project with Division Advanced Medicine Promotion, which had adopted by CEPI (Coalition for Epidemic Preparedness Innovation) in 2018. Our role is to handle the matters related to clinical trials. This project has been conducted by a consortium composed of the University of Tokyo, Stanford University, European Vaccine Initiative, and International Centre for Diarrhoeal Disease Research, Bangladesh.

６）Other matters to be noted

None.

（４）Challenges and future prospects

Many types of occupations, such as data manager, monitor, and intellectual property expert, are indispensable to carry out TR. Our challenges are to increase the number of staff and to maintain the ability to support TR. Many staffs are hired using external research funding. Solutions are to obtain more external research funding for employment, and to aggressively focus on first-in-human studies to increase the attractiveness of our activities. Our future prospect is to secure adequate human resources by above activities, and to support TR until regulatory approval.

Center for Antibody and Vaccine Therapy

（１）Members

Professors	Hirotoshi Tanaka, Kohei Tsumoto
Project Professor	Yataro Daigo
Project Associate Professors	Satoru Nagatoishi, Motohisa Yamamoto
Senior Assistant Professor	Noritada Yoshikawa
Project Senior Assistant Professor	Atsushi Takano
Assistant Professor	Hiroki Yamazaki
Postdocs	1
Graduate students	3
Technicians	4
Others	3

（２）Research objectives

The aim of this center is to develop novel therapy for patients with various diseases including cancers and autoimmune diseases. Moreover, attractive clinical trials are ongoing in collaboration with IMSUT research groups and others.

Our specific projects are

- Developing a novel therapy preventing glucocorticoid-induced muscle atrophy in patients with rheumatic diseases
- Developing a novel therapy to improve abnormal fat distribution in patients taking GC therapy
- Development of novel therapeutic modalities against metabolic syndrome targeting the skeletal muscle-liver-fat signalling axis
- Clarification of functional crosstalk between GR and sex hormone receptors for body composition and metabolic regulation
- Clarification of the effect of ageing for regulation of energy storage in skeletal muscle and adipose tissues
- Translational Research and Clinical Trial of Division of Rheumatology
- Novel therapeutic target discovery for solid cancers
- Development of therapeutic cancer vaccine
- Integrated genomics-based discovery of new biomarkers for cancer immunotherapy
- Detection of neoantigen-reactive T cell clones based on the clonal expansion using next-generation sequencing of TCRβ complementarity-determining region 3

- Molecular characterization of tumor microenvironment molecules as diagnostic and therapeutic targets
- Clinical significance of PD-L1-positive cancer-associated fibroblasts in pN0M0 non-small cell lung cancer
- Identification of lung cancer susceptibility loci by genome-wide association studies
- Scientific Platform of Supporting Cohort Study and Biospecimen Analysis
- Technical Capabilities and Limitations of Optical Spectroscopy and Calorimetry Using Water-Miscible Solvents: The Case of Dimethyl Sulfoxide, Acetonitrile, and 1,4-Dioxane
- Biophysical characterization of the breast cancer-related BIG3-PHB2 interaction: Effect of non-conserved loop region of BIG3 on the structure and the interaction
- Structural features of methionine aminopeptidase2-active core peptide essential for binding with S100A4
- Highly sensitive biomolecular interaction detection method using optical bound/free separation with grating-coupled surface plasmon field-enhanced fluorescence spectroscopy (GC-SPFS)
- An epitope-directed antibody affinity maturation system utilizing mammalian cell survival as readout
- Exploring designability of electrostatic complementarity at an antigen-antibody interface directed by mutagenesis, biophysical analysis, and molecular dynamics simulations
- Control of Protein Adsorption to Cyclo Olefin Polymer by the Hofmeister Effect
- Affinity Improvement of a Cancer-Targeted Antibody through Alanine-Induced Adjustment of Antigen-Antibody Interface
- Phospholipid Membrane Fluidity Alters Ligand Binding Activity of a G Protein-Coupled Receptor by Shifting the Conformational Equilibrium

（３）Activity reports

１）Medical Activities

We vigorously conducted patient management at outpatient clinic (4 days per week) and ward (over 100 patients) in collaboration with Department of Rheumatology and Allergy at IMSUT Hospital. Moreover, we, as a translation of our original research, are working with several clinical trials for verification of novel treatment for various diseases.

２）Research Activities

We published 23 and 26 original research papers in peer-review journals, and reported 25 and 27 research papers in various academic meetings, in 2017 and 2018, respectively.

３）Education Activities

We take charge of at least 4 lectures for graduate students every year.

４）Social Activities

We published 10 and 11 review articles in Japanese medical journals in 2017 and 2018, respectively. We performed 7 collaborations with pharmaceutical companies in 2 years.

５）International Activities

We are promoting several international collaborative projects for clinical development of our original research.

６）Other matters to be noted

None.

（４）Challenges and future prospects

We will continue original research and develop novel therapeutic approach for treatment of various intractable diseases in collaboration with IMSUT research groups and other domestic or foreign laboratories.

Therapeutic Vector Development Center

（1）Members

Professor	Tomoki Todo
Project Associate Professor	Minoru Tanaka
Technicians	2

（2）Research objectives

One of the essential missions of the Institute of Medical Science is to carry out the results from bench to clinic. To achieve this, investigational drugs planned to be used in clinicals trials need to be manufactured according to cGMP (current Good Manufacturing Practice), which is the standard for manufacturing pharmaceuticals and quality control. The cGMP-grade manufacturing is maintained by systematic Standard Operating Procedures (SOP) in the Therapeutic Vector Development Center. We have obtained and maintained ISO9001 certification since 2014, which is an international standard for quality control systems. In order to manufacture cGMP-grade oncolytic virus product, the facility and equipment are regularly validated. Therapeutic Vector Development Center also maintains a system that can support cGMP manufacturing of samples from outside of the university.

（3）Activity reports

1）Medical Activities

From April 2016 to March 2019, the goal of the Therapeutic Vector Development Center is to manufacture and systematically store investigational drugs and regenerative medical products used for gene therapy, oncolytic virus therapy, cell therapy, etc. We also support development of manufacturing process and regulatory compliance. We are accepting two projects related to the production of clinical-grade oncolytic HSV-1 and oncolytic measles virus. The system to support cGMP manufacturing has been maintained and ISO9001 certification was updated. There have always been problems to secure financial resources for fixation of the equipment deteriorated over time of 20 years since its establishment.

2）Research Activities

None.

3）Education Activities

Lectures on SOPs, laws, and public standards are given to new project members before entering the room, and regular re-education and training is given to those who are qualified to enter the facility.

４）Social Activities

We can systemically support projects from outside the university.

５）International Activities

None.

６）Other matters to be noted

The TVDC consists of two units; 1) Vector Unit, the primary suite for viral vector production and *ex vivo* transduction; and 2) Cell Unit, the suite for cell processing capable of generating therapeutic cells such as dendritic cells for immunotherapy and gene therapy. Each unit has two independent compartments kept as a Class 10,000 clean level. The facility and equipment are regularly validated to fulfill the cGMP standard.

（４）Challenges and future prospects

Although the Therapeutic Vector Development Center plays a critical role in the development of translational research in Japan, the current facility is too deteriorated for a further use, relocation to Building 1, which has been scheduled since before, should be put into action promptly.

IMSUT CORD

（１）Members

Associate Professor	Tokiko Nagamura-Inoue
Assistant Professor	Kazuaki Yokoyama
Postdocs	1
Technicians	8
Others	1

（２）Research objectives

The umbilical cord blood and cord tissue bank of the research hospital, The Institute of Medical Science, The University of Tokyo (IMSUT CORD) was established in 2016. IMSUT CORD is a biobank that supplies umbilical cord blood and umbilical cord tissue or derived cells for regenerative medicine and immunotherapy not only for basic/preclinical research and development, but also for cell therapy (regenerative medicine products) in clinical use.

（３）Activity reports

１）Medical Activities

The umbilical cord (UC) is a rich source of mesenchymal stromal cells (MSCs). UC-derived MSCs (UC-MSCs) possess many advantageous features: (1) ease of collection, storage, and transport; (2) abundant sources with high proliferation capacity; (3) multipotency to differentiate into various tissue cells including osteoblasts, chondrocytes, adipocytes, and neurons; (4) low immunogenicity with significant immunosuppressive ability; (5) tissue repair potency; (6) migration ability toward inflammatory or injured sites, subsiding inflammation and repairing the damaged tissues, and (7) no donor age-dependent variations. IMSUT CORD supplies frozen cord blood and UC-MSCs for research purposes based on joint research and material transfer agreements to for-profit companies and researchers in non-profit academic facilities in Japan and internationally. The establishment of a stable supply system for the source matter of cell therapy has been supported by the Japan Agency for Medical Research and Development (AMED) since 2018 (T angamura-Inoue, principal investigator) .

We obtained the product cells of UC-MSCs, namely IMSUT-CORD, from the master cell bank and supplied them to an investigator-initiated clinical trial of treatment-resistant severe acute graft-versus-host disease (GVHD) in 2018. The clinical trial for acute GVHD was supported by the AMED (T angamura-Inoue, principal investigator).

２）Research Activities

To establish the stable supply system of CB and UC-MSCs with safe and quality assurance, we acquired ISO9001:2015, an international standard for quality management systems, in June 2019. We supplied UC-MSC and/or CB for research and development approved by the institutional review board. This research includes studies on GVHD, immunological disease, cerebral palsy, osteogenesis, frail, endothelial cell regeneration, neonatal/infant chronic lung disease, and others. A recent publication regarding this research is listed below:

1. Nagamura-Inoue T, Nagamura F., Umbilical Cord Blood and Cord tissue bank as a source of allogeneic use. IntechOpen. 2020. DOI: 10.5772/intechopen.91649

３）Education Activities

None.

４）Social Activities

We conducted a collaborative research study with the companies Human Life Cord Inc. Stem Cell Institute Inc. (2017 – present), NIPRO Corp. (2020 –), and PharmaBio Inc. (2018) on research new methods of processing samples, quality control tests, and sample banking.

５）International Activities

None.

６）Other matters to be noted

Please visit our website for more information: http://imsutcord.umin.jp

（４）Challenges and future prospects

Our processing and cryopreservation technology for obtaining qualified cell products have been transferred to companies that conduct the later phases of clinical trials and who provide commercialization to supply the cells to the patients efficiently. We will supply master cells, intermaediate product cells, or product cells for clinical use on demand by companies and researchers.

Department of Nursing

（１）Members

Director	Eiko Yoshii
Deputy Directors	Minayo Hisahara, Junko Izumi
Nurse Managers	8
Nurse Chiefs	11
Nurses	74
Nursing assistants	14

（２）Organizational goals

1. Provide nursing with grounds

   1) Acquisition and thoroughness of correct skills and strengthening of assessment, 2) Improving quality through visualization of nursing, 3) Training and support for highly specialized nurses

2. Actively promote team medical care and IPW（Inter-professional Work）

   1) Promotion of multi-job collaboration, 2) Promote activities within and across-the-world departments of full-time nurses, 3) Promotion site for participation in team medical care for nursing assistant Clark

3. Protect patient rights and support decision-making

   1) Active involvement at each stage of informed consent, 2) Enhancement of ethics conferences and death conferences, 3) Strengthen discharge support and home care support

4. Creating an environment where nurses can work lively

   1) Enhance the work of nursing staff and promote work and life in harmony,

   2) Each nurse realizes the growth and the role of the profession, 3) Training of managers using competency assessment and nursing management standards

5. Cooperate in hospital management

（３）Activity reports

１）Medical Activities

1. Provide nursing with grounds

As a nursing team, in order to provide optimal nursing care for patients, we have established a system for accepting new recruits, and have been working to improve the nursing practice of each nurse by utilizing educational and training opportunities, pair systems, online education tools, etc. Each department practices careful nursing, and patients write thanks. In addition, the pair system provides new recruits with a pair of nurses, are engaged in the care of patients with peace of mind, and are an opportunity to learn from each other. However, each nurse is not able to make full use of the pair system as an advantage for medical safety and business improvement.

2. Actively promote team medical care and IPW（Inter-professional Work）

Nurses participate in conferences such as medical care, clinical research, and discharge support through multi-job collaboration, contributing to team medical care. In cancer rehabilitation, we worked with physical therapists to provide support with an eye to the lives of patients after discharge.

3. Protect patient rights and support decision-making

In order to be involved in patient decision-making support, he has been engaged in training sessions on medical ethics, holding multi-disciplinary ethics conferences, attending informed consent (IC), and learning how to support decisions. As a result, information sharing with doctors before IC and confirmation of how to understand and receive patients and their families have become established.

4. Creating an environment where nurses can work lively

Although we are working to create a workplace that is comfortable to work in each department, the turnover rate of nurses has increased to 19.8% (14.8% in FY18) in FY19. The number of people taking paid leave increased by 17.4 days. Nurse satisfaction situation, there is also the reopening of the 5th floor ward, night shift personnel is decreasing, in the situation that the night shift full-time employee is always five to six people, 7-to-1 nursing arrangement is maintained.

5. Cooperate in hospital management

The nursing department cooperated with the reopening of the 5th floor ward, the establishment of medical examinations from overseas and endoscopic health checkups in Minato Ward, clinical research on Ebola and the inactivated vaccine inlet (P1), special projects to enhance Shirokane and Hongo, and the medical care system for the spread of new coronavirus infection.

２）Research Activities

We continuously conduct nursing research on keywords such as "daily life support for hemophilia patients", "nursing of hematopoietic stem cell transplantation", "clinical research nursing", and "competency study group". He is continuously involved in the preparation of nursing standards and educational programs for clinical research nursing. The Copitensy Study Group is also held on an ongoing basis to evaluate the effectiveness of the development of managers.

３）Education Activities

As a nursing department, we accepted hospital training at the following four universities.

- the Department of Health Sciences and Nursing at the University of Tokyo
- The University of Tokyo's Medical Information And Life Sciences,
- Department of Psychology, Faculty of Human Sciences, Bunkyo University
- Faculty of Nursing, Tokyo Ariake University Of Medical And Health Sciences

And we continue to hold training as a designated training facility for clinical transfusion nurses

certified by the Society. In addition to contributing to the development of students and nursing staff, it is also an opportunity to train our nursing staff.

４）Social Activities

We have accepted "one-day nursing experience learning" and "return to work support training" of the Tokyo Nurse Plaza project, and cooperate in the spread and enlightenment project of the nursing profession.

５）International Activities

None.

６）Other matters to be noted

None.

（４）Challenges and future prospects

In FY20, while responding to the new coronavirus infection, we will operate the 5th floor ward, which resumed in FY19, establish a system for accepting patients related to palliative medicine and urology, and operate the nursing department so that value can be found in the work of nursing, and we will strive to establish nursing staff. To this end, we will continue to work on nursing practice with the challenges of creating a comfortable working environment, medical safety and infection control, training nursing staff, and maintaining the quality of nursing.

Department of Pharmacy

（1）Members

Pharmacy Director	Seiichiro Kuroda
Others	12

（2）Missions and Features

The Department of Pharmacy seeks to provide high-quality pharmaceutical care services. We contribute to the team approach to patient-oriented medical care and provides a drug distribution services. We are also trying to contribute to propel the right use of medicines for patients.

（3）Activity Reports

1）Medical Activities

We continue a high quality pharmaceutical approach and contribute to medical treatment in IMSUT HOSPITAL.

2）Research Activities

We will continue to make great efforts with self-study to find and solve clinical questions in practice and give back them to medical care in the future.

3）Education Activities

We accept to clinical trainee of the other University of Pharmacy.

We perform the bedside teaching and educate them about the knowledge and skill as clinical pharmacist.

4）Social Activities

None.

5）International Activities

None.

6）Other matters to be noted

None.

（4）Challenges and future prospects

IMSUT hospital has a mission to confront an intractable disease.

Therefore it is necessary for IMSUT pharmacist to manage the proper use of medicine.

IMSUT Distinguished Professor Unit

Division of Stem Cell Therapy

（１）Members

IMSUT Distinguished Professor	Hiromitsu Nakauchi
Project Assistant Professor	Hideki Masaki
Postdocs	2
Technicians	2
Others	6

（２）Research objectives

Our goal is to "Establish a New Frontier of Stem Cell Therapy by Connecting the Basic Science and Clinical Medicine." We are working to uncover new diseases, elucidating the causes of disease and developing therapeutic modalities by connecting the knowledge and methodology of basic science such as immunology, molecular biology, cell biology and developmental engineering with clinical medicine.

We are also actively collaborating with international institutes including Stanford University in the US and MRC Cambridge Stem Cell Institute in the UK.

（３）Activity Reports

１）Research Activities

Our department was established at April 2017, focusing on creation of fully functional human organ from human pluripotent stem cells in animal body by using developmental process. We are the only group in Japan allowed to develop human-mouse chimeras in uterus at this moment. We have provided proof-of-principle experimental data showing the advantages of organ creation utilizing mouse-rat interspecies chimeras and blastocyst complementation technique; by injecting normal embryonic stem cells into organ/tissue deficient embryos, we successfully created donor-cell derived pancreas, thymus and kidney. In the process of creating mouse-rat interspecies chimeras, we observed high incidence of abnormalities, such as malformation in specific organs/tissues and inflammations in various tissues. We are investigating the underlying mechanisms to cause those abnormalities in order to generate inter-species chimera more efficiently. Based on the experience and knowledges we accumulated through generating intra- and inter-species chimeras, we started human-mouse chimera development in mice uterus from September 2019, right after the approval of our research plan from MEXT. Now we are in the process of finding the problems that prevent formation of human-animal chimeras, and trying to solve each problem step by step.

２）Education Activities

2017/ 5/ 27 The University of Tokyo EMP

2017/ 11/ 17 The University of Tokyo EMP

2017/ 12/ 18 Tokyo University of Science lecture

2018/ 6/ 30 The University of Tokyo EMP

2018/ 11/ 19 Tokyo University of Science lecture

2018/ 12/ １ The University of Tokyo EMP

2018/ 12/ 12 Toyo University Special lecture

2019/ 11/ 27 The University of Tokyo EMP

【Facility tour】

2018/ 4/ 25 Okazaki Junior High School affiliated to Aichi University of Education

2018/ 11 /5 Keio Girls Senior High School

2019/ 6/ 19 Johnouchi High School

2019/ 9/ 5 Shimotsuma 1st High School

３）Social Activities

None.

４）International Activities

Collaborating with Nakauchi lab at Stanford University for characterization of interspecies chimeras and development of genome editing technology.

Collaborating with Smith lab at MRC Cambridge Stem Cell Institute for establishment and characterization of non-human primate pluripotent stem cells.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

As described above, human-mouse chimeric embryos are difficult to develop to full term. Engrafted human cells were lost in later developmental stages, or human cells survived embryos caused degeneration or malformation. We will clarify underlying mechanisms that prevent incorporation of human engrafts, and genetically modify host animals to enable to give birth chimeric animals carrying human organ carrying.

Division of Mucosal Immunology

（1）Members

Project Professor	Hiroshi Kiyono
Project Associate Professor	Yosuke Kurashima
Project Assistant Professor	Rika Nakahashi
Postdocs	2
Technicians	5
Others	6

（2）Research objectives

In higher mammals, the mucosal immune system consists of an integrated network of tissues, lymphoid and mucous membrane-associated cells, and effector antibody molecules for providing the first line of defense against pathogenic microorganisms and allergens which encounter through the mucosal surfaces by inhalation and ingestion. In contrast, tolerance in the mucosal immune system represents the most common response of the host to its environment in order to create and maintain the homeostasis. In this regard, the mucosal immune system establishes tolerance to continuously ingested several thousand different food proteins as well as to our indigenous microflora colonizing in the digestive tract, which provides biological benefits to the host. Our major goals are defining the cellular and molecular mechanisms of the mucosal immune system, which is sophisticatedly regulated, elaborated, and the flexible first line of surveillance and protective system. To this end, our mission in the research and development is to establish an infrastructure system for the prevention and treatment of immune- and infectious-diseases by evolutionally novel and fusion strategies using agriculture and bioengineering science including botany and engineering knowledge and technologies.

（3）Activity Reports

1）Research Activities

- Rice expressing B subunit of cholera toxin (CT-B), MucoRice-CTB has been developed by the adaptation of rice transgenic system as a rice-based oral vaccine against diarrheal diseases. We conducted a double-blind, randomized, placebo-controlled, three-cohort, dose-escalation phase I study to evaluate the safety, tolerability, and efficacy of MucoRice-CTB. This phase I clinical trial showed that MucoRice-CTB induces neutralizing antibodies against diarrheal toxins in a gut microbiota-dependent manner, without major adverse events.
- We have been studying the cellular and molecular mechanisms for the induction of antigen-specific mucosal and systemic immune responses by nasal immunization using the cationic nanogel vaccine delivery system. The outcomes of the study gain the essential knowledge of nasal vaccination strategies and facilitate the development of effective and safe nasal vaccines against respiratory pathogens such as *Streptococcus pneumoniae* and *Hemophilus influenza.*

These studies are further explored to develop cationic nanogel-based nasal vaccines for SARS-CoV2.

- It has been shown that nasal immunization elicits antigen-specific immune responses in the female reproductive tract in addition to the lower and upper respiratory tracts. Thus, we have been examined the involvement of chemokine receptors and their ligands for $CD4^+$ T cell migration into the vaginal mucosa.
- Our group has been elucidating roles of mesenchymal-myeloid cell interactions for the maintenance of tissue-based homeostasis which preventing the development of intestinal allergy and inflammation. New information obtained by these studies are contributing to our understanding of the cellular and molecular interactions involving the intestinal homeostasis and disorders, and facilitate the novel diagnostic and treatment strategies.
- During this reporting period (April 2016 to present), we have published 34 peer-reviewed original papers and 12 of which are closely related to the projects described above. In addition, we have published 15 review papers.
- We have submitted one patent application (2016-234717: Development and clinical application of fibrosis-associated molecule-specific antibodies).

２）Education Activities

- Seven graduate students have been graduated before April 2018. Among them, three students obtained Ph.D. degrees while 4 students graduated with MS degrees.
- We have accepted three internship students from the Tokyo College of Biotechnology and provided necessary guidance in the area of mucosal immunology to support their research program for the graduation.

３）Social Activities

- We have obtained grant aid from the AMED CiCLE program together with Astellas Pharmaceutical Inc, Asahi Kogyosha Co. LTD. and Chiba University. The main task of this grant is to establish a stable manufacturing system for MucoRice-CTB as an oral vaccine and test the efficacy and safety of MucoRice-CTB in the clinical trials (Phase Ib and II).
- We have established a collaborative contract with Astellas Pharmaceutical Inc to develop MucoRice-based new oral vaccines by using a novel oral adjuvant system.
- We have been developing novel nasal vaccines against respiratory infectious diseases together with Hana Vax Inc. as a collaborative effort.
- Non-disclosure agreement has been sealed with Boehringer Ingelheim and Chiba University based on our preexisting intellectual property.

４）International Activities

We have established a collaborative program among the University of California, San Diego, Chiba University, and our laboratory to study mucosal immunology and allergy since 2016 until now.

５）Other matters to be noted

- Under the unfortunate COVID-19 circumstances, our laboratory has initiated the project on the adaptation of our knowledge and technology (e.g., cationic nanogel vaccine antigen delivery system) for the development of SARS-CoV-2 nasal vaccine for the induction of dual protections at the entry site of airway epithelium and inside of lung by secretory and serum antibodies. This project is now being conducted with the National Institute of Infectious Diseases under the support of AMED.

- For advancing our knowledge in the mucosal immune system for the creation of homeostatic and protective environments in the digestive tract to the control of infectious diseases in developing countries, we have been involved in the Science and Technology Research Partnership for Sustainable Development (SATREPS) program offered by the Japan International Cooperation Agency (JICA) and Japan Agency for Medical Research and Development (AMED). Under the project of ”Surveillance and Laboratory Support for Emerging Pathogen of Public Health Importance in Ghana”, we are working together with Ghanaian scientists at Noguchi Memorial Institute for Medical Science, the University of Ghana on the metagenome analyses of pathogens, hosts and commensal microorganisms for advancing the genome-based host interaction with the pathogen and beneficial bacteria which can be applied for the surveillance system in Ghana.

（４）Challenges and Future prospects

- We will continuously keep our high performance in the research areas of mucosal immunology and mucosal vaccinology in a comparable fashion to last or further advancing the next 5 years. In this regard, we will continue to press forward the projects described above in order to further understand the cellular and molecular induction and regulation of mucosal immunity and advance our mucosal vaccine development by continuously conducting the fusion science with introduction of evolutionally novel ideas and technics from different scientific areas into our laboratory just like our group brought in the agriculture and bioengineering science including the rice transgenic and nanogel engineering knowledge/technology.

- In order to maintain our research activities as well as to be involved and contribute to the

continuous advancement of IMSUT as one of the leading medical science institutes, it will be essential to incessantly seek new research supports from national and international funding agencies. We will continuously provide our team player sprits to the rest of the IMSUT colleagues and laboratories for creating new scientific programs which can be led to new funding opportunities.

Corporate Sponsored Research Program

Project Division of Molecular and Developmental Biology

（1）Members

Project professor	Sumiko Watanabe
Postdocs	2
Graduate students	11
Technicians	2

（2）Research objectives

Our long-term goal is to understand the molecular mechanisms which coordinately regulate differentiation and maintenance of neural retina. As mechanisms of retinal development, we focus on histone methylation to reveal retinal lineage specific regulatory system. We are also studying on molecular mechanisms of photoreceptor degeneration and development to rescue photoreceptors from degeneration especially focusing on microglia. To clarify how microglia and other immuno-competent cells affect pathogenesis of retina, and development of new therapeutic strategy is our ultimate goal.

（3）Activity Reports

1）Research Activities

1. Analysis of roles and molecular basis of microglia in photoreceptor degeneration in the retina

Photoreceptor degeneration is a major cause of blindness. Microglia are known to play key roles in the pathogenesis and progression of neural degeneration. We established several new system to analyze photoreceptor degeneration in vitro by organ or primary cell culture, and human iPS cells. In addition, using one of such systems, we made screening of effects of the naturally occurring molecules on microglial activation and identified apigenin as a strong suppressor of microglial activities.

2. Molecular basis and development of new therapeutic strategy for retinal photoreceptor degeneration. We established several retinitis pigmentosa, inherited photoreceptor degeneration disease leading to blindness, patients derived humas iPS cell lines. Using the cells and other experimental systems, we revealed mechanism how mutations of certain genes leads to photoreceptor death in the retina. This work is in collaboration with Prof Bruce Conklin of UCSF.

3. NAD and lipid metabolism in the development and maintenance of the retina. Both NAD synthesis related gene and enzymes in the lipid metabolism lead retinitis pigmentosa by mutations in their gene loci. By using mouse-models and human iPS cells we analyze that how biochemical disturbance of NAD and lipid metabolism lead to failure of maintenance of photoreceptor. Although previous works are working on these issues individually, we hypothesize that the NAD metabolic

circuit and lipid homeostasis affect vice versa. We found that in fact, perturbation of NAD metabolism affects the membrane phospho-lipid contents.

4. Establishment of platform of molecular basis of the retina. We made a series of RNA-seq of retina at various developmental stages, and fractionated retinal cells to rod/microglia/Muller glia/other cells from normal and degenerating retinas, microglia and macrophage of normal and degenerating retinas. In addition, several knockout mice derived retinal cells were also served to RNA-seq. As epigenetic mechanisms, ChIP-seq of several antibodies recognize histone methylated moiety had been performed. These databases are used for almost all of our works, and published one were referred by foreign researchers.

5. Epigenetic mechanisms of retinal development. We are analyzing enzymes related to histone H3K4methylation, H3K27methylation, H3K36methylation on retinal development. We found all these systems are working on cell type and stage specific manner during retinogenesis.

２）Education Activities

Research: Advising the works for students of Ph.D- and master-course (Ph.D candidate 5, master course students 6)

Lectures: School of Medicine, Medical-kyotsu lecture

Soonchunhyang University(SCHU) as adjunctive professor (Sumiko Watanabe)

Gifu pharmaceutical University, special lecture

Nagasaki University school of medicine, special lecture

Thesis degree committee member; School of Medicine, School of Science

OIST (Okinawa Institute of Science and Technology)

３）Social Activities

Sumiko Watanabe: Committee chair, Ethical committee (GC Lymphotec co)

Sumko Watanabe: Organizer, The emergence of Genome based drug discovery

４）International Activities

Soonchunhyang University(SCHU) as adjunctive professor (Sumiko Watanabe)

５）Other matters to be noted

None.

（４）Challenges and Future prospects

Currently, we are working on two main focusing epigenetic mechanisms during retinal development and photoreceptor degeneration mechanisms. There are several projects are on-going such as microglia,

immune-competent cells in retina, histone methylation and demethylation etc, and we use several different systems i.e. human iPS cells, primary cultures, cell lines with diverse technologies. Although the projects are independently performed, the results suggested the issues what we are analyzing are related each other and orchestrated to achieve proper development and maintenance of the retina. Our whole picture gives number of points that had not been recognized to relate each other, and we believe that the such knowledge served new insight for approach to develop drugs and therapeutic strategies.

Project Division of Fundamental Study on Cutting Edge of Genome Medicine

（１）Members

Professor	Arinobu Tojo
Project Associate Professor	Hiroshi Yasui
Postdocs	1
Technicians	2
Others	1

（２）Research objectives

The objectives for the period from April 2016 - June 2020 (4 years and 3 months) were: 1) to publish six papers on genomic cancer medicine research from the Department of Hematology/Oncology, and ten papers from the Division of Fundamental Study on Cutting Edge of Genome Medicine, 2) to organize educational activities for the general public, and 3) to initiate three international collaborative studies.

（３）Activity Reports

１）Research Activities

Goals: The Division of Fundamental Study on Cutting Edge of Genome Medicine has conducted primary research, which aimed to establish a system for promoting the practical application of genomic cancer medicine in Japan.

Achievements: The Department of Hematology/Oncology of IMSUT hospital has published eight papers, reporting the results of the research on the practical application of cancer genome medicine. The Division of Fundamental Study on Cutting Edge of Genome Medicine has published 21 papers (Annual Reports 2016, 2017, 2018, 2019). It can be considered that the Division of Fundamental Study on Cutting Edge of Genome Medicine has achieved satisfactory results concerning the publication of papers on the field. However, the importance of drug discovery and drug development in genomic cancer medicine increases year by year as the data of cancer genetic testing suggest that there are not enough treatment options available. The division started research on drug discovery and drug development in the second half of 2017. Since the results of this research have not yet been published, we are trying to raise the level of translational research awareness among the faculty members, to help further establish an appropriate research system for the development of novel cancer drugs.

２）Education Activities

Goal: The division does not conduct educational activities for graduate students; however,

educational activities for the public were organized in an attempt to reach out and communicate the recent developments in the field of cancer genomics.

Achievement: One lecture on genomic cancer medicine was given to university students, and three lectures were given to the public.

３）Social Activities

Goal: In order to promote public acceptance of genomic cancer medicine in Japan, the division aimed to conduct a survey for both experts and the public in Japan and the United States.

Achievement: Our research, entitled “Japan-US Comparative Study for Promoting Cancer Genome Medicine,” was selected as “excellent research” by the Pfizer Health Research Promotion Foundation at the 26th International Joint Research Grant meeting in December 2019. We investigated and discussed the awareness of all stakeholders, including patients, physicians, researchers, genome counselors, and the general public, on genomic cancer medicine. Hearings and discussions were held at the New York premises of the University of Tokyo.

４）International Activities

Goal: The division aims to start three international collaborations related to the promotion of genomic cancer medicine.

Achievement: Four international collaborative studies have started during this period. The first, which began in the second half of 2017, is a US-Japan comparative study to promote genomic cancer medicine. The US-based investigators who participate in the study are Robert Nussbaum (Invitae Corp., USCF), Nikhil Munshi and Teru Hideshima (Dana-Farber Cancer Institute, Harvard University).

The second study, which began in the second half of 2018, is research on artificial intelligence in medicine, in collaboration with several companies in the United States and China.

The third research, which began in the second half of 2017, focuses on the development of novel immunotherapy drugs in multiple myeloma, in collaboration with Kenneth Anderson (Dana-Farber Cancer Institute, Harvard University). The project expanded in Asia in the second half of 2019 and now includes joint research with Professor Hu Jianda, Fuzhou Medical University Union Hospital. The collaboration further extended to the academic exchange between the IMSUT and the Fujian Institute of Hematology, Fujian Medical University, in June 2020.

５）Other matters to be noted

None.

（４）Challenges and prospects

The objectives of the research conducted by this division have evolved from the establishment of a system for promoting the practical application of genomic cancer medicine in Japan to international research on genomic cancer medicine and artificial intelligence. In the future, we will encourage the development of novel cancer drugs, as well as in-vitro diagnostics, to exploit the data from cancer genetic testing.

Social Cooperation Research Programs

Project Division of RNA Medical Science

（１）Members

Project Associate Professor	Masaki Takahashi
Postdocs	1
Others	6

（２）Research objectives

In this division, we aim to create artificial aptamers to target proteins of therapeutic interest and to uncover the molecular mechanism underlying the versatile interaction between nucleic acid and protein of biological significance.

（３）Activity Reports

１）Research Activities

This division has been working on RNA science for drug discovery and basic science through development of novel platform technologies for generating and discovering functional RNAs, mainly RNA aptamers. Briefly, we conducted studies 1) to elucidate degradation mechanism of endogenous mRNAs, 2) to explore microRNAs associated with human diseases for developing another therapeutic strategy, and 3) to establish platform technologies for developing RNA aptamers as a medical agent. As a research activity, we set the goal to publish six or more publications in peer-reviewed journals, and to file at least one IP application for a developed product that seem to possess high potential as a pharmaceutical molecule.

In consequence, we have carried out three research themes described above and resulted in one paper for “1)” (Hashimoto, Y. et al., *Biochem Biophys Res Commun.*, 484(1):1-7 (2017)), one paper for “2)” (Fukuoka M., et al., Mol Ther Nucleic Acids., 11:79-90 (2018)), and three papers for “3)” (Takahashi, M. et al., *Biochimie*, 131: 77-84 (2016), Takahashi, M. *Biochimie*. 145:63-72 (2018), Imashimizu M, et al., *Biology Methods and Protocols*, 3(1)bpy004 (2018)), in addition to publication of 17 peer-reviewed journals where we joined as collaborator. Regarding IP application, we have filed one IP application for an RNA aptamer against TGF-beta by collaborating with an aptamer company, RIBOMIC Inc.

Therefore, it is considered that our set goal has been mostly achieved regarding research activity.

２）Education Activities

To contribute to education, we set the goal of engaging in at least two educational activities.

Consequently, one lecture was delivered in 2017 as an academic frontier lecture to pre-semester students in the College of Liberal Arts and Sciences. By introducing recent advances in nucleic acid-based therapeutic agents, it seemed to be able to contribute education to students. In addition, we served as facilitator for two institutional seminars as part of educational activity. Thus, our aim in education seems to be achieved.

３）Social Activities

Our division, a social cooperation research program, was established in April 2012 under a joint research agreement between the University of Tokyo and RIBOMIC Inc that is startup for developing RNA aptamer as pharmaceutical molecules. Through the social collaboration, as a goal in social activity, we aimed to file at least one IP application for a promising aptamer. Regarding an RNA aptamer raised against transforming growth factor-β1 (TGF-beta1), we have successfully developed and filed its IP application by collaborating with the company. We will continue to engage in research activities aimed at realizing drug discovery based on the advantage of our social collaboration.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

While we have generally been able to achieve various goals, the number of achievements is not much. Given the number of staff in our division, it seems to be no wonder, but in order to improve the number and quality of our output, we will make efforts to secure human resources by stably raising budget. Then, we would like to create and disseminate our achievements more than ever before.

Project Division of Systems Immunology Research (-2019.9)

（１）Members

Project Assistant Professor	Yasumasa Kimura
Project Professor	Satoshi Uematsu
Graduate students	1
Technicians	1

（２）Research objectives

1. Build an analysis pipeline that enables high-speed metagenome data analysis after the next-generation sequence
2. Build an intestinal virome analysis pipeline.
3. Create a database of intestinal bacteria and virus of 100 healthy Japanese people
4. Create the method to examine host-parasite association between intestinal bacteria and bacteriophages
5. To verify the probiotic effect of yogurt on aging

（３）Activity Reports

１）Research Activities

1. Construction of metagenomic data analysis pipeline

In collaboration with Professor Satoru Miyano of the Human Genome Center and Professor Seiya Imoto of the Health Intelligence Center, we have succeeded in constructing a ultr-high speed metagenome analysis pipeline by using GHOST-MP developed by Professor Yasushi Akiyama of Tokyo Institute of Technology on Super computers SHIROKANE and Kei. We can finish the homology search of results of Mi-seq analysis (1run) within 6 minutes. This was one of the world's fastest analysis pipelines at that time.

2. Construction of intestinal virome analysis pipeline

Intestinal lumen contains not only bacterial flora but also resident viral flora. Most of viruses are bacteriophage (phage) that host bacteria. With the development of next-generation sequence analysis, it has become possible to obtain the whole genome of intestinal phage without anaerobic culture of host bacterium, which is technically difficult. However, the preparation of reference genome data for enteric viruses has not progressed, and 99.9% or more cannot be detected. In this area, the difficulty of this analysis is expressed by the word “Viral Dark Matter”. The sequence fragments obtained by the next-generation sequence analysis were assembled accurately and as long as possible, the ORFs were predicted on the created contigs, and the pseudo-cloning of the viral genome can be performed on supercomputer. Furthermore, virus classification was performed,

which enabled to show the composition of the intestinal virus flora. At he end of 2018, we have implemented a pipeline that can automate the classification on the supercomputer Shirokane of the Institute of Medical Science.

3. Creation of a database of intestinal bacteriome and virome of 100 healthy Japanese people

By the end of 2017, the feces of 100 healthy Japanese people had been collected, and the database of intestinal bacteriome and virome of 100 healthy Japanese people was completed during FY2018. The database of bacterial and viral flora in the same stool is the world's first achievement and will be published within 2020.

4. Create the method to examine host-parasite association between intestinal bacteria and bacteriophages

It is possible to search the host of intestinal phage using the results of metagenomic analysis. By using the database of intestinal bacteriome and virome in the same feces of 100 healthy Japanese perople, it is possible to detect the lysogenic phage that becomes prophage. In addition, by extracting the CRISPR spacer sequence from the bacterial metagenomic analysis results, it is possible to search the sequence of phages that had been infected in the past. Based on this information, it became possible to predict the infection relationship including lytic phages.

5. Verify the probiotic effect of yogurt on aging

Through joint research with Meiji Co., Ltd., we conducted an omics analysis on the effects of LB51 yogurt on aging. This research was also a joint research with Professor Eberl of the Institute of Pasteur in France and published the paper in 2018 (Int Immunol. 2018 Jun 26; 30 (7): 319-331.).

２）Education Activities

We provided research guidance for Yuki Usui, a graduate student at the leading graduate school of the Graduate School of Medicine, The University of Tokyo. One of our missions was to train hybrid next-generation researchers who can carry out both experimental and informatics research. In a joint research with Meiji Co., Ltd., she conducted an experiment on the aging effect of yogurt herself, performed omics data analysis centered on informatics analysis under the guidance of Assistant Professor Kimura, and created a dissertation. (Int Immunol. 2018 Jun 26; 30 (7): 319-331.). As part of a leading graduate program, she also studied for three months at the La Jolla Institute for Immunology in San Diego, USA. In addition, her skill in informatics analysis was evaluated, and after graduation she was employed by Chugai. We not only trained hybrid researchers, but also succeeded in career paths to companies.

３）Social Activities

1. Collaboration with Meiji Co., Ltd.

"Analysis of changes in intestinal microbiota and effects of probiotics upon aging and various stress stimuli" (FY2017),
"Metagenome of intestinal microbiota for healthy Japanese "Analysis" (FY2018)
(the principal investigator was Satoshi Uematsu)
2. Collaboration with EA Pharma Co., Ltd.
"Identification of specific intestinal bacteriophages and enterobacteria in patients with Crohn's disease"
(the principal investigator was Satoshi Uematsu)

４）International Activities

In 2015, "Research on strengthening infectious disease surveillance system and intestinal mucosal infection protection against cholera, HIV, etc. in Ghana" was adopted in the AMED SATREPS program with Professor Hiroshi Kiyono as the research representative. In this task, we supported metagenomic analysis at the Noguchi Research Institute, the University of Ghana. A technical staff dispatched from the University of Ghana was instructed how to extract nucleic acids from feces and how to operate a next-generation sequencer. In addition, we trained two graduate students of the University of Ghana for metagenomic data analysis, and established a system for autonomous metagenomic analysis at the University of Ghana.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

A database of intestinal flora and virus flora will be published. In the future, it will be necessary to control intestinal bacteria using phages for various diseases. In addition, we believe that phage therapy will be an indispensable treatment method against multidrug-resistant bacteria, which has become a global problem. We think that it is necessary to carry out social implementation of phage therapy in Japan and, if possible, to establish a center in the Institute of Medical Science to practice phage therapy.

Project Division of Advanced Regenerative Medicine (-2017.9)

（１）Members

Project Associate Professor	Satoshi Yamazaki
Postdocs	2
Graduate Students	1
Technicians	3
Others	1

（２）Research objectives

In order to further enhance the research system of regenerative medicine, we will proceed with basic research such as culture research using hematopoietic stem cells and mesenchymal stem cells that are tissue stem cells, differentiation research into various tissue cells, analysis of cell function, etc. The mission of this department is to develop advanced regenerative medicine products and develop human resources who can play an active role internationally. In addition, because it is a social collaboration research department with Rohto Pharmaceutical Co., Ltd., it is a project department that has the characteristics of combining the technology and experience of universities and companies.

（３）Activity Report

１）Research Activities

Focused on mesenchymal stem cells, we developed efficient isolation and culture methods from tissues, methods for inducing differentiation into various tissue cells, and new quality control methods for the purpose of producing high-quality mesenchymal stem cells. Conducted the basic research aimed at. Furthermore, we had developed and developed human resources for advanced regenerative medicine products targeting intractable diseases, which were said to be impossible to cure with conventional drugs such as low molecular weight compounds.

２）Education Activities

None.

３）Social Activities

From joint research with Rohto Pharmaceutical Co., Ltd., we have conducted research aimed at developing mesenchymal stem cell expansion technology and treatment of intractable diseases, and have also jointly applied for patents.

４）International Activities

None.

5）Other matters to be noted

None.

（4）Challenges and Future prospects

This Division has completed and closed as of September 30, 2017.

Project Division of International Advanced Medical Research

（１）Members

Project Associate Professor　　Koichiro Yuji

（２）Research objectives

The mission of the Project Division is to apply changes in advanced medical research at the Institute of Medical Science at the University of Tokyo (IMSUT).

（３）Activity Reports

１）Research Activities

Our activities include field research in which innovative medicine will be implemented; cross-disciplinary education of physicians, researchers, and professionals; and collaboration in innovative projects in the Coastal Area Life Innovation Comprehensive Special Zone for International Competitiveness Development.

The division's goal for the period of April 2016 - March 2019 was to make one or more recommendations on bottlenecks and solutions for advanced medicine. We researched on bottlenecks and solutions for the utilization of artificial intelligence in the medical field. The result of the study was cited in the Ministry of Health, Labour and Welfare Director's Notice in December 2018. Besides, we compiled the report on the utilization of artificial intelligence in the medical field by the Science Promotion Council of the Japan Medical Association.

About concerning the bottlenecks in advanced medicine, we believe we have achieved our goal. However, we were not able to make sufficient recommendations for solutions. We aim to make at least one recommendation for a specific solution in the future.

２）Education Activities

Training of human resources to promote advanced medicine was conducted.　The division's goal for the period of April 2016 - March 2019 was to develop one or more specialists. At IMSUT hospital, which is a training affiliation of the Japanese Society of Clinical Pharmacology, two physicians were certified as Board-certified Clinical Pharmacologists and one was certified as a fellow by the Japanese Society of Clinical Pharmacology.

About concerning human resource training, we believe we have achieved our goal in clinical pharmacology. However, we were unable to educate and train specialists in other fields. In the future, we will continue to train specialists in clinical pharmacology, and aim to develop human resource training in other fields.

３）Social Activities

The division's goal for the period of April 2016 - March 2019 was to compile a project proposal for the promotion of advanced medicine in the Coastal Area Life Innovation Comprehensive Special Zone for International Competitiveness Development. However, the project proposal remains in the planning stage. We will aim to draft an appropriate proposal with a deadline of three years or less.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

We have achieved several missions in our research and training activities, but there are still challenges that remain in the field of social activities, and we will aim to draft an appropriate proposal in the future.

Project Division of ALA Advanced Medical Research (-2020.3)

（１）Members

Project Professor	Kenzaburo Tani
Project Senior Associate Professor	Yasushi Soda
Assistant Professors	Shohei Miyamoto, Yasuki Hijikata
Postdocs	1
Graduate students	1
Technicians	2
Others	8

（２）Research objectives

We have been heavily involved in developing gene /cell therapy and drug therapy for intractable disease including cancers. From April 2016 to March 2019, our projects are as follows. a) Evaluation of 5-aminolevulinic acid(5-ALA) as therapeutic modality for malignancies, b) Development of detection methods for circulating tumor cells using 5-ALA, c) Development of therapeutic methods for intractable hematological disorders using 5-ALA, d) Clinical development of safe and effective Coxsackie virus type B3(CVB3) virotherapy, and e) Establishment of iPS cells using novel non-transmissible measles virus (MV) vector. We will report our new findings to international journals and also translate these new findings to clinical field.

（３）Activity Reports

１）Research Activities

a) Evaluation of 5-aminolevulinic acid(5-ALA) as therapeutic modality for malignancies; We have been trying to find the combination effects of Coxsackie virus type B3(CVB3) with 5-aminolevulinic acid(5-ALA) against malignancies.

b) Development of detection methods for circulating tumor cells using 5-ALA; We could flow cytometrically detect possible protoporphyrin IX (PpIX) positive tumor cell fraction after the coculture of peripheral blood cells with 5-ALA. We have been trying to identify these PpIX-positive cells as real tumor cells using single cell analysis method.

c) Development of therapeutic methods for intractable hematological disorders using 5-ALA; Sickle cell disease (SCD) is one of the most prevalent congenital hematological disorders due to the production of mutant hemoglobin S synthesis caused by the point mutation of hemoglobin beta chain gene. We introduced SCD model mice and have been trying to observe the possible

therapeutic effects of 5-ALA to SCD (patent submitted).

d) Clinical development of safe and effective Coxsackie virus type B3(CVB3) virotherapy; We have been developing CVB3 virotherapy as a new therapeutic modality for malignancy (PCT/JP2014/060988). To clinically develop the next generation safer CVB3 virotherapy, we use miRNA technology and have developed the second generation CVB3 (Jia Y, et al., Mol Ther Oncolytics 12:246-258, 2019). We also have been trying to translate the gene-modified CVB3 to clinical field.

e) Establishment of iPS cells using novel non-transmissible measles virus (MV) vector; We have developed novel non-transmissible MV vector and successfully established iPS cells using the MV vector. Interestingly, the MV vector could produce both of the primary and the naïve iPS cells (patent submitted, Hiramoto T, et al., Mol Ther 28:129-141, 2020). We could also develop blue light sensitive MV virotherapy in vitro and in vivo (patent submitted, Tahara M, et al., Proc Natl Acad Sci USA 116: 11587-11589,2019).

２）Education Activities

Mr. Jia Y, the first author of Mol Ther Oncolytics 12:246-258, 2019, obtained Ph.D. degree in the University of Tokyo and started working in The Second Xiangya Hospital of Central South University as a pediatrician. Prof. Tani lectured medical and/or dental students in Kyushu University, Yamaguchi University and Miyazaki University.

３）Social Activities

We collaborated with neopharma Japan Co., Ltd, Shinnihonseiyaku Co., Ltd and Neoprecision Therapeutics Co., Ltd.

４）International Activities

Dr. Soda collaborated with Dr. Inder Verma at Salk Institute, USA and published collaborated data (Verma S, et al., Proc Natl Acad Sci USA 116:7363-7370, 2019).

５）Other matters to be noted

None.

（４）Challenges and Future prospects

We could publish our new findings in international journal. We, however, still need proceed clinical translation to help patients suffered from intractable diseases including cancers.

Project Division of Advanced Biopharmaceutical Science

（1）Members

Professors	Hirotoshi Tanaka, Kouhei Tsumoto
Project Associate Professor	Satoru Nagatoishi
Others	2

（2）Research objectives

Research activities: Publish at least 5 papers in international scientific journals, at least 10 papers at international conferences and at domestic conferences every year. At least 10 presentations are made each year. Also, in the social cooperation section, we will publish a paper on joint research with a company every year from the second year of social cooperation. We will publish at least one paper.
Educational activities: For more than a dozen graduate students in Kohei Tsumoto's laboratory, who are also working in this laboratory, to earn their degrees.

（3）Activity Reports

1）Research Activities

Nine papers were presented in FY2017 and twelve in FY2018. We presented five papers in international conferences in FY2017 and three in FY2018. Domestic conferences presented 31 papers in FY2017 and 31 in FY2018. The number of papers presented each year is more than the target number, and we have fully achieved the results.

2）Education Activities

Two doctoral degree examinations were conducted inand six in FY 2018 (three of which were working PhD students). Five of them were employed (two were in research positions at major pharmaceutical companies).

3）Social Activities

We have achieved our goal with the publication of one paper in FY 2018 on the collaboration with a company.

4）International Activities

None.

5）Other matters to be noted

Three press releases

（４）Challenges and Future prospects

From 2019 onwards, our goal is to publish at least five papers in international scientific journals, and to publish the results of our research in international conferences. We will present at least 10 papers every year at a national conference. In this division, we publish at least one paper on joint research with a company every year.

Project Division of Cancer Biomolecular Therapy

（１）Members

Project Professor	Hideaki Tahara
Project Associate Professor	Hiroaki Uchida
Postdocs	5
Graduate students	1
Technicians	3
Others	2

（２）Research objectives

To publish two research reports from the Division of Bioengineering (transferred to the Project Division of Cancer Biomolecular Therapy in April 2018) in European-language scientific journals each year.

To submit an application for or obtain one patent from this division per year.

To provide all postgraduates enrolled in this division an education enabling them to obtain their degrees.

（３）Activity Reports

１）Research Activities

To date, the Division of Bioengineering (transferred to the Project Division of Cancer Biomolecular Therapy in April 2018) has made progress in fundamental research aimed at clinical application to cancer immunotherapy, oncolytic virotherapy, and antibody-based cancer therapy. Between April 2016 and March 2019, the targets in this division have been cancer immunotherapy based on understanding of immune-regulatory mechanisms by cancer cells; oncolytic virotherapy using receptor-retargeted oncolytic herpes simplex virus (RR-oHSV); and exploration of novel antibodies applicable to antibody-drug conjugates. The expected outcome during the relevant time was publication of about six reports in European-language journals, application for or obtaining three patents, and development or strengthening of academic-industrial links on the basis of the research results. The actual outcome has been that 19 reports of the research results have been published in European-language journals, applications have been submitted for seven patents, five patents have been obtained, and academic-industrial links have been established with Ono Pharmaceutical Co., Ltd. It is therefore considered that, from all perspectives, including publication in European-language journals, applying for and obtaining patents, and academic-industrial links, the outcome has been satisfactory. We see no problems during the relevant period. The teaching staff and the graduate students will continue their effort to make progress in research.

２）Education Activities

We have conducted the educational activities of postgraduates in this division. The target for this division from April 2016 to March 2019 was to provide education such that three special research students would be awarded PhDs, one special research student would be awarded a master's degree, and five students would be awarded master's degrees internally. The outcome was that three special research students were awarded PhDs, one special research student was awarded a master's degree, and four students were awarded master's degrees internally. One of the master's students had to take time off to recover from illness, but has continued to be supported, and it has been decided that he/she will return to college in April 2019. It is therefore considered that the outcome of the educational activities in this division has been satisfactory. It is not considered that there have been any problems during the relevant period. Progress will continue to be made with educational activities in future, centered on the professors.

３）Social Activities

This division initiated to collaborate with Ono Pharmaceutical Co. in 2017. In addition, a social cooperation research program was set up together with Ono Pharmaceutical Co. in 2018. Furthermore, Dr. Uchida (Project Associate Professor) has applied for a patent on the basis of collaboration with Daiichi-Sankyo Co., Ltd.

４）International Activities

Dr. Uchida (Project Associate Professor) has applied for and obtained patents on the basis of achievements in the University of Pittsburgh, USA.

５）Other matters to be noted

None.

（４）Challenges and Future prospects

Taken together, it is considered that, from all perspectives, including research activities, educational activities, social activities, and international activities, the outcome in this division has been satisfactory. It is not considered that there have been any problems during the relevant period. The teaching staff and the graduate students will continue their effort to make progress in research.

Project Division of Genetic Medicine and Disease Prevention

（１）Members

Professor	Yoshinori Murakami
Project Professor	Takayuki Morisaki
Postdocs	1
Others	4

（２）Research objectives

Most human diseases, from cancer to common diseases, develop and progress through the combinations and interactions of genetic background, acquired environmental exposure, life style factors and aging. Therefore, in order to promote healthy lives of citizens, it is a prerequisite to identify health risks of individuals both at the time of birth and later in life and to provide them with appropriate approaches to disease prevention when necessary. For this purpose, the Project Division of Genomic Medicine and Disease Prevention was established on July 1, 2019 in cooperation with Nippon Telegram and Telephone Cooperation (NTT). The goal of our project is to develop personalized and precision prevention of diseases by integrating genomic information, health records and life style data into a new predictive program of disease prevention for the healthy life of individuals.

（３）Activity Reports

１）Research Activities

Project Division of Genetic Medicine and Disease Prevention was established in July 2019 to obtain scientific evidence to develop a new predictive program for disease prevention for healthy lives of individuals by integrating genomic information into the classic health-related information, such as individual health records, life style data and age.

The goal of the research activity in FY2019 of this Project Division is, therefore, to establish a “GenoVision” project. In this project, the employees of NTT group who got periodic physical examinations and provided an informed consent are recruited to a comprehensive survey program of individual SNPs. The purposes of this program are as follows. 1) To return the results of the selected SNPs to participants, which are directly involved in the activities of important biological enzymes for maintaining the healthy lives of individuals. 2) To obtain basic information for the research on polygenic risk scores for establishing a next-generation approach to promoting healthy life on the basis of the genomic information of individuals.

For this purpose, numerous relevant publications were searched comprehensively and the candidate SNPs were selected to meet the following three criteria. 1) The SNPs are directly involved in the enzymatic functions or expression. 2) The enzymatic activities are directly involved in

pathological or unhealthy phenotypes. 3) The enzymatic dysfunction and the resultant unhealthy phenotype are shown to be mitigated by behavioral changes. On the basis of these criteria, SNPs at the *MTHFR* gene affecting the activity of methylenetetrahydrofolate reductase for folic acid production and SNPs at the *ADH1B* and the *ALDH2* genes affecting the activity of alcohol dehydrogenase and aldehyde dehydrogenase, respectively, for alcohol metabolism were selected as the initial targets of this project. Recruitment of participants started in June 2020 and the individual SNPs are being analyzed. Thus, research achievements of this Project Division in FY2019 are satisfactory.

２）Education Activities

Since the Project Division of Genomic Medicine and Disease Prevention has been established as a Social Cooperation Research Program with NTT and has not been integrated into the graduate school systems in the University of Tokyo, the division currently has no education activity.

３）Social Activities

Project Division of Genomic Medicine and Disease Prevention concluded a joint research agreement with NTT Life Science Corporation and designed and constructed a collaborative “GenoVision” project as described above. This Division is also collaborating and cooperating on the project with the Center for Disease Prevention, NTT Medical Center, Tokyo.

４）International Activities

None.

５）Other matters to be noted

None.

（４）Challenges and future prospects

The next goal of the Project Division of Genomic Medicine and Disease Prevention is comprehensive SNP analysis of individual participants and combinatorial study with healthy records and life-style data for establishing polygenic risk score to predict susceptibilities of diseases, which will start after “GenoVision” system is launched. The total number of participants in the “GenoVision” project is estimated to be around 60,000 cases, although the estimation might be changed by the COVID-19 epidemic. Staff scientists for this project division are being recruited.

External Review Meeting

Date & Time: Thursday, January 21st, 2021. 9:00-11:00
Meeting style: Online meeting via the Zoom website

<Schedule>

09：00	Opening declaration, Introduction of participants, Description of meeting schedule
	Welcoming remarks from the Dean of IMSUT
	Presentation of IMSUT's general statement (Dean Yuji Yamanashi)
09:15	Presentation of Group 3 (Prof. Kensuke Miyake)
	Presentation of Group 2 (Prof. Yoshinori Murakami)
	Presentation of Group 1 (Prof. Atsushi Iwama on behalf of Prof. Mutshiro Takekawa)
	Presentation of Group 0 (Prof. Seiya Imoto)
	Presentation of Group 4 (Prof. Toshio Kitamura)
	Presentation of Group 5 (Prof. Yasuhiro Yamada)
	Presentation of IMSUT Hospital (Prof. Arinobu Tojo)
09:55	Q&A
10:05	Exchange of Views (External Review committee members only)
10:35	Comment from the Chairman of External Review committee
	Individual Comments from each committee member
10:55	Closing declaration

[Moderator: Vice-Dean Makoto Nakanishi]

Report of the External Review Committee

I Overall assessment of the state of IMSUT

1. Organization and research implementation/support/promotion system

It would be important to highlight the scientific achievement and vision of the institution for the last and next 4 years as a story rather than individual values. There are very few female and foreign PIs at any level. IMSUT could make a more concerted effort in the recruitment to promote gender balance and internationalization.

We can see some discrepancy between structure of Departments (G０-5） and their mission.

More simple structure of Department/Center such as Infection/Immunity, Genome/Cancer and Stem cell biology, including translational studies at each level may be efficient to show up the international branding in the research.

2. Research activities and dissemination of research results

IMSUT is one of the biggest institutes affiliated to University. (Fuchi-ken). The number of peer-reviewed papers has been significant. In particular, it is impressive that the percent of papers of IF10 or greater reached 16% in FY2019. They demonstrated the strong research achievement in the fields of genomics, microbiology/immunology and cancer and stem cell biology. To show the integrity in scientific vision unique to IMSUT, however, some common concept/aim should be proposed to establish interdisciplinary science. Especially, more interdisciplinary study may be required, such as in bioengineering and chemical biology. To do so, it is also important to collaborate within the Institute or with the department of University of Tokyo (Hongo and Kashiwa campus).

Although they are looking to expand the translational research in the affiliated hospital, it is still under way and is not very visible. The number of domestic and international patents also increased over the review period; however, it is not clear how many of those are licensed to be commercialized and resulted in revenue generation for IMSUT.

3. Education activities and development of young scientists

As a leading research Institute, they should be more international in attracting young researchers from abroad. They should strengthen the implementation of the programs that promote exchange of young researchers between Japan and overseas countries. Although each center has tried to recruit talented young PIs, more solid tenure-track system should be introduced. It is important to articulate all the current efforts supporting career development of students and postdoctoral fellows into an institutional vision for training the next generation of researchers,

4. Social cooperation and contributions to academia

It is questionable that IMSUT has distinct recognition even in Japan. The press coverage is often about University of Tokyo. It may be advisable to try to promote IMSUT as a national leader in one or two topics. This lack of distinctive branding is probably more of a problem from an international point of view. Perhaps a series of internationally-recognized workshops or conferences in one or two topics with clear IMSUT brand would help.

5. International activities

The quantity of international research activities and projects is impressive. However, the report should single out a couple of them to elaborate on their impact, especially some big international projects where IMSUT plays a leading role. The information on international recruitments at every level should be addressed.

II Assessment of the specific IMSUT departments/centers

G0 Human Genome Center：

Human Genome Center (HGC), including Health Intelligence Center before its merge into HGC, plays a unique role in IMSUT. In addition to regular research and educational activities, HGC has a mission to develop and maintain an informatics infrastructure for biomedical sciences in Japan with its supercomputer system SHIROKANE. There have been significant improvements of this infrastructure together with new developments of AI and other informatics technologies, which result in a large number of collaborative projects with both Japanese and overseas researchers. The mission of HGC is to promote human genome research and personalized medicine. Key to linking sequenced genomes to any meaningful features for use in personalized medicine lies in informatics technologies.

A newly formed laboratory for ELSI (ethical, legal and social issues) can work for a unique and effective combination of research activities.

It is unclear how artificial intelligence and each research department will be integrated with the current programmatic priorities to further the goals of the institution.

G1 Department of Basic Medical Sciences：

The strength of the research is on 1) normal and malignant hematopoietic stem cells, 2) iPSCs chimerism for organ replacement, and 3) translational research for cell replacement therapies. This could be more strongly highlighted in the overall presentation of Group 1 and articulated as a strength for the overall research mission of the institution.

Clarifying the intra- and inter-collaboration within Group 1 and with other departments/centers in the institute by highlighting joint publications/projects/funding would help with the evaluation of the integration of this group.

G2　Department of Cancer Biology：

Department of Cancer Biology in IMSUT has long played and is still playing a central role at the frontier of basic life sciences, e.g., biochemistry, molecular biology, and genetics, in Japan. In addition to the basic cancer sciences, this department is currently making stronger efforts to promote translational research based on original findings in each laboratory.

This is inevitably quite a small number of researchers in the very competitive area of molecular cancer research. Each group is successful in its own area. However, it may be possible to make more combined impact by effort to focus of all the groups on particular types of cancer, or particular approaches to therapy.

G3　Department of Microbiology and Immunology：

Department of Microbiology and Immunology is well organized to focus on the interaction between host and pathogen. The department is composed of 5 unique divisions. They aim to develop novel therapeutics and prophylaxis of infectious diseases. Especially, they are now playing an important role in the basic virology and vaccine science of COVID19. However,
tighter collaboration and stronger leadership will be required.

Group 3 has a track record of research successes and important contributions to science; ensuring adequate funding and recruitment of young researchers will be critical for continued success.

G4　Advanced Clinical Research Center：

Group 4 consists of cellular therapy, infectious disease and genome medicine. Thus, it seems to be miscellaneous. They are aiming for the translation research. Thus, affiliated hospital should be a hospital for Experimental/Clinical research.

G5　Center for Experimental Medicine and Systems Biology：

G5 also seems to be miscellaneous. It might be time to reorganize G5 within IMSUT.

1. The long-term goal of **the laboratory of Developmental Genetics** has been to generate genetically manipulated mice. The focus has been on various developmental questions using manipulation of mouse embryos. The laboratory has been closed in 2018.

2. **The Division of Stem Cell Pathology** studies epigenetic regulation with focuses on the cellular differentiation, the maintenance of cellular identity, and the pathogenesis including age-related diseases such as cancer at the organismal level. Productivity of the division has been excellent as documented by 10 strong publications in good journals.

3.**The Laboratory of Innate Immunity** works on understanding molecular mechanisms controlling pathogen sensing and TLR responses. The report lists thirteen publications in visible international

journals.

4. **The Laboratory of Reproductive Systems Biology** focuses on mechanisms of germ cell development, spermatogenesis, and fertilization. In addition, the laboratory is a core member of the "Gene Manipulated Mouse Section" and performs collaborative projects by generating gene-manipulated mice with other divisions of IMSUT. They list the production of 20 gene manipulated mouse strain per year. Productivity of the laboratory has been excellent with 14 published papers over the last 3 years.

5. **The Laboratory of Systems Biology** investigates the role of certain cytokines in the development of allergic disorders such as asthma and dermatitis, and autoimmune disorders such as arthritis. As judged by the publications, the laboratory is involved in numerous collaborations resulting in more than 40 publications over the last 4 years.

6. **The Division of Genome Engineering** uses genome engineering technologies, such as ZFNs, TALENs, and CRISPR-associated (Cas) nucleases and attempts to overcome limitations of current technology. The laboratory is collaborating with a number of other groups producing genetically modified mice. This has resulted in 8 publications in 2019.

7. **The Laboratory Animal Research Center** houses mice and rats under SPF conditions and provides services for mouse embryo manipulation and for generating genetically modified animals with genome editing technologies. The laboratory has been successful in generating gene manipulated mice that serve as useful models for a variety of collaborative projects.

8. The Kai Laboratory, using mouse models, is focused on research on various viruses such as Nipa and Morbillivirus. The output of the laboratory is high with 14 publications in international journals over the last 3 years.

9. **The Division of Animal Genetics** generated various engineered immune deficient mouse and rat models for xenotransplantation. They list 9 publications that are also listed in the Division of Genome Engineering output (both centers are directed by Dr. Mashimo).

10. **The Animal Center** is a centralized facility to house various animals equipped with barrier housing rooms for biohazardous experiments, X-ray Irradiator, MRI and IVIS imaging system. The facility provides services to derive mice by IVF and performs embryo manipulations for generating genetically modified mice.

11. **The Amami Laboratory** of Injurious Animals houses non-human primates and has a BSL3 facility. The center focuses on tropical diseases and is involved in numerous outside collaborations. Projects include the study of Habu venom, development of methods for controlling vivax malaria using owl monkeys, analysis of the pathogenesis of measles virus and elucidation of biological characteristics of New World monkeys. Work from the laboratory has been published in 9 papers over the last 3 years. They should discuss about the future plan of this laboratory.

Hospital：

Organization appears to be too diverse in comparison with the manpower. They should clarify the clinical focus, for example, in the cancer program and gene therapy in the hospital which could provide some joint activities. It is essential to tightly linked with the University Hospital in Hongo or general hospital nearby to maintain the advanced standard therapy.

III. Comprehensive review of IMSUT

The platform of research institutes affiliated to University. (Fuchi-ken) has not been so well explained in the web. Thus, overseas researchers could not understand the position of Fuchi-ken in the academy in Japan.

We hope IMSUT should play a role model in Fuchi-ken. IMSUT should discuss about the development/direction to World Premier International Research Center (**WPI**) Initiative.

In WPI, 13 research centers are tackling great challenges in order to establish “Highly visible research centers”, which attract top-notch researchers from all over the world and further improve the quality of Science and Technology. They should discuss about the future (10-years) shape of IMSUT from the aspect of research system in Japan. The mission of Fuchi-ken should be evaluated every 5 years, since the project may change as time goes by.

Appendix (regarding the format)

There is a lack of information on the overall number of faculty (senior/junior) within the entire institution and its evolution (new recruit/departed members) over the last 4 years. The same is also missing for the number of trainees (student/postdocs) and supporting staff members, making it difficult to assess the dynamic growth of the institution. Information and the distribution between male/female and domestic/foreigner researchers for each of those categories (faculty/trainee/staff) would also be informative in order to assess their efforts in achieving greater integrations over the last 4 years. The suggestion would be to share the common table in IMSUT, showing the evolution of those numbers over the period being evaluated, and to state the objectives of the institution regarding recruitment policy for the next evaluation period.

It is suggested for the annual faculty evaluation is to avoid an over emphasis on number of publications, amount of grants, etc. It is more important to ask for clear statement of both short-term and mid-/long-term impact. For short-term: the best or most interesting result this year is. For mid/long

term: how the results of 5 years ago now show an observable impact (e.g. citation or other forms of usage) on the field.

Postscript

Through the external review process, we discovered a lot about ourselves from an objective perspective. Prior to the committee meeting, we conducted a self-inspection and evaluation of the current situation in our laboratories and departments over the past four years, and reported the results to the committee. At the committee meeting, we also explained and discussed current and future pressing issues with the reviewers. Despite the meeting's online nature, we were confident that the external reviewers' comments would provide essential guidance for us to improve as an international and multidisciplinary institute in the fields of medical science. Thankfully, the reviewers provided their external review summary in the form of reports based on objective analysis. This report is invaluable, because it is summarized as a consensus of leading scientists from various research fields and nations. Finally, we would like to express our deepest gratitude to the reviewers for all their efforts amidst the current COVID-19-imposed circumstances, and take this report seriously as a critical guide for further strengthening our institute.

March 30, 2021
Yuji Yamanashi
Dean of IMSUT