IMSUT Hospital

Department of Medicine (Department of Hematology/Oncology)
内科（血液腫瘍内科）

Professor	Arinobu Tojo, M.D., D.M.Sc.	教　授	医学博士	東　條　有　伸
Associate Professor	Satoshi Takahashi, M.D., D.M.Sc.	准教授	博士（医学）	高　橋　　聡
Associate Professor	Yoichi Imai, M.D., Ph.D.	准教授	博士（医学）	今　井　陽　一
Associate Professor	Tokiko Nagamura-Inoue, M.D., D.M.Sc.	准教授	博士（医学）	長　村　登紀子
Project Associate Professor	Hiroshi Yasui, M.D., D.M.Sc.	特任准教授	博士（医学）	安　井　　寛
Assistant Professor	Tomohusa Fukuyama, M.D., D.M.Sc.	助　教	博士（医学）	福　山　朋　房
Assistant Professor	Seiko Kato, M.D., D.M.Sc.	助　教	博士（医学）	加　藤　せい子
Assistant Professor	Takaaki Konuma, M.D., D.M.Sc.	助　教	博士（医学）	小　沼　貴　晶
Assistant Professor	Seiichiro Kobayashi, M.D., D.M.Sc.	助　教	博士（医学）	小　林　誠一郎
Assistant Professor	Muneyosi Futami, M.D., D.M.Sc.	助　教	博士（医学）	二　見　宗　孔
Assistant Professor	Toyotaka Kawamata, M.D., D.M.Sc.	助　教	博士（医学）	川　俣　豊　隆
Assistant Professor	Kazuaki Yokoyama, M.D., D.M.Sc.	助　教	博士（医学）	横　山　和　明
Assistant Professor	Junya Makiyama, M.D., D.M.Sc.	助　教	博士（医学）	牧　山　純　也

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.

1. Artificial intelligence (AI)-guided precision medicine approach to hematological malignancies.

Yokoyama K[1,7], Yokoyama N[2,6], Nakamura S[3], Ogawa M[3], Takei T[3], Kobayashi M[3], Ando S[1], Kondo K[1], Mizusawa M[1], Isobe M[1], Tanoue S[1],

Kawamata T[1], Makiyama J[1], Konuma T[1], Kato S[1], Imai Y[1], Takahashi S[1,3], Shimizu E[4], Yamaguchi R[4], Imoto S[5], Furukawa Y[2,6], Miyano S[4], Tojo A[1,3]: [1]Department of Hematology/Oncology, IMSUT Hospital [2]Department of Applied Genomics, IMSUT Hospital [3]Division of Molecular Therapy [4]Laboratory of Genome Database [5]Division of Health Medical Data Science [6]Division of Clinical Genome Research [7]Center for Gene and Cell Therapy

Next generation sequencing (NGS) of cancer genome is now becoming prerequisite for accurate diagnosis and proper treatment in clinical oncology (Precision oncology). While the genomic regions for NGS expand from a certain set of genes to whole exome or whole genome, the resulting sequence data becomes incredibly enormous, and then makes it quite laborious to translate the genomic data into medicine, so-called annotation and curation. We organized a clinical sequencing team and established a bidirectional (bed to bench and bench to bed) system to integrate clinical and genomic data in blood cancers. We also started a collaborative research with IBM Japan to adopt artificial or augmented intelligence (AI), Watson for Genomics (WG), to the pipeline of medical informatics. Genomic DNA was prepared from cancer cells as well as normal tissues (buccal swab) in each patient and subjected to NGS. Sequence data was analyzed using an in-house semi-automated pipeline in combination with WG, which was used to identify candidate driver mutations and relevant pathways, from which applicable drug information was deduced. Until now, we have analyzed as many as 200 patients with hematological malignancies including AML, MDS, MPN, et al., and could obtain many informative findings. Although actionable mutations are quite insufficient for clinical practice mainly due to the lack of available molecular-targeted agents, our preliminary results indicate that AI can be a promising support tool for precision medicine.

2. Nested polymerase chain reaction with specific primers for Mucorales in the serum of patients with hematological malignancies.

Hirano M[1,2], Ota Y[3], Koibuchi T[4], Takei T[1,2], Takeda R[2], Kawamata T[2], Yokoyama K[2], Uchimaru K[2,5], Yotsuyanagi H[4], Imai Y[2], Tojo A[1,2].: [1]Division of Molecular Therapy [2]Department of Hematology/Oncology, IMSUT Hospital [3]Department of Diagnostic Pathology, IMSUT Hospital [4]Department of Infectious Diseases and Applied Immunology, IMSUT Hospital [5]Laboratory of Tumor Cell Biology, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences

Mucormycosis is an opportunistic infection occurring in immunocompromised hosts with hematological malignancies. Mortality due to mucormycosis in patients with hematological malignancy is high. However, the clinical symptoms of mucormycosis are poorly characterized, and diagnosis is difficult due to the lack of specific culture or serological markers or antigens. We present two cases in which nested polymerase chain reaction with specific primers was used in the serum of patients with hematological malignancies.

3. Monocyte subsets and their phenotypes during treatment with BCR-ABL1 tyrosine kinase inhibitors for Philadelphia chromosome-positive leukemia.

Konuma T[1], Kohara C[2], Watanabe E[3], Mizukami M[4], Nagai E[4], Tanoue S[1], Isobe M[1], Jimbo K[2], Kato S[1], Ohno N[1], Takahashi S[1,2], Tojo A[1,2].: [1]Department of Hematology/Oncology, IMSUT Hospital [2]Division of Molecular Therapy [3]IMSUT Clinical Flow Cytometry Laboratory [4]Department of Laboratory Medicine, IMSUT Hospital

BCR-ABL1 tyrosine kinase inhibitors (TKIs) are effective agents in the treatment of Philadelphia chromosome-positive leukemia. However, vascular events have developed in some patients receiving each TKI. The perturbation of circulating monocyte subsets and their expressions of chemokine and scavenger receptors are associated with the development of cardiovascular events. Here, we examined the subsets of circulating monocytes and their phenotypes in 51 patients treated with imatinib, nilotinib, and dasatinib, and 11 healthy subjects in our institute. Except for a negative association between the number of classical monocytes and imatinib treatment, the proportions and numbers of monocyte subsets were not significantly associated with TKI treatment. However, chemokine receptors, CCR2, CX3CR1 on classical monocytes, and scavenger receptor, CD204, on intermediate and non-classical monocytes were significantly associated with TKIs. These data demonstrated the relationships between alterations of chemokine and scavenger receptors on different monocyte subsets and the TKI treatments.

4. Clinical feature of CIDP in adult T-cell leukemia-lymphoma patients after allogeneic stem cell transplantation.

Hirano M[1,2], Imai Y[1], Jimbo K[1,2], Ogawa M[1,2], Ochi K[1,2], Kawamata T[1], Yokoyama K[1,2], Ohno N[1], Uchimaru K[1], Tojo A[1,2].: [1]Department of Hematology/Oncology, IMSUT Hospital [2]Division of Molecular Therapy [3]Center for Gene and Cell Therapy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a progressive or recurrent neurological disorder caused by diffuse demyelination of peripheral nerves with muscle weakness or sensory disorder. Immunological abnormality is supposed to be involved in its pathogenesis. There are few reports about CIDP developed after allogeneic stem cell transplantation (allo-SCT). We investigated clinical feature of adult T-cell leukemia-lymphoma (ATL) patients who experienced CIDP after allo-SCT. We retrospectively analyzed 44 ATL patients who underwent allo-SCT at National Cancer Center Hospital after induction chemotherapy at our hospital. There were 3 patients (2men, 1 female, 57-68 years, 2 lymphoma type, and one acute leukemia type) with polyneuropathy. They achieved partial remission by induction chemotherapy. Complete remission was achieved after peripheral blood SCT and they developed chronic graft versus host disease (cGVHD) in multiple organs. Polyneuropahty occurred from 1 month to 7 years after SCT. Based on the results of nerve conduction study, examination of cerebrospinal fluid, and MRI, the polyneuropathy in all cases was diagnosed as CIDP. HTLV-I-associated myelopathy was excluded by negative HTLV-1 antibody or absence of myelopathy. Neither corticosteroid nor intravenous immunoglobulins was effective. Existence of accompanied cGVHD suggested the possibility that CIDP occurred due to some immune reaction related to allo-SCT. It seems necessary to expand our study to investigate the probability of occurrence, mechanism, and appropriate treatment.

5. Clinicopathological analysis of 14 cases of HIV associated lymphoma in IMSUT hospital

Andoh S[1], JMakiyama J[1], Mizusawa M[1], Kondoh K[1], Kawamata T[1], Yokoyama K[1], Koibuchi T[2], Yasui H[1], Ota Y[3], YImai Y[1], Yotsuyanagi H[2], Tojo A[1]: [1]Department of Hematology / Oncology, IMSUT hospital. [2]Department of Infectious Diseases and Applied Immunology, IMSUT hospital. [3]Department of Pathology and Laboratory Medicine, IMSUT hospital.

Treatment of human immunodeficiency virus (HIV) associated lymphoma is still challenging, partly due to increased toxicities caused by adverse interaction between agents for chemotherapy and antiretroviral therapy (ART). Integrase strand transfer inhibitor (INSTI) has been enrolled in ART for HIV infection since 2008 in Japan. We performed clinicopathological analysis of patients (pts) with HIV associated lymphoma diagnosed and treated in our institution between 2008 and 2017. Fourteen pts were applicable to this study. All but one pt were male. Median age was 50 years old. Eight pts had diffuse large B-cell lymphoma, in which 2 pts were positive for EBV-encoded small RNA without concurrent use of ART. Extranodal lesions were confirmed in 10 pts; 2 pts had central nervous system involvement without concurrent use of ART. Median CD4 lymphocyte counts were 131/μL and median HIV-RNA titers were 7,700 copies/mL. Overall response rate was 86% after first-line therapy. INSTI was used for 13 pts during the treatment. Both chemotherapy and ART was conducted in 11 pts; rituximab was omitted in the first course in 7 of 9 pts with B-cell lymphoma. Among 11 pts, 6 pts developed febrile neutropenia and 8 pts experienced CMV antigenemia. The median follow-up period was 10.5 months. Those pts who responded first-line therapy have not relapsed during the follow-up. Neither CD4 lymphocyte counts nor HIV-RNA titers correlated with survival. INSTI could improve safety and efficacy of chemotherapy against HIV associated lymphoma.

6. Adult T-cell leukemia/lymphoma-related ocular manifestations: analysis of the first large-scale national survey.

Kamoi K[1,2], Uchimaru K[1,3], Tojo A[1,4].: [1]Department of Hematology/Oncology, IMSUT Hospital [2]Graduate School of Medical and Dental Science, Tokyo Medical and Dental University [3]Laboratory of Tumor Cell Biology, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences [4]Division of Molecular Therapy

Adult T-cell leukemia (ATL) is a rare and aggressive T-cell malignancy with a high fatality rate, resulting in a lack of information among ophthalmologists. Here we investigated the state of ophthalmic medical care for ATL and ATL-related ocular manifestations by conducting a first large-scale nationwide survey. The survey was conducted on a total of 115 facilities, including all university hospitals throughout Japan that are members of the Japanese Ophthalmological Society and regional core facilities that are members of the Japanese Ocular Inflammation Society. Data were collected, and the nationwide data on the state of medical care for ATL-related ocular manifestations and ATL-associated ocular findings were categorized, tallied, and analyzed. Of the 115 facilities, 69 (60%) responded. The survey showed that, overall, 28 (43.0%) facilities have experience in providing ophthalmic care to ATL patients. By analyzing the 48 reported cases of ATL-related ocular manifestation, common ATL-related ocular lesions were intraocular infiltration (22 cases, 45.8%) and opportunistic infections (19 cases, 39.6%). ATL-related ocular manifestations are most commonly diagnosed "based on blood tests and the characteristic ophthalmic findings". All cases of opportunistic infection were cytomegalovirus retinitis. Dry eye (3 cases, 6.3%), scleritis (2

cases, 4.2%), uveitis (1 case, 2.1%), and anemic retinopathy (1 case, 2.1%) were also seen. With regard to distribution, a large number of ATL cases (31 cases, 64.6%) were seen in central and metropolitan areas. Given that intraocular infiltration and cytomegalovirus retinitis are common among ATL patients, ophthalmologists should keep this in mind in their practice.

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IMSUT Hospital

Department of Infectious Diseases and Applied Immunology
感染免疫内科

Head, Professor	Hiroshi Yotsuyanagi, M.D., D.M.Sc.	教　授	博士(医学)	四　柳　　宏[*1]
Senior Assistant Professor	Tomohiko Koibuchi, M.D., D.M.Sc.	講　師	博士(医学)	鯉　渕　智　彦
Assistant Professor	Michiko Koga, M.D., D.M.Sc	助　教	博士(医学)	古　賀　道　子[*1]
Assistant Professor	Eisuke Adachi, M.D., D.M.Sc.	助　教	博士(医学)	安　達　英　輔

【兼務】
[*1]Division of Infectious Diseases, The Advanced Clinical Research Center
（先端医療研究センター感染症分野）

Founded in 1981, Department of Infectious Diseases and Applied Immunology (DIDAI) started HIV clinic in 1986. In 2018, 23 new patients with HIV infection have visited to our hospital and 555 patients in total are currently under our clinical management. The total number of in-patients with HIV-infection during 2018 was 27, several beds in our ward have been constantly occupied by patients with not only HIV-infection but also other infectious diseases. Since the number of the staff members of DIDAI is too small to care both outpatients and in-patients, members of the Division of Infectious Diseases and the Department of Infectious Disease Control join the clinic. IMSUT hospital provides the most up-to-date medical treatment to HIV-infected patients in Japan. DIDAI is also a treatment center in Japan for international infectious diseases such as malaria and dengue fever.

1. Treatment of HIV infection in IMSUT hospital: Statistical characteristics of HIV infected patients in IMSUT hospital this year

Tomohiko Koibuchi, Michiko Koga[1], Hidenori Sato, Lay Ahyoung Lim, Eisuke Adachi, Tadashi Kikuchi, Takashi Odawara, Hiroshi Yotsuyanagi[1]: [1]Division of Infectious Diseases, The Advanced Clinical Research Center,

23 new patients with HIV-1 infection visited to our hospital this year (from January 1 to December 31, 2018), and 555 patients in total are under medical management in our outpatient clinic. The total number of HIV-infected in-patients during 2018 was 27. The number of total patients declined in 1997, as shown in Fig. 1, because a part of patients as well as medical stuffs moved to newly established AIDS Clinical Center in International Medical Center of Japan. However, the number of patients started to increase again after 1998 in accordance with Japanese statistics of HIV-infected patients (Fig. 1). Anti-retroviral therapy (ART) has been introduced to 551 HIV-infected patients in our hospital, and most of their HIV viral loads have been well controlled. After one year of ART, the viral loads become less than 100 copies/ml in 99.1% of HIV-infected patients in our outpatient clinic, presumably underscored by the change in the method of quantitative HIV-RNA assay. Conse-

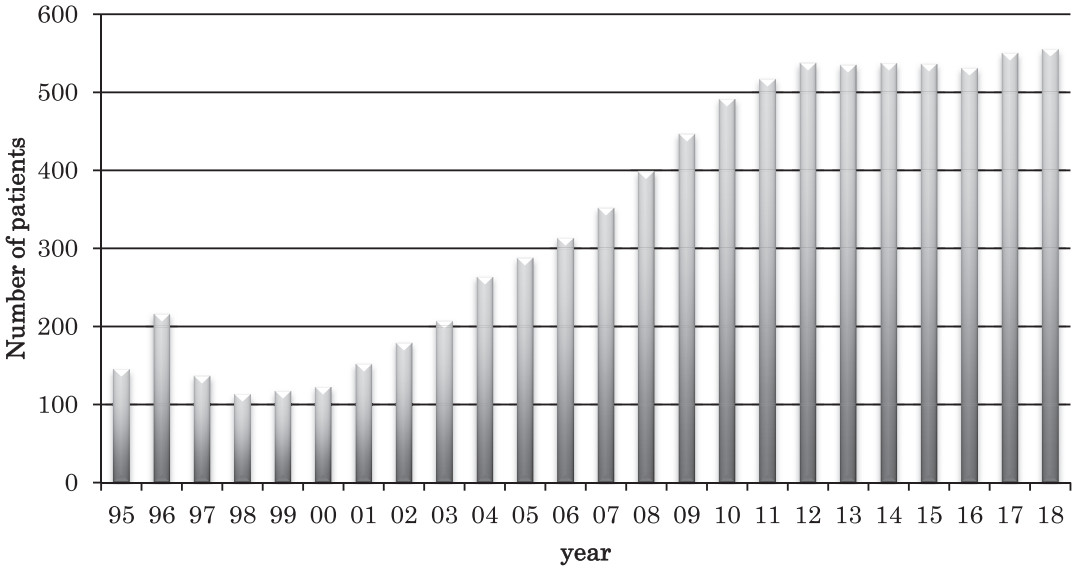

Figure 1. Number of HIV-infected outpatients in IMSUT Hospital

quently, the patients are able to maintain good condition as long as they keep excellent drug adherence rates. The clinical management of HIV-infected patients have been changing from how to treat opportunistic infections into how to control patients with ART.

2. Creating Practice Guidelines for Treatment of HIV-infected Patients in Japan

Tomohiko Koibuchi, Michiko Koga[1], Hidenori Sato, Lay Ahyoung Lim, Eisuke Adachi, Tadashi Kikuchi, Takashi Odawara, Hiroshi Yotsuyanagi[1]: [1]Division of Infectious Diseases, The Advanced Clinical Research Center

The Japanese guidelines for treatment of HIV-infected patients have been established since 1998 with support from Ministry of Health, Labor and Welfare. The representatives from our department have played critical roles in development of the current practice guidelines in Japan. It is vital to create practice guidelines that are specific for the unique genetic and social backgrounds of the HIV-infected population in Japan. In collaboration with other Japanese HIV-experts, the physicians from our department update the practice guidelines annually, as we deem necessary. The guidelines are available at http://www.haart-support.jp/guideline.htm and used widely by Japanese clinicians. They have been viewed 22,081 times in 2018 on the website. In Japan, where the number of HIV-experts are limited compared to other countries, the practice guidelines have substantially improved the standard of care for the HIV-infected patients in our country.

3. Treatment and Clinical Research of Tropical Diseases in IMSUT hospital

Tomohiko Koibuchi, Michiko Koga[1], Hidenori Sato, Lay Ahyoung Lim, Eisuke Adachi, Tadashi Kikuchi, Takashi Odawara, Hiroshi Yotsuyanagi[1]: [1]Division of Infectious Diseases, The Advanced Clinical Research Center

Dozens of important medicines essential for treat ment of tropical or parasitic diseases are not licensed in Japan. For instance, artesunate and injectable quinine for falciparum malaria, pyrimethamine and sulfadiazine for toxoplasmosis, etc. are not licensed. Research Group on Chemotherapy of Tropical Diseases, Research on Publicly Essential Drugs and Medical Devices, Grant from the Ministry of Health, Labour and Welfare had been established to cope with this situation. We are the medical institution of the research group using these orphan drugs if needed, and colleting clinical data. Also, we have clinics for overseas travelers. This year, more than one hundred overseas travelers visited our clinic. The reasons of their visit included prescription of malaria prophylaxis, hepatitis A/B vaccination, other general health consultation, or treatment of tropical diseases such as malaria, intestinal amebiasis, post-exposure prophylaxis of rabies and so on.

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IMSUT Hospital

Department of Rheumatology and Allergy
アレルギー免疫科

Professor	Hirotoshi Tanaka, M.D., D.M.Sc.	教　授（兼務）	医学博士	田　中　廣　壽
Senior Assistant Professor	Noritada Yoshikawa, M.D., D.M.Sc.	講　師	博士（医学）	吉　川　賢　忠
Assistant Professor	Hiroki Yamazaki, M.D., D.M.Sc.	助　教	博士（医学）	山　崎　広　貴

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. As part of an elite teaching hospital, we also contribute to preparing the next generation of leading academic physicians, scientists and clinician-educators.

1. Clinical activities in IMSUT Hospital

Hirotoshi Tanaka, Noritada Yoshikawa, Hiroki Yamazaki, Erika Matsubara

Rheumatologists at our division provide state-of-the-art diagnosis and treatment for systemic autoimmune diseases (total number of patients were approximately 5,000 per year). Our physicians have active basic and clinical research projects and also are involved in training of rheumatology specialists.

Rheumatologic services offered at IMSUT Hospital include:

- Outpatient consultations
- Outpatient specialty care for patients with 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. Development of novel approaches to overcome undesired side effects of glucocorticoid therapy

Hirotoshi Tanaka, Noritada Yoshikawa, Hiroki Yamazaki, Akiko Souta - Kuribara, Erika Matsubara, Yuki Tasaka, Aya Oda, Masaaki Uehara, Mayu Nishimura, Satoshi Fukuyama*, Yoshihiro Kawaoka*: *Division of Virology, Department of Microbiology and Immunology, Institute of Medical Science, The University of Tokyo

Glucocorticoids (GC) have been used clinically for decades as potent anti-inflammatory and immunosuppressive agents. Nevertheless, their use is severely hampered by the risk of developing side effects. Therefore, efforts to understand the complex mechanisms underlying function of GC and GC receptor (GR) are ongoing. Our recent achievement has been applied in clinical settings in IMSUT Hospital.

(i) Developing a novel therapy preventing glucocorticoid-induced muscle atrophy in patients with rheumatic diseases

Reduction of skeletal muscle mass and resulting weakness of peripheral and respiratory muscles cause various clinical problems such as fatigue, frailty, compromised lung function, and worse quality of life. Maintaining skeletal muscle mass and strength, therefore, is critical to preserve full activity, prevent obesity, and decrease the risk of heart disease, diabetes, and cancer. In rheumatology field, reduction of skeletal muscle mass and strength are often critical to negatively affect prognosis of the patients. Especially, prolonged GC treatment for rheumatic disorders accelerates skeletal muscle atrophy known as GC-induced myopathy. However, there is no standardized intervention to prevent or treat this GC side effect. To overcome this issue, we have studied precise mechanisms of GC-induced skeletal muscle atrophy and revealed that administration of branched-chain amino acids (BCAA) ameliorates GC-induced muscle atrophy in animal model. Based on this research, we conducted a clinical trial in IMSUT Hospital and revealed that BCAA supplementation in patients with rheumatic disorders taking GC might be safe and, at least in part, improve their skeletal muscle mass, strength, and function. However, we should use more effort to improve the efficacy of BCAA administration for increasing skeletal muscle mass and establish easily assessable and reliable marker of reduced muscle mass instead of well-validated tools including dual energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), or computed tomography (CT), which are limited to studies and can hardly be routinely established given the high costs and low availability of these methods. Therefore, we are now challenging to establish a novel protocol to administrate BCAA with patients and to identify non-invasive biomarkers for detecting the subjects affected or at risk of GC-induced myopathy and various types of muscle atrophy.

(ii) Developing a novel therapy to improve abnormal fat distribution in patients taking GC therapy

Accumulation of triglyceride stores in selected adipose and extraadipose sites is recognized increasingly as a determinant of insulin sensitivity and its attendant cardiovascular risk. Cushing's syndrome or prolonged GC treatment is responsible for accumulation of fat in selected adipose tissue depots, especially in the face, nape of the neck, and visceral compartments including liver, resulting both clinical and cosmetic problem. We created a mouse model mimicking Cushing's syndrome by free-access drinking of GC solution. We analyzed and compared body fat distribution of such Cushing's mouse model with that of control mouse by micro computed-tomography (CT). We revealed that Cushing's mouse model showed similar fat distribution to human Cushingoid. Moreover, we found that several serum biochemical markers for insulin resistance and cholesterol profile are correlated with fat mass evaluated by micro CT. Now, we are challenging to overcome not only metabolic disorders but also abnormal fat distribution by using Cushing's mouse model and micro CT. We found several candidate compounds and target molecules to ameliorate Cushingoid and are further investigating. For example, an omega-3 fatty acid, eicosapentaenoic acid (EPA), modulates mRNA expression levels of several GC receptor (GR) target genes involved in glycolytic pathway and TCA cycle in skeletal muscles. Moreover, we investigated that selective blockade of skeletal muscle GR by muscle specific knockout of GR in which GC-induced Cushingoid metabolic disorders were mitigated.

3. Development of novel modalities optimizing metabolic condition and body composition targeting transcriptional apparatus

Hirotoshi Tanaka, Noritada Yoshikawa, Hiroki Yamazaki, Akiko Souta - Kuribara, Erika Matsubara, Yuki Tasaka, Aya Oda, Masaaki Uehara, Mayu Nishimura, Satoshi Fukuyama*, Yoshihiro Kawaoka*: *Division of Virology, Department of Microbiology and Immunology, Institute of Medical Science, The University of Tokyo

(i) Development of novel therapeutic modalities against metabolic syndrome targeting the skeletal muscle-liver-fat signalling axis

We have developed an efficient system to screen out the target genes of GR in GC-responsive tissues, and are working with clarification of tissue-specific effects of GC in skeletal muscles. We investigated that a mutually exclusive crosstalk between mTOR and GR coordinately regulates anabolic and catabolic metabolism in skeletal muscle, suggesting the critical importance of the interaction of GR and mTOR in the regulation of metabolism-volume coupling in skeletal muscle. Recently, we have created skeletal muscle - specific GR knockout mice (mGRKO) and revealed that mGRKO show significant increase of their myofiber size and muscle mass and loss of adipose tissues, suggesting that mGRKO mimic the opposite phenotype against metabolic syndrome. Metabolically, mGRKO mice show a drastic shift of energy utilization and storage in muscle, liver and adipose tissues. We investigated that the resulting depletion of plasma alanine serves as a cue to increase plasma levels of fibroblast growth factor 21 (FGF21) and activates liver-fat communication, leading to the activation of

lipolytic genes in adipose tissues. Both Cushing's mouse model and leptin-deficient ob/ob mice exhibited metabolic syndrome involving central obesity, fatty liver, and impaired glucose tolerance. As expected, mGRKO mitigated such metabolic unhealthy phenotype. Targeting the skeletal muscle-liver-fat signalling axis involving glucose-alanine cycle, therefore, would be a novel approach for treatment of patients with obesity, diabetes and metabolic syndrome.

(ii) Clarification of functional crosstalk between GR and sex hormone receptors for body composition and metabolic regulation

It is well known that body composition differs by sex. This sexual dimorphism in human body composition has major implication for sex differences in the risk of various diseases including metabolic syndrome. Although the metabolic syndrome tends to appear more often and/or earlier in adult males than in females, the differences in incidence decrease sharply after menopause, suggesting that sex hormones and their receptors play a certain role in metabolic pathways. Globally, in the metabolic syndrome, there is a decrease in the functions of the androgen-estrogen system. This decrease in systemic sex hormones may have tissue-specific effects on androgen and/or estrogen-responsive tissues such as adipose tissue and skeletal muscle. Recently, impaired estrogen receptor α (ERα) and androgen receptor (AR) action has shown to promote obesity and metabolic dysfunction in humans and mice. On the other hand, we revealed that mGRKO shows the opposite phenotype against metabolic syndrome. Therefore, we hypothesized that clarification of functional crosstalk between GR and ERα/AR in adipose tissue and skeletal muscle contributes to developing a novel therapeutic modality for metabolic syndrome. In addition of mGRKO, we created mERαKO, mGR/ERα double KO, mARKO and mGR/AR double KO. We found that each receptor is involved in regulation of body composition and its sexual dimorphism. Moreover, at least in skeletal muscle, functional crosstalk between GR and ERα and between GR and AR exist and such crosstalk may regulate plasticity of metabolic regulation in skeletal muscle and adipose tissues.

(iii) Clarification of the effect of ageing for regulation of energy storage in skeletal muscle and adipose tissues

Ageing is accompanied by major changes in body composition that can negatively affect functional status in older adults, including a progressive decrease in muscle mass, strength, and quality, accompanied by an increase in fat mass. Such loss of muscle mass and increase of fat mass have recently been termed sarcopenic obesity, which is a high-risk geriatric syndrome related to functional impairment, increased mortality and reduction in quality of life. Because mGRKO shows the opposite phenotype against sarcopenic obesity, analyzing the effect of aging for regulation of energy storage in skeletal muscle and adipose tissue in mGRKO contributes to understanding biological significance of functional communication among multiple organs and the mechanism of sarcopenic obesity. We revealed that mGRKO may be resistant to age-related loss of muscle volume and gain of fat mass.

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IMSUT Hospital

Department of General Medicine
総合診療科

Head, Professor	Hiroshi Yotsuyanagi, M.D., D.M.Sc.	教授(兼務)	博士(医学)	四　柳　　宏	*1
Project Professor	Takayuki Morisaki, M.D., D.M.Sc.	特任教授(兼務)	医学博士	森　崎　隆　幸	*2
Associate Professor	Yoshihiro Hirata, M.D., D.M.Sc.	准教授(兼務)	博士(医学)	平　田　喜　裕	*3
Senior Assistant Professor	Yasuo Matsubara, M.D., D.M.Sc.	講　師	博士(医学)	松　原　康　朗	
Project Assistant Professor	Yasuki Hijikata, M.D., D.M.Sc.	特任助教(兼務)	博士(医学)	土　方　康　基	*4

【兼務】
*1Division of Infectious Diseases, The Advanced Clinical Research Center
（先端医療研究センター感染症分野）
*2Division of Molecular Pathology, Department of Cancer Biology
（癌・細胞増殖部門　人癌病因遺伝子分野）
*3Division of Advanced Genome Medicine, The Advanced Clinical Research Center
（先端医療研究センター先端ゲノム医学分野）
*4Corporate Sponsored Research Programs, Social Cooperation Research Programs, Project Division of ALA Advanced Medical Research（寄付研究部門・社会連携研究部門　ALA先端医療学社会連携研究部門）

The division of general medicine was founded in 2017 taking over the department of advanced medical science. Our aim is to practice total human medical care at IMSUT hospital conducting exploratory clinical research. The members specialize in gastroenterology, oncology, cardiology, endocrinology/metabolism. We have just started our new project in general medicine.

1. Treatment of drug-resistant *Helicobacter pylori* infection

Matsubara Y., Hirata Y.

Some patients fail to respond first- and second-line *Helicobacter pylori* (*H. pylori*) eradication therapy, but third-line eradication is not always done. Meanwhile, penicillin allergy patients do not take routine eradication medicines because insurance coverage regimens in japan include penicillin. In IMSUT, *H. pylori* out-patient clinic, we give eradication therapy for these patients at their own expense, and high rates of successful eradication have been achieved.

2. Endoscopic examination in IMSUT Hospital (Department of General Medicine)

Matsubara Y., Hirata Y.

709 cases of upper gastrointestinal endoscopy and 228 cases of colonic endoscopy were performed from April 1 to December 31, 2017. We have diagnosed relatively rare disease (e.g. infectious disease, malignancy, other disease) in patients with immune dysfunction. We also participated in endoscopic health check up in Minato Ward.

3. Treatment of patients with advanced cancer.

Hijikata Y.

Patients with various types of cancer were treated by standard therapy including chemotherapy, molecular target drugs, immune checkpoint blockade, surgery and radiation therapy. Some of them were treated using next-generation sequencing to guide cancer therapy. By the help of special patient support team undergirded by conference twice a week, overall survival of our patients was longer than respectively reported overall survival. Importantly, it looked like they enjoyed their stay in our hospital. We actively make use the patient's cancer genome data to introduce the best treatment for patient refractory to standard treatment after the approval of our ethical committee. We also are trying to start clinical trials of the personalized neoantigen-based dendritic cell vaccine for patients with esophageal cancer.

4. Successful clinical sequencing for the treatment of patients with cancer who are refractory to standard treatments.

Hijikata Y.

(Case report)

Advances in clinical sequencing have enabled the discovery of actionable alterations that yield clinical benefits. Here, we report successful clinical results for lenalidomide in a case of refractory Sézary syndrome (SS) case based on clinical sequencing.

A 75-year-old male was diagnosed with SS (T4N3 M0B1b) in 2015. He had received various treatments in multiple hospitals, including prednisone, PUVA, extracorporeal photopheresis, bexarotene, romidepsin, total skin electron beam therapy, brentuximab vedotin, IFN α-2b, methotrexate, and pembrolizumab, but his skin lesions did not respond adequately to these therapeutic modalities.

The patient was admitted to our hospital on November 24, 2016. Generalized erythroderma, clinical stage IIIA, was observed. Mogamulizumab was administered, and partial response as Stage 1A was observed on December 27, 2016. However, three new erythema nodosum-like lesions appeared on his upper back and expanded to the trunk (Stage IIB) in January 2017. VP-16 was started on February 27, 2017. Although a part of the skin tumor shrank temporarily, it regrew in April 2017. From April to July 2017, skin electron beam therapy was applied, followed by vorinostat from July 31 for a month, but both had limited effects.

After obtaining informed consent, whole exome sequencing (WES) and RNA sequencing was performed on the biopsied skin tumor for comparison with normal tissue, followed by analysis by our hospital curators using GSEA (Gene Set Enrichment Analysis) and the IBM Watson artificial intelligence (AI). Although WES did not show any actionable mutation, actionable targets were identified based on RNA sequencing and GSEA. Manual curation excluded the ibrutinib, idelalisib, palbociclib, and dasatinib options chosen by AI because evidence for SS was lacking. Mogamulizumab, pembrolizumab, and brentuximab vedotin were already used during his protracted clinical course. Denileukin diftitox was excluded because the latest immunohistochemistry of the lesions showed that they were CD25(−). The two remaining candidates were ipilimumab and lenalidomide. The patient was reluctant to be treated with ipilimumab as its mechanism of action is similar to that of pembrolizumab. We chose lenalidomide because of NF-κB pathway activation in this patient. Lenalidomide binds the Cullin 4 ring-E3 ubiquitin ligase-cereblon complex and degrades lymphoid transcription factors IKZF1 and IKZF3, leading to a decrease in NF-κB. Additionally, a phase II trial of lenalidomide monotherapy for refractory SS revealed effectiveness, and a phase III trial of maintenance therapy was reported. Lenalidomide was administered for 21 days of a 28-day cycle from September 11, 2017. After the first course of treatment, all skin tumors except for one on his sternal region disappeared. The sternal tumor grew gradually and was irradiated with 20 Gy in December 2017. The fifth course of lenalidomide was completed on February 3, 2017. All tumors, including sternal lesions, disappeared, and he finally achieved a complete response.

As far as we aware, this is the first case report to succeed in using clinical sequencing for SS patients. Further clinical studies using clinical sequencing and accumulation of information are needed for AI to be used for routine clinical practice.

5. Diagnosis and management of patients with genetic vascular diseases.

Takayuki Morisaki

Patients and family members with genetic vascular diseases including connective tissue disorders like Marfan syndrome and related diseases were diagnosed by taking their history, physical examination, imaging including echo-cardiography and genetic examination. These patients were followed-up and managed also by doctors in other medical institutions. Study to identify novel pathogenic genes for genetic vascular diseases was being performed.

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IMSUT Hospital

Department of Applied Genomics
ゲノム診療科

Professor	Yoichi Furukawa, M.D., Ph.D.	教　授（兼務）	博士（医学）	古　川　洋　一
Professor	Yoshinori Murakami, M.D., Ph.D.	教　授（兼務）	医学博士	村　上　善　則
Associate Professor	Tsuneo Ikenoue, M.D., Ph.D.	准教授（兼務）	博士（医学）	池　上　恒　雄

Our department has been working on the application of human genome information in clinics. As clinical services in IMSUT Hospital, 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 sequencing for the implementation of genomic medicine

1. Genetic test of human neoplasms

Nozomi Yusa, Yoichi Furukawa

As a part of clinical service, we have performed genetic analysis of human neoplasms such as leukemia and colorectal cancer. In 2018, a total of 550 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.

2. Genetic counseling and related activities

Yoichi Furukawa, Yoshinori Murakami, Yataro Daigo, Tsuneo Ikenoue, Koichiro Yuji, Makoto Hirata, Reiko Sada, Mitsuko Nakazawa, Momoyo Ohki[1], Yoshinari Miyamoto[2], Masae Ono[3], Masahiko Suzuki[4], Mayumi Tamari[4], Toshihiro Tanaka[5], Shiro Ikegawa[6], Hidewaki Nakagawa[6], Natsuko Watanabe[7], Ai Yoshihara[7], Toru Akiyama[8]: [1]Bunkyo University, [2]National Center for Global Health and Medicine, [3]Tokyo Teishin Hospital, [4]Jikei Medical University, [5]Tokyo Medical and Dental University, [6]Center for Integrative Medical Sciences, RIKEN, [7]Ito Hospital, [8]Jichi Medical University.

We provided genetic counseling and genetic tests to clients who visited our counseling clinic. In 2018, we had a total of 51 counseling cases including hereditary breast and ovarian cancer, familial adenomatous polyposis, Lynch syndrome, Turcot syndrome, Peutz-Jeghers syndrome, Marfan syndrome, Usher syndrome, Leber hereditary optic neuropathy, Wiskott-Aldrich syndrome, Charcot-Marie-Tooth disease, spinal and bulbar muscular atrophy, spinocerebellar ataxia, myotonic dystrophy, and congenital epidermolytic ichthyosis. 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.

3. Application of liquid-based genetic diagnosis for the screening of endometrial cancer

Kiyoko Takane[1], Kiyoshi Yamaguchi[1], Tsuneo Ikenoue, Yoichi Furukawa: [1]Division of Clinical Ge-

nome Research, Advanced Clinical Research Center

We have started a study to elucidate the usefulness of liquid-based genetic diagnosis (LBGDx) for screening of endometrial cancer (EC) in collaboration with Department of Obstetrics and Gynecology, Sapporo Medical University. Although liquid-based cytology (LBC) has increased the sensitivity of cytological diagnosis of EC compared with conventional smear cytology, the sensitivity of LBC for the detection of EC is between 70% and 96% and remains unsatisfactory. For LBGDx, we carried out amplicon sequencing of five genes including *PTEN*, *PIK3CA*, *CTNNB1*, *KRAS*, and *TP53* using 48 LBC subjects who underwent endometrial screening. Among 20 samples that were later confirmed as EC, LBC classified 15 samples as "positive or suspicious for malignancy", indicating that the sensitivity of cytology alone was 75% (15/20). On the other hand, LBGDx identified at least one pathogenic variant in 19 subjects that include 17 EC, indicating that the sensitivity of LBGDx alone was 85% (17/20). Although five EC were negative for malignancy by LBC and three were negative for pathogenic mutations by LBGDx, the combination of LBC and LBGDx would successfully diagnose all 20 EC. These data suggested that LBGDx is a useful strategy to improve the sensitivity of screening of EC by LBC.

4. Clinical sequencing for the implementation of genomic medicine

Kiyoshi Yamaguchi[1], Tsuneo Ikenoue, Yoichi Furukawa, Mitsuhiro Komura[2], Eigo Shimizu[2], Rui Yamaguchi[2], Tetsuo Shibuya[3], Satoru Miyano[2,3], Takanori Hasegawa[4], Seiya Imoto[4], Masayuki Kobayashi[5], Kazuaki Yokoyama[5], Arinobu Tojyo[5], Koichiro Yuji[6]: [1]Division of Clinical Genome Research, Advanced Clinical Research Center, [2]Laboratory of DNA Information Analysis, [3]Laboratory of Sequence Analysis, Human Genome Center, [4]Division of Health Medical Data Science, Health Intelligence Center, [5]Division of Molecular Therapy, [6]Division of International Advanced Medical Research, Advanced Clinical Research Center

Cancer cells accumulate multiple genetic and epigenetic changes in the genome. Next-generation sequencing (NGS) allowed us to analyze the comprehensive human genome, and facilitated the identification of germline changes responsible for hereditary diseases and somatic alterations in human neoplasms. In collaboration with Human Genome Center, Health Intelligence Center, and Advanced Clinical Research Center, we have been working on the determination of germline mutations in patients suspected of hereditary colon tumor and application of a cognitive computing system for the personalized medicine. These projects are aimed to use the information of personal genome and/or cancer genome in clinic, and apply the data for their diagnosis and treatment.

In the first project, we have applied NGS technology for unexplained cases with familial polyposis. For example, we had a patient with synchronous carcinomas and oligo-polyps in the colon. Although we suspected Lynch syndrome on the basis of the patient's family history, any pathogenic mutations in the mismatch repair genes including *MSH2*, *MLH1*, and *MSH6* were not found in the patient. Subsequently, whole-genome sequencing of the peripheral blood DNA identified a frameshift mutation in the *POLE* gene. Recently, mutations in the polymerase genes have been identified as rare cause of multiple early-onset adenomas and carcinomas, a condition termed polymerase proofreading associated polyposis (PPAP). These data indicated the patient with PPAP, and demonstrated the usefulness of NGS in clinical diagnosis of cancer.

In the second project, we have been testing interpretation of genomic data using IBM Watson for Genomics (WfG). After written informed consent was obtained from the patients with colorectal, breast, gastric, gallbladder cancer, and hepatoblastoma, they were enrolled in this study. Genetic alterations in their tumors were determined by NGS and the data were subsequently analyzed by WfG. The results of WfG including predicted driver mutations and suggested actionable drugs were discussed in the Tumor Board meeting of this project, which is held every two weeks.

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IMSUT Hospital

Department of Radiology
放射線科

Associate Professor	Akira Kunimatsu, M.D., D.M.Sc.	准教授　博士(医学)	國　松　　聡
Senior Assistant Professor	Hiroyuki Akai, M.D., D.M.Sc.	講　師　博士(医学)	赤　井　宏　行
Assistant Professor	Koichiro Yasaka, M.D., D.M.Sc.	助　教　博士(医学)	八　坂　耕一郎

Department of Radiological Technology
放射線部

Associate Professor	Akira Kunimatsu, M.D., D.M.Sc.	准教授　博士(医学)	國　松　　聡
Head Radiologic Technologist	Yoshirou Satake, RT	放射線技師長	佐　竹　芳　朗

The Department of Radiology undertakes radiology service at IMSUT hospital. Our expertise includes general diagnostic radiology, neuroradiology, clinical nuclear medicine, and radiation therapy. Board-certified radiologists at the Department of Radiology conduct all examinations of CT, MRI, and nuclear medicine. Radiological reports are made by the radiologists. In addition, several clinical studies are being conducted in collaboration with other departments or institutions. We also investigate the technical aspects of molecular imaging with intact small animals for its application to preclinical studies using optical imaging system and MRI.

The Department of Radiological Technology constitutes the hospital radiology service together with the Department of Radiology. Plain radiography, dual-energy X-ray absorptiometry, and barium studies are also available at the Department of Radiological Technology, other than CT, MRI, and radioisotope examinations. More than 10,000 patients visit our department every year. Radiologic technologists at the department make an effort to provide high quality medical images in daily practice as well as to reasonably reduce radiation exposure of a patient during examination.

Deep learning for radiological imaging of the liver

Yasaka K, Akai H, Kunimatsu A, Abe O[1], Kiryu S[2]: [1]Department of Radiology, Graduate School of Medicine, The University of Tokyo, [2]Department of Radiology, Graduate School of Medical Sciences, International University of Health and Welfare

We investigated whether deep learning technique can be applied to radiological imaging diagnosis of the liver. First, we investigated the performance of a convolutional neural network (CNN) model in differentiating liver masses at dynamic contrast agent-enhanced computed tomography (CT). By using CT image sets of liver masses (unenhanced, arterial, and delayed) and category data (category A, classic hepatocellular carcinomas [HCCs]; category B, malignant liver tumors other than classic and early HCCs; category C, indeterminate masses or mass-like lesions [including early HCCs and dysplastic nodules] and rare benign liver masses other than hemangiomas and cysts; category D, hemangiomas; and category E, cysts) as input data and reference data, respectively, supervised training was performed. The performance of the trained CNN was tested with 100 liver mass image sets. Accuracy of differential diagnosis of liver masses was 0.84. Area under the receiver operating characteristic curve for differentiating categories A-B from C-E was 0.92. In conclusion, deep learning with CNN showed high diagnostic performance in differentiation of liver masses at dynamic CT.

Second, we investigated the performance of a deep convolutional neural network (DCNN) model in the staging of liver fibrosis using gadoxetic acid-enhanced hepatobiliary phase magnetic resonance (MR) imaging. This retrospective study included patients for whom input data (hepatobiliary phase MR images, static magnetic field of the imaging unit, and hepatitis B and C virus testing results available, either positive or negative) and reference standard data (liver fibrosis stage evaluated from biopsy or surgical specimens obtained within 6 months of the MR examinations) were available. Supervised training was performed by using the DCNN model to minimize the difference between the output data (fibrosis score obtained through deep learning [FDL score]) and liver fibrosis stage. Fibrosis stages F4, F3, and F2 were diagnosed with areas under the ROC curve of 0.84, 0.84, and 0.85, respectively. In conclusion, the DCNN model exhibited a high diagnostic performance in the staging of liver fibrosis.

Third, we investigated whether liver fibrosis can be staged by deep learning techniques based on CT images. The portal phase images with age and sex data of patients were used for training a deep convolutional neural network (DCNN) with the histopathological fibrosis stage used as reference. Supervised training was used to minimize the difference between the liver fibrosis stage and the fibrosis score obtained from deep learning based on CT images output by the model. The areas under the receiver operating characteristic curves (with 95% confidence intervals) for diagnosing significant fibrosis (≥F2), advanced fibrosis (≥F3) and cirrhosis (F 4) by using FDLCT scores were 0.74 (0.64-0.85), 0.76 (0.66-0.85) and 0.73 (0.62-0.84), respectively. In conclusion, liver fibrosis could be staged by using a deep learning model based on CT images, with moderate performance.

The inhibitory effect of gadoxetate disodium on hepatic transporters: a study using indocyanine green.

Akai H, Yasaka K, Kunimatsu A, Nojima M[4], Inoue Y[5], Abe O, Ohtomo K[6], Kiryu S: [4]Division of Advanced Medicine Promotion, The Advanced Clinical Research Center, The Institute of Medical Science, The University of Tokyo, [5]Department of Diagnostic Radiology, Kitasato University School of Medicine, [6]International University of Health and Welfare

We performed this experiment to assess the inhibitory effect of gadoxetate disodium on the transporter system using indocyanine green (ICG). Groups of six female B6 Albino mice were injected with the test agent (0.62 mmol/kg gadoxetate disodium) or phosphate-buffered saline (control) 10 min before injection of ICG. Identical fluorescence images were subsequently obtained to create time-efficiency curves of liver parenchymal uptake. The study was performed on hypothermic and normothermic mice. The logarithms of the absorption rate constants (logKa values) and of the elimination rate constants (logKe values) were calculated for each experimental condition, and between-group differences were compared using Student's t-test. As a result, the logKe values of the test group were lower than those of the control group at both temperatures (-6.52 vs. -5.87 under hypothermic conditions and -4.54 vs. -4.14 under normothermic conditions), and both differences were statistically significant (p=0.037, 0.015 respectively). In terms of the logKa values, although the difference did not reach statistical significance (p=0.052), the test group had lower values than the control group under hypothermic conditions (-0.771 vs. -0.376). In normothermic mice, the logKa values for the test and control groups were 0.037 and 0.277 respectively, thus not significantly different (p=0.404). In conclusion, Gadoxetate disodium inhibited ICG excretion. Thus, gadoxetate disodium inhibited the ATP-binding cassette sub-family C member 2 transporter.

Predicting prognosis of resected hepatocellular carcinoma by radiomics analysis with random survival forest

Akai H, Yasaka K, Kunimatsu A, Nojima M, Kokudo T[7], Kokudo N[7], Hasegawa K[7], Abe O, Ohtomo K, Kiryu S: [7]Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Graduate

School of Medicine, The University of Tokyo

We investigated the impact of random survival forest (RSF) classifier trained by radiomics features over the prediction of the overall survival of patients with resectable hepatocellular carcinoma (HCC). The dynamic computed tomography data of 127 patients newly diagnosed with resectable HCC were retrospectively analyzed. After manually setting the region of interest to include the tumor within the slice at its maximum diameter, texture analyses were performed with or without a Laplacian of Gaussian filter. Using the extracted 96 quantitative texture features, RSFs were trained using 5-fold cross-validation to predict the individual risk for each patient on disease free survival (DFS) and overall survival (OS). The associations between individual risk and DFS or OS were evaluated using Kaplan-Meier analysis. The effects of the predicted individual risk and clinical variables upon OS were analyzed using a multivariate Cox proportional hazards model. As a result, among the 96 quantitative texture features, RSF extracted 8 of high importance for DFS and 15 for OS. The RSF trained by these features distinguished two patient groups with high and low predicted individual risk ($p=1.1\times10^{-4}$ for DFS, 4.8×10^{-7} for OS). Based on the multivariate Cox proportional hazards model, high predicted individual risk (hazard ratio=1.06 per 1% increase, $p=8.4\times10^{-8}$) and vascular invasion (hazard ratio=1.74, p=0.039) were the only unfavorable prognostic factors. In conclusion, the combination of radiomics analysis and RSF might be useful in predicting the prognosis of patients with resectable HCC.

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IMSUT Hospital

Department of Palliative Medicine
緩和医療科

Professor	Arinobu Tojo, M.D., D.M.Sc.	教　授　医学博士	東　條　有　伸
Assistant Professor	Naoki Shimada, M.D., Ph.D.	助　教　博士(農学)	島　田　直　樹

This Department was established in July 1st, 2012 in conjunction with Department of Palliative Medical Science in the Graduated School of Medicine, The University of Tokyo, which was supported by the special grant from the Ministry of Education, Culture, Sports, Science and Technology, Japan. The aim of our department is to establish the scientific aspect of palliative medicine and to create novel personalized therapy to the pain, fatigue and other symptoms of patients with malignant disorders and other severe diseases, based on genetic and epigenetic analysis of the DNAs using the materials of each patient.

1. Prevalence of myofascial pain syndrome in patients with incurable cancer.

Ishiki H[1], Kinkawa J[2], Watanabe A[3], Watanabe C[1], Chiba T[1], Yasui H[4], Shimada N[1], Ariyoshi K[1], Nojima M[5], Iwase S[1], Tojo A[1,6], Imai K[7]: [1]Department of Palliative Medicine, IMSUT Hospital [2]Department of Joint Surgery, IMSUT Hospital [3]Department of Pharmacy, IMSUT Hospital [4]Center for Translational Research, IMSUT Hospital [5]Project Division of Fundamental Study on Cutting Edge of Genome Medicine [6]Department of Hematology/Oncology, IMSUT Hospital [7]Office of Support for Platforms for Advanced Technologies and Research Resources

Myofascial pain syndrome (MPS) is a condition that involves skeletal muscles. It is caused by overload or disuse of muscles and is characterized by extreme tenderness in the muscles with taut bands. Treatment for MPS is different from that for cancer-related pain. Cancer patients have many factors that cause restriction of body movement and posture. Although cancer patients appear to demonstrate risk factors for MPS, its prevalence has not been reported in patients with incurable cancer. This study was conducted to investigate the prevalence of MPS in patients with incurable cancer. A retrospective chart review. The data for patients with incurable cancer who received palliative care at our department between September 2015 and March 2016 were investigated. We examined the prevalence of MPS, which was diagnosed on the basis of the Rivers criteria (RC) and Simons criteria (SC). We also examined the following factors associated with MPS: performance status (PS), use of medical devices, and primary cancer sites. The primary outcome was the prevalence of MPS based on RC. Secondary outcomes included the prevalence of MPS based on SC and the relationship between MPS and either PS or medical devices. Thirty-four patients with incurable cancer were identified. MPS based on RC or SC was detected in 10 (29%) and 20 (59%) patients, respectively. Twenty-two of 34 patients who complained of pain, 10 (45%) had MPS based on RC and 20 (90%) had MPS based on SC. Age and central venous port were risk factors for MPS by multivariate analysis. A very high prevalence of MPS was detected in our study population. MPS should be considered when patients with incurable cancer complain of pain.

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IMSUT Hospital

Department of Surgery
外科

Professor	Arinobu Tojo, M.D., D.M.Sc.	教授(兼)	医学博士	東　條　有　伸
Associate Professor	Masaru Shinozaki, M.D., Ph.D.	准教授	博士(医学)	篠　崎　　大
Senior Assistant Professor	Giichiro Tsurita, M.D., Ph.D.	講　師	博士(医学)	釣　田　義一郎
Clinical Senior Assistant Professor	Kentaro Yazawa, M.D., Ph.D.	病院講師	博士(医学)	谷　澤　健太郎

The missions of our department are to provide surgical service for patients with surgical or gastrointestinal disease, such as malignancy or benign colon anal disease, and to develop and conduct clinical research and clinical trials in early stages (mainly, Phase I and II) on patients at the Research Hospital. We have also been offering diagnostic and therapeutic endoscopy, including upper and lower gastrointestinal endoscopic examinations.

1. Treatment for gastrointestinal malignancy

We focus on treatment of gastrointestinal cancers such as colorectal or gastric cancers. As well as standard radical surgery, surgery that emphasizes not only curability but also postoperative function preservation was performed by using preoperative chemotherapy and/or radiotherapy. Regarding advanced unresectable cancer or recurrent cancer cases, chemotherapy or palliative therapy was performed. If there is scientific evidence, we will also support non-indication treatment, and will also support participation in clinical trials. Immediate or emergency hospitalization is also possible for patients with poor general status.

2. Treatment for benign colon anal disease

Especially for anal disorders such as internal hemorrhoids, inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, or functional disorders such as irritable bowel syndrome, medical treatment at specialty hospitals was performed.

3. Endoscopic examination or treatment

Under cooperation with Department of general internal medicine, we performed many upper gastrointestinal endoscopies and colonoscopies without major complications. For the patients' satisfaction, we aggressively perform endoscopic resection of colorectal neoplasms and avoid operation as much as possible. Our fellows have learned gastrointestinal endoscopic technique and have made great progress.

4. Hospital collaboration, personnel exchange

As a part of clinical education, we sent junior fellows belonging to our department to clinical city hospitals, Dr. Yuichiro Yoshioka to Joban Hospital and Dr. Yuki Azuma to Tsujinaka Hospital, and conversely invited Dr. Yohei Morita belonging to Tsujinaka Hospital to our department to undergo surgery and endoscopy.

5. International research activities

Dr. Tomohiro Kurokawa, a senior fellow belonging to our department, has studied at Massachu-

setts General Hospital in Boston. We also performed many research presentations at international conferences and published many papers to international journals

Publications

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IMSUT Hospital

Department of Anesthesia
麻酔科

Associate Professor Ryo Orii, M.D., Ph.D.
Assistant Professor Reiko Shibata, M.D.

准教授 博士(医学) 折井 亮
助 教 医学士 柴田玲子

Our clinical practice and clinical studies have been focused on (1) anesthetic management in patients undergoing major surgery including joint arthroplastic surgery for hemophilia patients, variable surgical procedures for translational researches (2) assessment of functional failure of the internal valve of anesthesia machine (3) assessment of reliability of cardiac output measurements (4) risk management of medical electronic devices in Research Hospital.

1. Anesthetic management for carrier hemophilia.

Hemophilia is X-linked gene disease with the activity abnormality of the coagulation factor. The hemophilia A is caused by factor VIII abnormality, and the hemophilia B is caused by factor IX abnormality. Careful hemostatic management is required in perioperative care of the hemophilic patients. It is usually recommended that we perform coagulation factor replacement therapy and hemostatic monitoring.

We experienced anesthesia management of the orthopedic surgery of patients with hemophilia B that underwent living-donor liver transplantation for cirrhosis due to the hepatitis C virus this time. We carried out hemostatic monitoring and perioperative management, but did not require coagulation factor replacement therapy. There were no complications such as postoperative bleeding and infection.

Female hemophilia patients are often not informed as carriers themselves, and there is a possibility that medical practice may be performed without recognizing them as hemophilia patients.We experienced anesthesia of a female hemophilia patient and safety managed anesthesia with appropriate hemostatic management.

2. Assessment of functional failure of the internal valve applying maximum and positive end-expiratory pressure of anesthesia machine

Equipment-related complications, whatever its cause, should be prevented by checking the breathing system prior to general anesthesia. We found irregularities with some of the anesthesia machines at our department, which was related to a ventilator-related problem that recurred after application of positive end-expiratory pressure (PEEP) during general anesthesia.

3. Assessment of reliability of cardiac output measurements.

Knowing a patient's cardiac output (CO) could contribute to a safe, optimized hemodynamic control during surgery. Precise CO measurements can serve as a guide for resuscitation therapy, catecholamine use, differential diagnosis, and intervention during a hemodynamic crisis. Despite its invasiveness and intermittent nature, the thermodilution technique via a pulmonary artery catheter (PAC) remains the clinical gold standard for CO measurements. LiDCO rapid™ (LiDCO, London, UK) and FloTrac/Vigileo™ (Edwards Lifesciences, Irvine, CA)

are less invasive continuous CO monitors that use arterial waveform analysis. We found both devices tended to underestimate the caluculated CIs when the CIs were relatively high. These proportional bias produced large parcentage errors in the present study.

4. Risk management of medical electronic devices.

We ourselves engage in preventive maintenance and care of the life support machines including instruments for mechanical ventilation or blood purification and defibrillator. We also supervise physicians during clinical usage of these instruments. We have promoted dual-directional information system with the Division of Clinical Trial Safety Manage on malfunctions or incidents of the rest of medical electronic devices in this hospital in collaboration.

IMSUT Hospital

Department of Joint Surgery
関節外科

Senior Assistant Professor Hideyuki Takedani, M.D. D.M.Sc.
Assistant Professor Kumiko Ono, M.D. D.M.Sc.

講 師 博士(医学) 竹 谷 英 之
助 教 博士(医学) 大 野 久美子

Department of Joint Surgery was established in 2006. Our mission is evaluation and treatment of hemophilic arthropathy. In Japan, many hospitals are able to control bleeding for haemophilia by concentrates, however there are few hospitals focus on surgical treatments except us. Many haemophilia patients come to our department from all over Japan. We evaluate their joint condition and function roentgenographically and physiotherapeutically and decide indication of surgical treatment. Many of patients will be performed joint arthroplasties and arthroscopic synovectomy to improve their quality of life.

Surgical treatment for haemophilia

From 2006 to 2018, more than 220 surgical treatments for hemophilia included other coagulation diseases such as deficiency factor VII or Von Willebrand disease. Some of them have the deficiency factor antibody as well.

Publications

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IMSUT Hospital

Department of Surgical Neuro-Oncology
脳腫瘍外科

Professor	Tomoki Todo, M.D., Ph.D.	教　授	博士(医学)	藤　堂　具　紀
Associate Professor	Yasushi Ino, M.D., Ph.D.	准教授	博士(医学)	稲　生　　靖
Project Associate Professor	Minoru Tanaka, M.D., Ph.D.	特任准教授	博士(医学)	田　中　　実
Senior Assistant Professor	Hiroyuki Momota, M.D., Ph.D.	講　師	博士(医学)	百　田　洋　之
Assistant Professor	Seisaku Kanayama, M.D.	助　教		金　山　政　作
Assistant Professor	Lushun Chalise, M.D., Ph.D.	助　教	博士(医学)	チャリセ　ルシュン
Assistant Professor (Thoracic surgeon)	Yoshinori Sakata, M.D., Ph.D.	助　教（呼吸器外科医）	博士(医学)	坂　田　義　詞

Department of Surgical Neuro-Oncology was established in 2011. All kinds of brain tumors, especially malignant glioma, are treated at our department. Malignant glioma is incurable by standard therapy alone, therefore refined, personalized treatment regimens utilizing non-standard radiation therapy and chemotherapy are considered. In addition, innovative therapy such as oncolytic virus therapy is applied whenever possible. Based on scientific evidence and findings from basic research, we conduct advanced medical practices in addition to standard therapy.

A phase II clinical trial of a replication-competent, recombinant herpes simplex virus type 1 (G47Δ) in patients with glioblastoma

Genetically engineered, conditionally replicating herpes simplex viruses type 1 (HSV-1) are promising therapeutic agents for cancer. We have developed a triple-mutated oncolytic HSV-1, G47Δ, by introducing an additional genetic mutation to the viral genome of G207, an oncolytic HSV-1 used in clinical trials for glioblastoma in the United States. We have been conducting a phase II clinical trial of G47Δ in patients with recurrent or residual glioblastoma since December 2014. Patients with a single lesion (≧1cm) of recurrent or residual glioblastoma after initial radiation therapy concomitant with temozolomide chemotherapy, age 18 or older, and with a good performance status are enrolled. The primary end point is a 1-year survival ratio. According to the clinical protocol, the interim analysis was performed in July 2018 and showed good results.

A clinical study of G47Δ in patients with progressive olfactory neuroblastoma

A phase I clinical trial of G47Δ in patients with progressive olfactory neuroblastoma was approved by the government in August 2013, and the patients are currently being accrued. Olfactory neuroblastoma is a rare cancer that arises at the base of the skull, deep in the nasal cavity, and there is no effective treatment once it recurs. In this clinical protocol, G47Δ is injected into the recurred tumor via nasal cavity, and the injections are repeated every 4 weeks.

A clinical study of G47Δ in patients with malignant pleural mesothelioma

A phase I clinical trial of G47Δ in patients with malignant pleural mesothelioma was approved by the government in March 2018, and the patients are currently being accrued. Malignant pleural mesothelioma is a rare asbestos-induced malignancy

with an estimated incidence of approximately 2,000 new cases per year in Japan. In this clinical protocol, G47Δ is injected into the pleural cavity, and the injections are repeated every 4 weeks (max. 6 times).

Treatment of malignant glioma patients

Our department started treating in-patients in April 2012. Standard craniotomies and image guided stereotactic biopsies of deep seated lesions, as well as 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 motor evoked potential monitoring, intraoperative ultrasonography and an ultrasonic surgical aspirator. A total of 38 operations were carried out in 2018, including 32 gliomas, 3 primary central nervous system lymphoma and 3 malignant pleural mesothelioma.

Patients with newly diagnosed malignant glioma have been treated with high dose or standard dose radiation therapy and concomitant chemotherapy. Temozolomide was administered to glioma patients during radiation therapy followed by a maintenance therapy 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. Small recurrent glioma lesions are treated with extended field stereotactic radiosurgery. To enhance the efficacy of stereotactic radiosurgery (SRS), the irradiation field is enlarged to include as many tumor cells as possible that are invasive to the surrounding tissue. This approach demonstrated 93% local control in patients who received 20 Gy to a 0.5-1.0 cm extended field SRS, whereas 47% of patients who received 20 Gy to the gadolinium-enhancing margin only.

Treatment of primary central nervous system lymphoma

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 has been used as a treatment option.

IMSUT Hospital

Department of Medical Informatics
医療情報部

Associate Professor	Akira Kunimatsu, M.D., D.M.Sc.	准教授	博士(医学)	國松	聡
Senior Assistant Professor	Hiroyuki Akai, M.D., D.M.Sc.	講師	博士(医学)	赤井	宏行
Assistant Professor	Koichiro Yasaka, M.D., D.M.Sc.	助教	博士(医学)	八坂	耕一郎

Department of Medical Informatics is engaged in management of hospital information system, including infrastructure for the system, at the Institute of Medical Science (IMSUT) Hospital. Hospital information system enables a medical staff to securely provide patient care and helps to conduct clinical research. The current hospital information system has been renewed for better patient care since 2017. In addition, we make a substantial contribution to development and improvement of infrastructure for a regional community-based medical cooperation network between IMSUT hospital and other healthcare providers.

1. Management and operation of hospital information system and network

Akira Kunimatsu, Hiroyuki Akai, Koichiro Yasaka

We offer services related to the hospital information system of the IMSUT hospital. We work together with IT service room of IMSUT, and Information Technology Center of the University of Tokyo. We are obliged to maintain the hospital information service and the network system for better medical care, ensuring that patient medical records are saved in a standard format and are easily transferrable to other healthcare providers.

Our missions are as follows:

- Supervision, development, operation, and management of the hospital information system
- Education on the hospital information system to the medical staff
- Development and management of the network infrastructure for securely dealing with patient personal information and clinical records
- Day-to-day management and operation of hospital information system and network
- General work concerning the operation of hospital information system and network

2. IT support to community-based healthcare provider network

Akira Kunimatsu, Hiroyuki Akai, Koiciro Yasaka

"Community-based integrated care systems" is a keyword for the Japanese healthcare system in this decade. IMSUT hospital belongs to its own community-based healthcare provider network and we continuously improve infrastructure for mutual cooperation in the network.

The hospital information system has been renewed since 2017. We hope that the latest electronic health record system will help to refer patients from hospital to clinic and from clinic to hospital in the network.

IMSUT Hospital

Department of Cell Processing and Transfusion
セルプロセッシング・輸血部

Associate Professor	Tokiko Nagamura-Inoue, M.D., Ph.D.	准教授 博士(医学)	長 村 登紀子
Assistant Professor	Kazuaki Yokoyama, M.D., Ph.D.	助 教 博士(医学)	横 山 和 明
Assistant Professor	Toyotaka Kawamata, M.D., Ph.D.	助 教 博士(医学)	川 俣 豊 隆

Our department was established in 1990, in order to manage the transfusion medicine and the cell processing for hematopoietic stem cell transplantation. In addition to the transfusion-related works, our department has supported translational researches and managed IMSUT-Cell Resource Center (IMSUT-CRC), which has been established in 1997. Recent our projects include Research Cord Blood Bank (RCBB), as National BioResource Project (NBRP) supported by AMED (MEXT) and umbilical cord blood and cord-derived mesenchymal stromal cells (UC-MSC) banking for clinical use supported by AMED (MHLW). Now we began to ship the UC-MSC for an investigator-initiated clinical trial for treatment of severe acute graft-versus-host disease. We also explore the clinical application of UC-MSC for newborn encephalopathy, some of which develop to cerebral palsy.

1. Transfusion medicine and related tests

Abe Y, Ogami K, Hiratak K, Yokoyama K, Kawamata T, Nagamura-Inoue T

In a part of Transfusion test and control, we control the blood transfusion products including concentrated Red Blood cells, Platelets, and Frozen plasma, and do blood typing, irregular antibodies test, and cross matching test. There are many patients with blood disease including hematopoietic stem cell transplantation. We carefully do the blood typing test, because the blood type of the patient transit to the donor type. We also collect the autologous blood for autologous transfusion for the patients with Hemophilia.

2. Peripheral Blood Stem Cell mobilization and collection:

Nagamura-Inoue T, Ogami K, Takahashi A, Kawamata T, Yokoyama K

For autologous peripheral blood Stem Cell Transplantation (PBSCT), we perform the apheresis for the patients with myeloma and malignant lymphoma after mobilization by G-CSF with or without new CXCR-4 inhibitor, Plerixafor. We evaluate the efficacy of mobilization by testing HPC and CD34 positive cells in peripheral blood on the day of apheresis and processing products. We perform the mobilization and apheresis for the patients out of IMSUT hospital by request.

3. Therapeutic application of Umbilical cord-derived mesenchymal stromal cells to the severe acute graft-versus-host-disease (aGVHD).

Nagamura-Inoue T, Takahashi A, Hori A, Okada M, Yamamoto Y, Nagamura F, Konuma T, Kato S, Saito Y, Takahashi S, Tojo A

Umbilical cord (UC) is a rich source of mesenchymal stromal cells (MSCs). MSCs have self-renewal capacity, multi-lineage differentiation potential and

the ability to migrate toward sites of inflammation or injury, where MSCs control the inflammation and repair the damaged tissues. UC-MSCs harbored the immunosuppressive effects. Even 3rd party donor UC-MSCs suppress the activated T cells stimulated by allogeneic dendritic cells, through IDO, PGE2, and HGF etc. We succeeded to produce the clinical-grade UC-MSCs (IMSUT-CORD). Since 2018, July, we started the UC-MSCs treatment for severe acute graft-versus-host disease (GVHD), as the investigator initiated clinical trial.

4. Therapeutic application of UC-MSCs to the cerebral palsy.

Mukai T, Takahashi A, Tojo A, Nagamura-Inoue T.

In the previous study, we demonstrated UC-MSCs have neurogenic differentiation potential and migration ability towards injured neuronal cells in vitro. We also established neonatal intraventricular hemorrhage (IVH) mice model, one of neonatal brain injuries and found that the intravenous injection of UC-MSCs improved behavioral outcome in IVH, by restoring periventricular reactive gliosis, hypomyelination, and periventricular cell death *in vivo*. Transplanted UC-MSCs migrated towards injured brain, but disappeared three weeks after injection. Interestingly, human brain-derived neurotrophic factor (BDNF) and hepatocyte growth factor (HGF) were elevated in the serum, cerebrospinal fluid and brain tissue of UC-MSCs injected mice. These results suggest that UC-MSCs ameliorate neuronal injury followed by functional improvement by secretion of neurotrophic factors such as BDNF and HGF rather than neuronal differentiation and eternal cell replacement, and that intravenous injection of UC-MSCs may be feasible treatment for neonatal brain injuries.

5. Research Cord Blood Stem Cell Bank / National BioResource Project (NBRP) (IMSUT-Cell Resource Center):

Izawa Y, Takahashi A, Yamamoto Y, Mihara Y, Natori M, Nagaya N., Takahashi A, Hori A, Nagamura-Inoue T,

"Research Cord Blood Bank" was established in 2004, supported by MEXT for the development of the medicine including Regenerative Medicine, immunological cell therapy, infection research, modified gene cell therapy, and drug discovery. Since 2012, July, this project has been incorporated in National BioResource Project (NBRP) of AMED. The research CB bank provides the processed and cryopreserved CB units (Nucleated cells, mononuclear cells, and CD34+ cells), to world-wide researchers via RIKEN Bioresource Center. Visit our website http://www.nbrp.jp/.

6. Management of Institute of Medical Science, University of Tokyo-Cell Resource Center (IMSUT-CRC):

Takahashi A, Shimazu T, Hori A, Okada M, Mori Y, Ichimura S, Nagamura-Inoue T

To promote the cell therapy in translational researches, IMSUT-Cell Resource Center (IMSUT-CRC) has been established in 1997 (originally called as Room for Clinical Cellular Technology (RCCT)). Until now, the following projects had been implemented; 1) CB cell processing for banking (1997-2008) (for Tokyo Cord Blood Bank, Research cord blood stem cell bank, and related sibling donors), 2) Dendritic cell therapies (1998-2001), 3) Regenerative therapy of alveolar bone derived from bone marrow mesenchymal cells (2005-2011), 4) Gene therapy for renal cancer (1998), 5) CB and UC-MSCs banking (IMSUT-CORD) (2012-present), and 6) aAVC-WT1 cell herapy Visit our website: http://www.ims.u-tokyo.ac.jp/dcpt/english/

Publications

1) Mukai T, Tojo A, and Nagamura-Inoue T, Umbilical cord-derived mesenchymal stromal cells contribute to neuroprotection in neonatal cortical neurons damaged by oxygen-glucose deprivation, *Front Neurol.*, in press
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3) 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.*, in press
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venous Administration of Human Umbilical Cord-Derived Mesenchymal Stem Cells in Neonatal Stroke Mice. *Front Neurol.* 9, 133-14(2018).
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IMSUT Hospital

Surgical Center
手術部

Professor	Tomoki Todo, M.D., Ph.D.		教　授	博士(医学)	藤　堂　具　紀
Project Associate Professor	Minoru Tanaka, M.D., Ph.D.		特任准教授	博士(医学)	田　中　　実

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. Our activities include the management of clean areas, 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 rooms are maintained at a NASA class 10,000 clean level. One operating room is maintained at a NASA class 1,000 clean level and specifically designed for neurosurgery and joint surgery. For prompt and sustained supply of sterilized materials, we keep the surgical tools for each department in sets of designated purposes.

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 room is located separately but adjacent to the surgical center.

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.

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.

Facts in the fiscal year 2017

Total number of operations	172
Planned operations	159
Emergency operations	18
General anesthesia	137
Spinal	0
Epidural	0
Local	35
Others	2

IMSUT Hospital

Department of Laboratory Medicine
検査部

Professor	Arinobu Tojo, M.D., D.M.Sc.	教　授　医学博士	東　條　有　伸
Assistant Professor	Tomohiro Ishigaki, M.D., D.M.Sc.	助　教　博士(医学)	石　垣　知　寛

The department of laboratory medicine consists of seven divisions: clinical hematology, biochemistry, serology, bacteriology, pathology, 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 clinical laboratory examinations in our hospital under stringent quality control and provides investigational laboratory analysis in collaboration with many other departments.
To facilitate translational research projects in this research hospital, we had established a special division named TR verification laboratory ten years ago. This division has been contributing in evaluating the safety of experimental therapeutic approaches and biopharmaceutical products for clinical trials.
As a central medical department, we are also taking part in clinical trials and researches conducted in our hospital.

1. Development of new therapy for adult T-cell leukemia and lymphoma (ATL).

Tomohiro Ishigaki.

Our research strategies are from basic to clinical. As basic researches, we have been analyzing adult T-cell leukemia and lymphoma (ATL) by use of *in-vitro* culture systems and *in-vivo* xenotransplantation mice models. We have discovered ATL cells are dependent on specific amino acids and proved that the restriction of these amino acids could prevent the proliferation of ATL cells. This research is awarded by the Japanese Society of HTLV-1 and Associated Diseases in September, and by the Japanese society for amino acid sciences in October 2018.

2. Highly sensitive flow cytometric analysis of cerebrospinal fluid for detection of adult T-cell leukemia and lymphoma (ATL) cells.

Tomohiro Ishigaki.

Along with clinical practice, we have been analyzing clinical samples from patients, trying to establish new clinical laboratory testings, and performing applied researches.

Flow cytometry is useful for the evaluation of minimal residual disease. Clinical laboratory testing for ATL, which was named HAS-Flow, had been established with the department of hematology/oncology. We made this testing more sensitive through improvement of the method and measurement. Minimal residual ATL cells could be detected even in samples with very few cells like cerebrospinal fluid. This method could be useful for very early detection of cerebrospinal infusion.

3. A relationship between left ventricular hypertrabeculation (LVHT) and therapy-related cardiac dysfunction in patients with hematological diseases.

Kouichi Kimura, Hisako Ishii, and Tomohiro Ishigaki.

Our division of clinical physiology performs many kinds of ultrasonographic examinations and echocardiography is an important one of them. A retrospective analysis was performed using echocardiographic records of patients with hematological diseases. We successfully elucidated left ventricular hypertrabeculation (LVHT) could be one of the risk factors for therapy-related cardiac dysfunction in hematological disorders.

4. GMP-based biosafety laboratory examinations for clinical and translational researches (TR verification laboratory)

Osamu Takahashi, Masato Suzuki, and Tomohiro Ishigaki.

Our department also functions as a safety-monitoring laboratory by examining the safety of new investigational therapeutic approaches. TR verification laboratory was funded by the Ministry of Education, Culture, Sports, and Technology (MEXT). We are examining the safety of bio-cellular materials for Translational Research (TR) clinical applications, such as gene therapies, viral therapies, and cell therapies, under GMP-based standards. At present, we are routinely examining bacteria, fungi, mycoplasma, and endotoxin contaminations by using molecular and biochemical techniques.

5. Laboratory contribution as a central medical department in many clinical researches and trials.

Hiroyuki Shingyochi, Motoko Mizukami, Etsuko Nagai, Osamu Takahashi, Masato Suzuki, Hiroko Shibata, and Tomohiro Ishigaki.

We are also taking part in other clinical trials and researches led by other departments in our hospital. Our laboratory members contributed to clinical investigations, such as a trial of new testing kits for detection of microorganism led by the department of infectious diseases, and analysis of monocyte subsets/phenotypes during treatment directed by the department of hematology/oncology, and other six clinical trials conducted in this hospital.

IMSUT Hospital

Center for Clinical Safety and Infection Control
医療安全・感染制御センター

医療安全・感染制御センターは医療安全管理部・感染制御部から構成されており，安全な医療が行えるよう心がけています.

Department of Clinical Trial Safety Management
医療安全管理部

Head, Professor	Hiroshi Yotsuyanagi, M.D., D.M.Sc.	教　授	博士(医学)	四　柳　　宏[*1]
Associate Professor	Yoichi Imai, M.D., D.M.Sc.	准教授	博士(医学)	今　井　陽　一
Head Nurse	Hatsuko Narita	看護師長		成　田　初　子
Associate Professor	Ayako Kamisato, D.M.Sc.	准教授	博士(医学)	神　里　彩　子

医師・看護師からなる医療安全管理部は平成13年7月に設立され，インシデント(出来事)・アクシデント(事故)を未然に防ぎ安全な医療を患者さんにお届けするために医療安全の遂行に取り組んでいます．特に，当院では血液疾患，感染症，免疫疾患，難治性固形腫瘍等を主に対象とし，移植医療を行っている特徴がありますので，それに沿った対応ができるように心懸けています.

The Medical Safety Management Division consisting of doctors and nurses 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.

Department of Iinfection Prevention and Control
感染制御部

Senior Assistant Professor	Tomohiko Koibuchi, M.D., D.M.Sc.	講　師	博士(医学)	鯉　渕　智　彦
Assistant Professor	Eisuke Adachi, M.D., D.M.Sc.	助　教	博士(医学)	安　達　英　輔
Nurse Manager	Miya Kogayu	看護師長		小　粥　美　香
Pharmacist	Shunsuke Kobayashi	薬剤師		小　林　俊　介
Clinical laboratory technician	Hiroko Shibata	臨床検査技師		柴　田　浩　子

医師・看護師・薬剤師・臨床検査技師・事務職員がICT(Infection Control Team)を構成し，病院内の各部署における感染症の発生状況や感染対策を把握した上で適切な対策を講じています.

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.

IMSUT Hospital

Center for Translational Research
トランスレーショナルリサーチ・治験センター

Professor	Fumitaka Nagamura, M.D., D.M.Sc.	教　授（兼務）	博士（医学）	長　村　文　孝
Associate Professor	Masanori Nojima, M.D., Ph.D., M.P.H.	准教授（兼務）	博士（医学）	野　島　正　寛
Project Associate Professor	Hiroshi Yasui, M.D., Ph.D.	特任准教授（兼務）	博士（医学）	安　井　　寛

Center for Translational Research was reorganized from Division of Clinical Trial Safety Management in 2014. Support for the conduct of clinical trials, especially for Translational Research (TR) is our major mission. Our roles on TR varies from the assistance for planning study design and writing protocol to the data confirmation by Case Report Form which is managed by Translational Research Coordinator (TRC) and the quality assurance of TRs by monitoring/audit. To protect the participants into TR and to conduct TR scientifically and ethically appropriately, we have organized TRC, which consists nurse, pharmacist, clinical laboratory technologist, dietitian, and clinical psychotherapist.

1. Promotion of Translational Research at IMSUT Hospital

All members of staff.

We have an unwavering commitment to deliver novel therapies through the conduct of translational research. To advance basic research findings into clinical application, we offer investigators the following services:

1) planning research and development (R & D) strategies, including selecting target diseases, planning product designs, and clarifying development pathways;
2) offering opportunities to consult an appointed patent attorney about acquisition and maintenance of intellectual property rights as well as patent strategies;
3) providing information necessary in preclinical phase of R & D, such as information on drug regulatory affairs and preclinical studies;
4) encouraging investigators to consult regulatory advisors of Pharmaceuticals and Medical Devices Agency (PMDA) in a timely manner;
5) participating in investigator-regulator meetings to help investigators deal with issues pointed out in the meetings;
6) advising on clinical trial design so that feasible and scientifically appropriate trials are conducted;
7) reviewing clinical study protocols, consent forms, and related documents in prior to Institutional Review Board examination to ensure the quality of clinical trials conducted at IMSUT Research Hospital;
8) assigning Translational Research Coordinators (TRCs) to each translational research project in the clinical trial phase; TRCs help patients participating in clinical trials to understand study protocols and to cope with negative emotions including fear, confusion, and depression; TRCs assist investigators.

2. Statistics and Quality control in Clinical Trials

Masanori Nojima, Motoki Amai, Mitsumi Tokunaga, Fumitaka Nagamura

We have planned and performed data management, monitoring, and statistical works in clinical trials.
[Data management]: Planning, EDC and CRF pre-

paration, registration, allocation, database management, data cleaning, coding
[Monitoring]: Monitoring for drug management
[Statistics]: Planning and perform for statistical analyses, Sample size calculation.

3. Support for the investigator-initiated clinical trials under an Investigational New Drug Application

All members of staff

Our mission is to develop efficient approaches for conducting investigator-initiated clinical trials under Investigational New Drug application (IND) to promote translational research. In 2018, we supported four investigator-sponsored clinical trials under IND by site management as well as project management. These four clinical trials were: oncolytic virus for glioma, peptide therapy for after rejection of non-small cell lung cancer, novel gene-induced adjuvant cells for acute myelogenous leukemia, and umbilical cord derived mesenchymal stromal cells for severe acute graft-versus-host disease.

4. Scholastic Program for the Graduate Students of Nurses in the Area of Translational Research.

Minako Kouno, Riyo owada, Fumitaka Nagamura

TR is the early phase of clinical trials, which applied the developments of basic researches for patients with incurable and/or life-threatening diseases. Highly educated nurses are indispensable for the conducts of TRs in terms of the protection of participants in TRs and the conducts of scientifically appropriate TRs. We developed the scholastic program for the graduate students of nurses in the area of TR. We planned and implemented the one-week program to foster the expert research nurse aimed at the graduate students. It consists of the lectures on the feature points of TR (e.g. ethical considerations of TR, and the role of research nurse), role-plays of TRC and obtaining Informed Consent, case conference, and the experience of the actual operations. We evaluated the reports and the questionnaires from the students to explore the degree of their understandings and satisfactions for this program. These reports and questionnaires were analyzed. Generally, our program meets the demands of the students, however, the improvement of the content on the experience of the actual operations is the next issue.

5. Statistical consulting

Masanori Nojima

Consulting for study design and statistical analysis in any type of clinical research including clinical research, basic medical/biological research. We have collaborated with other members in IMSUT and other institutions through the consulting.

Publications

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2. Adachi Y, Akino K, Nojima M, Himori R, Kikuchi T, Mita H, Nakamura M, Tsukuda H, Yamano HO, Sasaki Y, Yoshida Y, Kato Y, Nakase H, Endo T. Prognostic nutritional index and early mortality with percutaneous endoscopic gastrostomy. QJM. 2018 [Epub ahead of print]
3. Hirose J, Takedani H, Nojima M, Koibuchi T. Risk factors for postoperative complications of orthopedic surgery in patients with hemophilia: Second report. J Orthop. 2018; 15: 558-562.
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7. 長村文孝　代替療法　再生医療と遺伝子治療 Current Therapy 36(5): 68−73, 2018.
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IMSUT Hospital

Center for Antibody and Vaccine Therapy
抗体・ワクチンセンター

Professor	Hirotoshi Tanaka, M.D., D.M.Sc.		教　授	医学博士	田　中　廣　壽
Professor	Kouhei Tsumoto, Ph.D.		教　授(兼務)	博士(工学)	津　本　浩　平
Project Professor	Yataro Daigo, M.D., D.M.Sc.		特任教授	博士(医学)	醍　醐　弥太郎
Project Associate Professor	Satoru Nagatoishi, Ph.D.		特任准教授	博士(生命科学)	長門石　　曉
Senior Assistant Professor	Noritada Yoshikawa, M.D., D.M.Sc.		講　師(兼務)	博士(医学)	吉　川　賢　忠
Project Senior Assistant Professor	Atsushi Takano, M.D., D.M.Sc.		特任講師	博士(医学)	高　野　　淳

Our center was established in April 1st, 2012, in the memory of Professor Shibasaburo Kitasato, the founder and the first director of our institute, because the year 2012 was 120th anniversary of our institute which was built in 1892. Prof Kitasato was keen to utilize "serum therapy" for patients with infectious diseases and actually developed therapeutic sera from horses. Now, we can use monoclonal antibodies to cytokines and their receptors, growth factor receptors, cellular kinases, for treatment of autoimmune diseases and cancer. The aim of this center is to develop novel immunological therapy for patients with various diseases including cancers and autoimmune diseases. Moreover, attractive clinical trials are also ongoing in collaboration with research groups in IMSUT.

Tanaka Group

1. Clinical activities in IMSUT Hospital

Hirotoshi Tanaka, Noritada Yoshikawa, Hiroki Yamazaki*, Erika Matsubara*: *Department of Rheumatology and Allergy, IMSUT Hospital, The Institute of Medical Science, The University of Tokyo

Rheumatologists at our division provide state-of-the-art diagnosis and treatment for systemic autoimmune diseases (total number of patients were approximately 5,000 per year). Our physicians have active basic and clinical research projects and also are involved in training of rheumatology specialists.

Rheumatologic services offered at IMSUT Hospital include:

- Outpatient consultations
- Outpatient specialty care for patients with 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. Development of novel approaches to overcome undesired side effects of glucocorticoid therapy

Hirotoshi Tanaka, Noritada Yoshikawa, Hiroki Yamazaki, Akiko Souta-Kuribara, Erika Matsubara, Yuki Tasaka, Aya Oda, Masaaki Uehara, Mayu Nishimura, Satoshi Fukuyama*, Yoshihiro Kawaoka*: *Division of Virology, Department of Microbiology and Immunology, Institute of Medical Science, The University of Tokyo

Glucocorticoids (GC) have been used clinically for decades as potent anti-inflammatory and immunosuppressive agents. Nevertheless, their use is severely hampered by the risk of developing side effects. Therefore, efforts to understand the complex mechanisms underlying function of GC and GC receptor (GR) are ongoing. Our recent achievement has been applied in clinical settings in IMSUT Hospital.

(i) Developing a novel therapy preventing glucocorticoid-induced muscle atrophy in patients with rheumatic diseases

Reduction of skeletal muscle mass and resulting weakness of peripheral and respiratory muscles cause various clinical problems such as fatigue, frailty, compromised lung function, and worse quality of life. Maintaining skeletal muscle mass and strength, therefore, is critical to preserve full activity, prevent obesity, and decrease the risk of heart disease, diabetes, and cancer. In rheumatology field, reduction of skeletal muscle mass and strength are often critical to negatively affect prognosis of the patients. Especially, prolonged GC treatment for rheumatic disorders accelerates skeletal muscle atrophy known as GC-induced myopathy. However, there is no standardized intervention to prevent or treat this GC side effect. To overcome this issue, we have studied precise mechanisms of GC-induced skeletal muscle atrophy and revealed that administration of branched-chain amino acids (BCAA) ameliorates GC-induced muscle atrophy in animal model. Based on this research, we conducted a clinical trial in IMSUT Hospital and revealed that BCAA supplementation in patients with rheumatic disorders taking GC might be safe and, at least in part, improve their skeletal muscle mass, strength, and function. However, we should use more effort to improve the efficacy of BCAA administration for increasing skeletal muscle mass and establish easily assessable and reliable marker of reduced muscle mass instead of well-validated tools including dual energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), or computed tomography (CT), which are limited to studies and can hardly be routinely established given the high costs and low availability of these methods. Therefore, we are now challenging to establish a novel protocol to administrate BCAA with patients and to identify non-invasive biomarkers for detecting the subjects affected or at risk of GC-induced myopathy and various types of muscle atrophy.

(ii) Developing a novel therapy to improve abnormal fat distribution in patients taking GC therapy

Accumulation of triglyceride stores in selected adipose and extraadipose sites is recognized increasingly as a determinant of insulin sensitivity and its attendant cardiovascular risk. Cushing's syndrome or prolonged GC treatment is responsible for accumulation of fat in selected adipose tissue depots, especially in the face, nape of the neck, and visceral compartments including liver, resulting both clinical and cosmetic problem. We created a mouse model mimicking Cushing's syndrome by free-access drinking of GC solution. We analyzed and compared body fat distribution of such Cushing's mouse model with that of control mouse by micro computed-tomography (CT). We revealed that Cushing's mouse model showed similar fat distribution to human Cushingoid. Moreover, we found that several serum biochemical markers for insulin resistance and cholesterol profile are correlated with fat mass evaluated by micro CT. Now, we are challenging to overcome not only metabolic disorders but also abnormal fat distribution by using Cushing's mouse model and micro CT. We found several candidate compounds and target molecules to ameliorate Cushingoid and are further investigating. For example, an omega-3 fatty acid, eicosapentaenoic acid (EPA), modulates mRNA expression levels of several GC receptor (GR) target genes involved in glycolytic pathway and TCA cycle in skeletal muscles. Moreover, we investigated that selective blockade of skeletal muscle GR by muscle specific knockout of GR in which GC-induced Cushingoid metabolic disorders were mitigated.

3. Development of novel modalities optimizing metabolic condition and body composition targeting transcriptional apparatus

Hirotoshi Tanaka, Noritada Yoshikawa, Hiroki Yamazaki, Akiko Souta-Kuribara, Erika Matsubara, Yuki Tasaka, Aya Oda, Masaaki Uehara, Mayu Nishimura, Satoshi Fukuyama*, Yoshihiro Kawaoka*: *Division of Virology, Department of Microbiology and Immunology, Institute of Medical Science, The University of Tokyo

(i) Development of novel therapeutic modalities against metabolic syndrome targeting the skeletal muscle-liver-fat signalling axis

We have developed an efficient system to screen out the target genes of GR in GC-responsive tissues, and are working with clarification of tissue-specific effects of GC in skeletal muscles. We investigated that a mutually exclusive crosstalk between mTOR and GR coordinately regulates anabolic and catabolic metabolism in skeletal muscle, suggesting the critical importance of the interaction of GR and mTOR in the regulation of metabolism-volume coupling in skeletal muscle. Recently, we have created skeletal muscle-specific GR knockout mice (mGRKO) and revealed that mGRKO show significant increase of their myofiber size and muscle mass and loss of adipose tissues, suggesting that

mGRKO mimic the opposite phenotype against metabolic syndrome. Metabolically, mGRKO mice show a drastic shift of energy utilization and storage in muscle, liver and adipose tissues. We investigated that the resulting depletion of plasma alanine serves as a cue to increase plasma levels of fibroblast growth factor 21 (FGF21) and activates liver-fat communication, leading to the activation of lipolytic genes in adipose tissues. Both Cushing's mouse model and leptin-deficient ob/ob mice exhibited metabolic syndrome involving central obesity, fatty liver, and impaired glucose tolerance. As expected, mGRKO mitigated such metabolic unhealthy phenotype. Targeting the skeletal muscle-liver-fat signalling axis involving glucose-alanine cycle, therefore, would be a novel approach for treatment of patients with obesity, diabetes and metabolic syndrome.

(ii) Clarification of functional crosstalk between GR and sex hormone receptors for body composition and metabolic regulation

It is well known that body composition differs by sex. This sexual dimorphism in human body composition has major implication for sex differences in the risk of various diseases including metabolic syndrome. Although the metabolic syndrome tends to appear more often and/or earlier in adult males than in females, the differences in incidence decrease sharply after menopause, suggesting that sex hormones and their receptors play a certain role in metabolic pathways. Globally, in the metabolic syndrome, there is a decrease in the functions of the androgen-estrogen system. This decrease in systemic sex hormones may have tissue-specific effects on androgen and/or estrogen-responsive tissues such as adipose tissue and skeletal muscle. Recently, impaired estrogen receptor α (ERα) and androgen receptor (AR) action has shown to promote obesity and metabolic dysfunction in humans and mice. On the other hand, we revealed that mGRKO shows the opposite phenotype against metabolic syndrome. Therefore, we hypothesized that clarification of functional crosstalk between GR and ERα/AR in adipose tissue and skeletal muscle contributes to developing a novel therapeutic modality for metabolic syndrome. In addition of mGRKO, we created mERαKO, mGR/ERα double KO, mARKO and mGR/AR double KO. We found that each receptor is involved in regulation of body composition and its sexual dimorphism. Moreover, at least in skeletal muscle, functional crosstalk between GR and ERα and between GR and AR exist and such crosstalk may regulate plasticity of metabolic regulation in skeletal muscle and adipose tissues.

(iii) Clarification of the effect of ageing for regulation of energy storage in skeletal muscle and adipose tissues

Ageing is accompanied by major changes in body composition that can negatively affect functional status in older adults, including a progressive decrease in muscle mass, strength, and quality, accompanied by an increase in fat mass. Such loss of muscle mass and increase of fat mass have recently been termed sarcopenic obesity, which is a high-risk geriatric syndrome related to functional impairment, increased mortality and reduction in quality of life. Because mGRKO shows the opposite phenotype against sarcopenic obesity, analyzing the effect of aging for regulation of energy storage in skeletal muscle and adipose tissue in mGRKO contributes to understanding biological significance of functional communication among multiple organs and the mechanism of sarcopenic obesity. We revealed that mGRKO may be resistant to age-related loss of muscle volume and gain of fat mass.

Daigo Group

4. Novel therapeutic target discovery for solid cancers

Yataro Daigo, Atsushi Takano, Koji Teramoto, Hidetoshi Sumimoto, Yoshinori Murakami, Phung Manh Thang, Kayo Daigo, Tomoyuki Igarashi, Masako Nakamura, Tsevegjav Bayarbat, Zhu Ming

To identify molecules involved in human carcinogenesis and those which could be applied for the development of new molecular therapies and/or biomarkers, we had established a systematic screening system as follows; i) identification of overexpressed genes in the majority of solid cancers (lung, esophagus etc.) by genome-wide screening using the expression microarray in the combination of enrichment of tumor cell populations from cancer tissues by laser microdissection, ii) verification of no or little expression of each of candidate molecules in normal tissues by northern-blot analyses, iii) validation of the clinicopathological significance of its higher expression with tissue microarray containing thousands of archived solid cancers, iv) verification of a critical role of each target gene in the growth or invasiveness of cancer cells by RNAi and cell growth/invasion assays, v) evaluation of their usefulness as targets for passive immunotherapy using specific antibodies and/or as a serum biomarker for solid cancer by high throughput ELISA and proteomics analysis, if they are tumor-specific transmembrane or secretory proteins, vi) screening of the epitope peptides recognized by human histocompatibility leukocyte (HLA)-A*0201- or A*2402-restricted cytotoxic T lymphocyte (CTL) and dendritic cell (DC). This systematic approach identified dozens of molecules that appear to fall into the category of oncoantigens whose overexpression is an important feature of the malignant nature of cancer cells and that have very high immunogenicity to induce antigen-specific CTLs in

cancer patients. We further validated these molecules identified as potential targets for the development of antibodies, small-molecular compounds, growth-suppressive cell-permeable peptides, and cancer vaccines that could have a more specific and strong anti-cancer effect with minimal risk of adverse events. During this process, we found dozens of candidate molecules to be activated in various solid cancers including lung, esophagus, oral cavity, and breast cancers, as novel prognostic biomarkers and therapeutic targets.

5. Development of therapeutic cancer vaccine

Yataro Daigo, Atsushi Takano, Koji Teramoto, Hidetoshi Sumimoto, Koichiro Yuji, Hiroshi Yasui, Giichiro Tsurita, Kohzoh Imai, Yoshihide Fujiyama, Kazumasa Ogasawara

Using the systematic screening system shown above, we identified concoantigens which were overexpressed in the majority of cancers derived from lung, esophagus and urinary bladder and essential for the growth and/or survival of cancer cells, as targets for therapeutic cancer vaccine treatment against various solid cancers. We screened dozens of 9- or 10-amino-acid epitope peptides recognized by human HLA-A*0201 and/or A*2402-restricted CTL by ELISPOT assay. In IMSUT Hospital and its collaborative hospitals, International Conference on Harmonization (ICH) - Good Clinical Practice (GCP)-based clinical study using the combination of some of these peptides derived from oncoantigens in patients with lung cancer is now being conducted. In addition, new type of peptides-pulsed DC vaccination therapy is under development.

6. Integrated genomics-based discovery of new biomarkers for cancer immunotherapy

Yataro Daigo, Atsushi Takano, Koji Teramoto, Koichiro Yuji, Hiroshi Yasui, Giichiro Tsurita, Yoshihide Fujiyama, Kazumasa Ogasawara, Yusuke Nakamura

Immune responses play a critical role in various disease conditions including cancer. Although various immunotherapies are being developed, predictive biomarkers for the choice of effective therapy are urgently required. Using systematic cancer genomics approach on clinical materials obtained from cancer patients treated with cancer vaccine, peptides-pulsed DC vaccination therapy, or Immune checkpoint inhibitors, we are clarifying how molecular profiles of cancers can be used to identify biomarkers for predicting clinical outcomes. For example, there has not been a rapid, sensitive, comprehensive, and quantitative analysis method to examine T-cell or B-cell immune responses, therefore we developed a new approach to characterize tumor mutation burdens and T cell receptor (TCR) repertoire by sequencing millions of cDNA of exomes of cancer related genes as well as TCR α and β chains in combination with a newly-developed algorithm. Using samples from lung cancer patients, we are developing detailed information of neoantigen profiles of lung cancer patients and their TCR repertoire. This newly developed NGS platform can be applied to better understand immune responses in many disease areas including immune disorders, allergies, and organ transplantations.

7. Molecular characterization of tumor microenvironment molecules as diagnostic and therapeutic targets

Yataro Daigo, Koji Teramoto, Hidetoshi Sumimoto, Tomoyuki Igarashi, Atsushi Takano

Tumor microenvironment is supposed to be involved in tumor progression and drug resistance. To identify molecules that play crucial roles in cancer cells as well as tumor stromal cells such as cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs) and apply them for the development of new molecular therapies and/or biomarkers, we are characterizing various immune checkpoint molecules and cytokines in various solid cancer tissues and cells using cell-based assays and clinical cancer materials. Studies on molecular pathological role of these molecules are in progress, however, some of them are likely to be associated with malignant potential of cancer cells.

8. Identification of lung cancer susceptibility loci by genome-wide association studies.

Yataro Daigo, Atsushi Takano

To identify new susceptibility loci associated with lung cancer risk, we imputed data from genome-wide association studies (GWAS) of lung cancer. In our meta-analysis, we are identifying new loci that achieved genome-wide significance, marked by single nucleotide polymorphism (SNP). The results extend the catalog of regions associated with lung cancer risk and highlight the potential of genetic susceptibility alleles as a new biomarker for cancer risk prediction and prevention.

9. Scientific platform of supporting cohort study and biospecimen analysis

Yataro Daigo, Atsushi Takano, Koji Teramoto, Kohzoh Imai, Yoshinori Murakami

To support life science researchers in the field of basic life science, cancer diagnostics and therapeutics, we are collecting cancer tissue, serum, plasma, and peripheral blood mononuclear cell (PBMC) from patients with solid cancers originated from 30 organs. To date, we collected 55,000 clinical materials. We also constructed tissue microarray system covering about 5000 archived clinical cancers. Using these clinical materials, we are validating the clinicopathological significance of various candidate disease biomarkers as requested by researchers and contributed to their clinical application and publications in international journals.

Nagatoishi Group

Various antibodies have been approved for therapeutic use and currently examined in clinical development. Developments and improvements of technology for the discovery and optimization of high-potency antibodies, therefore, have greatly increased to find the specific and stable antibody with desired biological properties. Biophysical analyses of therapeutic antibody, particularly those of protein interaction and stability, are recognized as one of the critical procedures in the development of biopharmaceuticals, which would be assessed as an essential step to develop next generation antibodies. Development of analytical methods with quantitative and high-sensitive detection of antigen interaction, protein stability and biological function of antibody, therefore, has been intriguing for the pharmaceutic companies. In this division, we study biophysical analyses of various antibody to propose new strategy for development of the next generation antibody.

10. Thermodynamic and computational analyses reveal the functional roles of the galloyl group of tea catechins in molecular recognition.

Takahashi T, Nagatoishi S, Kuroda D, and Tsumoto K.

Catechins, biologically active polyphenols in green tea, exhibit various biological activities, such as anticancer and antiviral activities, arising from interactions with functional proteins. However, the molecular details of these interactions remain unclear. In this study, we investigated the interactions between human serum albumin (HSA) and various catechins, including some with a galloyl group, by means of isothermal titration calorimetry (ITC), differential scanning calorimetry (DSC), and docking simulations. Our results indicate that the galloyl group was important for recognition by HSA and was responsible for enthalpic gains derived from a larger buried surface area and more van der Waals contacts. Thus, our thermodynamic and computational analyses suggest that the galloyl group plays important functional roles in the specific binding of catechins to proteins, implying that the biological activities of these compounds may be due in part to the physicochemical characteristics of the galloyl group.

11. Molecular basis for governing the morphology of type-I collagen fibrils by Osteomodulin.

Tashima T, Nagatoishi S, Caaveiro JMM, Nakakido M, Sagara H, Kusano-Arai O, Iwanari H, Mimuro H, Hamakubo T, Ohnuma SI, Tsumoto K.

Small leucine-rich repeat proteoglycan (SLRP) proteins have an important role in the organization of the extracellular matrix, especially in the formation of collagen fibrils. However, the mechanism governing the shape of collagen fibrils is poorly understood. Here, we report that the protein Osteomodulin (OMD) of the SLRP family is a monomeric protein in solution that interacts with type-I collagen. This interaction is dominated by weak electrostatic forces employing negatively charged residues of OMD, in particular Glu284 and Glu303, and controlled by entropic factors. The protein OMD establishes a fast-binding equilibrium with collagen, where OMD may engage not only with individual collagen molecules, but also with the growing fibrils. This weak electrostatic interaction is carefully balanced so it modulates the shape of the fibrils without compromising their viability.

12. Biophysical analysis of the protein-small molecule interactions to develop small molecule drug discovery.

Nagatoishi S, Caaveiro JMM, Tsumoto K.

In small molecule drug discovery, researchers must find specific binders that interact with a target protein and inhibit its function in connection with human diseases. It is of critical importance to know the binding mode of compounds interacting with a target protein to assure hit validation and optimization. Biophysical analysis is a powerful quantitative approach to evaluate the binding modes of such candidates. Since the level of sensitivity of biophysical analysis is suitable to quantitatively detect the binding of fragment compounds, and because of the remarkable success of compound libraries of small molecules, the development and adaptation of biophysical analysis for these applications is in great demand. Herein, we describe the technical developments of biophysical methods, especially thermodynamic and kinetic analysis, for the purpose of screenings which employ small molecules. In addition, we discuss the interaction mechanisms of

small molecules to find hit compounds based on these biophysical analyses.

13. Discovery and optimization of inhibitors of the Parkinson's disease associated protein DJ-1.

Tashiro S, Caaveiro JMM, Nakakido M, Tanabe A, Nagatoishi S, Tamura Y, Matsuda N, Liu D, Hoang QQ, Tsumoto K.

DJ-1 is a Parkinson's disease associated protein endowed with enzymatic, redox sensing, regulatory, chaperoning, and neuroprotective activities. Although DJ-1 has been vigorously studied for the past decade and a half, its exact role in the progression of the disease remains uncertain. In addition, little is known about the spatiotemporal regulation of DJ-1, or the biochemical basis explaining its numerous biological functions. Progress has been hampered by the lack of inhibitors with precisely known mechanisms of action. Herein, we have employed biophysical methodologies and X-ray crystallography to identify and to optimize a family of compounds inactivating the critical Cys106 residue of human DJ-1. We demonstrate these compounds are potent inhibitors of various activities of DJ-1 in vitro and in cell-based assays. This study reports a new family of DJ-1 inhibitors with a defined mechanism of action and contributes toward the understanding of the biological function of DJ-1.

14. Inhibition of homophilic dimerization and disruption of cell adhesion by P-cadherin-specific small molecules from SPR-based assays.

Senoo A, Nagatoishi S, Moberg A, Babol LN, Mitani T, Tashima T, Kudo S, Tsumoto K.

The inhibitor for the homophilic dimerization of P-cadherin was discovered by SPR-based screening using fragment compounds. Our SPR assays identified a specific P-cadherin binder, which was able to inhibit the cell adhesion of living CHO cells that expressed P-cadherin.

15. A combination of 19F NMR and surface plasmon resonance for site-specific hit selection and validation of fragment molecules that bind to the ATP-binding site of a kinase.

Nagatoishi S, Yamaguchi S, Katoh E, Kajita K, Yokotagawa T, Kanai S, Furuya T, Tsumoto K.

19F NMR has recently emerged as an efficient, sensitive tool for analyzing protein binding to small molecules, and surface plasmon resonance (SPR) is also a popular tool for this purpose. Herein a combination of 19F NMR and SPR was used to find novel binders to the ATP-binding pocket of MAP kinase extracellular regulated kinase 2 (ERK2) by fragment screening with an original fluorinated-fragment library. The 19F NMR screening yielded a high primary hit rate of binders to the ERK2 ATP-binding pocket compared with the rate for the SPR screening. Hit compounds were evaluated and categorized according to their ability to bind to different binding sites in the ATP-binding pocket. The binding manner was characterized by using isothermal titration calorimetry and docking simulation. Combining 19F NMR with other biophysical methods allows the identification of multiple types of hit compounds, thereby increasing opportunities for drug design using preferred fragments.

16. Assessing the heterogeneity of the Fc-Glycan of a therapeutic antibody using an engineered Fcγreceptor IIIa-immobilized column.

Kiyoshi M, Caaveiro JMM, Tada M, Tamura H, Tanaka T, Terao Y, Morante K, Harazono A, Hashii N, Shibata H, Kuroda D, Nagatoishi S, Oe S, Ide T, Tsumoto K, Ishii-Watabe A.

The N-glycan moiety of IgG-Fc has a significant impact on multifaceted properties of antibodies such as in their effector function, structure, and stability. Numerous studies have been devoted to understanding its biological effect since the exact composition of the Fc N-glycan modulates the magnitude of effector functions such as the antibody-dependent cell mediated cytotoxicity (ADCC), and the complement-dependent cytotoxicity (CDC). To date, systematic analyses of the properties and influence of glycan variants have been of great interest. Understanding the principles on how N-glycosylation modulates those properties is important for the molecular design, manufacturing, process optimization, and quality control of therapeutic antibodies. In this study, we have separated a model therapeutic antibody into three fractions according to the composition of the N-glycan by using a novel FcγRIIIa chromatography column. Notably, Fc galactosylation was a major factor influencing the affinity of IgG-Fc to the FcγRIIIa immobilized on the column. Each antibody fraction was employed for structural, biological, and physicochemical analysis, illustrating the mechanism by which galactose modulates the affinity to FcγRIIIa. In addition, we discuss the benefits of the FcγRIIIa chromatography column to assess the heterogeneity of the N-glycan.

17. Development of drug discovery screening system by molecular interaction kinetics-mass spectrometry.

Obi N, Fukuda T, Nakayama N, Ervin J, Bando

Y, Nishimura T, Nagatoishi S, Tsumoto K, Kawamura T.

Six small-molecule binders of CAII were analyzed quantitatively using nPOI and MIK-MS, and the results were compared to published surface plasmon resonance (SPR) results. The nPOI and SPR results show good agreement, confirming the reliability of the analysis. Time-dependent binding results may be obtained by our MS sensorgram approach. Drugs that meet medical needs in a short period are required; this nPOI-LC-MS system is considered an important tool for rapid drug discovery.

18. A secondary RET mutation in the activation loop conferring resistance to vandetanib.

Nakaoku T, Kohno T, Araki M, Niho S, Chauhan R, Knowles PP, Tsuchihara K, Matsumoto S, Shimada Y, Mimaki S, Ishii G, Ichikawa H, Nagatoishi S, Tsumoto K, Okuno Y, Yoh K, McDonald NQ, Goto K.

Resistance to vandetanib, a type I RET kinase inhibitor, developed in a patient with metastatic lung adenocarcinoma harboring a CCDC6-RET fusion that initially exhibited a response to treatment. The resistant tumor acquired a secondary mutation resulting in a serine-to-phenylalanine substitution at codon 904 in the activation loop of the RET kinase domain. The S904F mutation confers resistance to vandetanib by increasing the ATP affinity and autophosphorylation activity of RET kinase. A reduced interaction with the drug is also observed in vitro for the S904F mutant by thermal shift assay. A crystal structure of the S904F mutant reveals a small hydrophobic core around F904 likely to enhance basal kinase activity by stabilizing an active conformer. Our findings indicate that missense mutations in the activation loop of the kinase domain are able to increase kinase activity and confer drug resistance through allosteric effects.

19. Characterization of glycoengineered anti-HER2 monoclonal antibodies produced by using a silkworm-baculovirus expression system.

Egashira Y, Nagatoishi S, Kiyoshi M, Ishii-Watabe A, Tsumoto K.

Silkworm-baculovirus expression systems are efficient means for the production of recombinant proteins that provide high expression levels and post-translational modifications. Here, we characterized the stability, glycosylation pattern and antibody-dependent cell-mediated cytotoxicity activity of anti-HER2 monoclonal antibodies containing native or glycoengineered mammalian-like N-glycans that were produced by using a silkworm-baculovirus expression system. Compared with a monoclonal antibody produced by using a Chinese hamster ovary cell expression system, the glycoengineered monoclonal antibody had comparable thermal stability and a higher antibody-dependent cell-mediated cytotoxicity activity. These results suggest that silkworm-baculovirus expression systems are next-generation expression systems potentially useful for the cost-effective production of therapeutic antibodies.

20. Production and characterization of a novel site-specific-modifiable anti-OX40-receptor single-chain variable fragment for targeted drug delivery.

Tanabe A, Nakano K, Nakakido M, Nagatoishi S, Tanaka Y, Tsumoto K, Uchimaru K, Watanabe T.

OX40 receptor (tumor necrosis factor receptor superfamily, member 4; CD134) is a T-cell co-stimulatory molecule that plays an important role in T-cell activation and survival. OX40 receptor is activated by its ligand, OX40L; and modulation of the OX40-OX40L interaction is a promising target for the treatment of autoimmune diseases and cancers. Here, we generated a high-affinity anti-OX40 single-chain variable fragment carrying a C-terminal cysteine residue (scFvC). Physicochemical and functional analyses revealed that the scFvC bound to OX40-expressing cells and was internalized via OX 40-mediated endocytosis without inducing phosphorylation of IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha), an important complex in the classical NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling pathway. In addition, mutation of the 36th cysteine residue in variable region of light chain enabled site-specific chemical modification to carboxy terminal cysteine and improved the thermal stability of the scFvC. These results suggest that this novel high-affinity anti-OX40 scFvC may be useful as a transporter for targeted delivery of small compounds, proteins, peptides, liposomes, and nanoparticles, into OX40-expressing cells for the treatment of autoimmune diseases and cancers.

21. PRDM14 directly interacts with heat shock proteins HSP90α and glucose-regulated protein 78.

Moriya C, Taniguchi H, Nagatoishi S, Igarashi H, Tsumoto K, Imai K.

PRDM14 is overexpressed in various cancers and can regulate cancer phenotype under certain condi-

tions. Inhibiting PRDM14 expression in breast and pancreatic cancers has been reported to reduce cancer stem-like phenotypes, which are associated with aggressive tumor properties. Therefore, PRDM14 is considered a promising target for cancer therapy. To develop a pharmaceutical treatment, the mechanism and interacting partners of PRDM14 need to be clarified. Here, we identified the proteins interacting with PRDM14 in triple-negative breast cancer (TNBC) cells, which do not express the three most common types of receptor (estrogen receptors, progesterone receptors, and HER2). We obtained 13 candidates that were pulled down with PRDM14 in TNBC HCC1937 cells and identified them by mass spectrometry. Two candidates-glucose-regulated protein 78 (GRP78) and heat shock protein 90-α (HSP90α)-were confirmed in immunoprecipitation assay in two TNBC cell lines (HCC1937 and MDA-MB231). Surface plasmon resonance analysis using GST-PRDM14 showed that these two proteins directly interacted with PRDM14 and that the interactions required the C-terminal region of PRDM14, which includes zinc finger motifs. We also confirmed the interactions in living cells by NanoLuc luciferase-based bioluminescence resonance energy transfer (NanoBRET) assay. Moreover, HSP90 inhibitors (17DMAG and HSP990) significantly decreased breast cancer stem-like $CD24^-$ $CD44^+$ and side population (SP) cells in HCC1937 cells, but not in PRDM14 knockdown HCC1937 cells. The combination of the GRP78 inhibitor HA15 and PRDM14 knockdown significantly decreased cell proliferation and SP cell number in HCC1937 cells. These results suggest that HSP90α and GRP78 interact with PRDM14 and participate in cancer regulation.

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IMSUT Hospital

Therapeutic Vector Development Center
治療ベクター開発センター

Professor	Tomoki Todo, M.D., Ph.D.	教　授　博士(医学)	藤　堂　具　紀
Associate Professor	Yasushi Ino, M.D., Ph.D.	准教授　博士(医学)	稲　生　　靖

The Therapeutic Vector Development Center (TVDC), formerly named Core Facility for Therapeutic Vectors, was established in 2002 as the first facility in Japanese academia for the clinical-grade production of viral or cellular vectors. The primary function of TVDC is to support clinical trials that require production of recombinant viral vectors, genetic modification and/or ex vivo manipulation of patients' tissue or cells under current Good Manufacturing Practice (cGMP) conditions.

Maintenance of the Standard Operating Procedures (SOPs)

The cGMP compliance is maintained by written SOPs. The SOPs codify all aspects of laboratory activities including facility design and operations of the personnel. The entire SOP document system is revised annually.

Adoption of ISO

In order to continuously improve the activities of TVDC, quality management system has been assessed by a third party. It is qualified to be in accordance with the requirements of the quality standards detailed in ISO9001: 2015; in the scope of development and manufacture of cell and gene therapy products.

Validation of TVDC

The TVDC consists of two distinct units; 1) Vector Unit, the primary viral vector production suite which may also function as ex vivo transduction suite; 2) Cell Unit, cell processing suite capable of generating therapeutic cells such as dendritic cells for immunotherapy and gene therapy. There are two self-contained vector production suites in the Vector Unit and two self-contained tissue culture suites in the Cell Unit. These suites are kept in Class 10,000 clean level. Periodical validation of the facility and the equipment in TVDC has been performed to ensure cGMP compliance.

Production of clinical grade oncolytic HSV-1

Multiple clinical lots of oncolytic herpes simplex virus type 1 (HSV-1) have been manufactured in the Vector Unit under cGMP by the members of the Division of Innovative Cancer Therapy.

Oncolytic MV project

A clinical grade oncolytic measles virus (MV) is in the process of manufacture in the Vector Unit by the members of the Laboratory Animal Research Center.

IMSUT Hospital

IMSUT CORD
臍帯血・臍帯バンク

Associate Professor　Tokiko Nagamura-Inoue, M.D., PhD.　准教授　博士(医学)　長　村　登紀子

IMSUT CORD is the umbilical cord blood (CB) and cord (UC)-derived cell bank. It has been established in IMSUT hospital, since 2016. The aim of IMSUT CORD is to collect, process/culture, cryopreservation, stock, and release the CB and UC/ UC-derived cells including mesenchymal stromal cells (MSCs) for clinical and research use. We have released CB and UC-MSCs to the collaborator to accelerate the translational researches in the fields of immunotherapy, regenerative medicine, disease specific drug discovery. Since 2018, July, we started to release the UC-MSCs products (namely IMSUT-CORD) for the investigator initiated clinical trial of the treatment of severe acute graft-versus-host disease (GVHD). We have also supplied UC-MSCs for researchers in Japan and internationally.

Umbilical Cord Blood and Cord/Cord-derived mesenchymal stromal cells banking (IMSUT CORD):

Nagamura-Inoue T, Takahashi A, Hori A, Yamamoto Y, Iwasawa I, Nagaya N, Miharu Y, Ogami K, Saito Y, Nagamura F, Tojo A

Umbilical cord (UC) is a rich source of mesenchymal stromal cells (MSCs). The 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 osteoblast, chondroblast, adipocyte, and neurons; (4) low immunogenicity with significant immunosuppressive ability, (5) tissue repair potency, (6) migration ability toward the inflammatory or injured sites, subsiding the inflammation and repairing the damaged tissues, and (7) no donor age-dependent variations. We established a cord blood/cord bank at the IMSUT hospital (IMSUT CORD) to supply umbilical cord-derived cells for research purposes based on joint research and material transfer agreements to for-profit companies and researchers in Japan and internationally.

We collect, process, culture, and cryopreserve the UC-MSCs with serum-free process for banking. Now we produce the product cells namely IMSUT-CORD from master cell bank.

We began to release IMSUT-CORD for an investigator-initiated clinical trial begun in 2018 for treatment of resistant severe acute graft-versus-host disease.

We are now preparing the IMSUT-CORD for the treatment of neonatal encephalopathy as the next clinical trial.

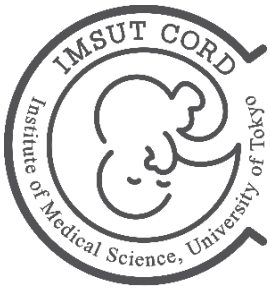
Development of a stable supply system for

Nagamura-Inoue T, Takahashi A, Kamisato A, Hori A, Yamamoto Y, Iwasawa I, Nagaya N, Miharu Y, Ogami K, Saito Y, Nagamura F, Tojo A

We are going to establish a stable system for supplying UC/ or UC-MSCs in the public interest from collection facilities (obstetrics and gynecology clinics) via IMSUT CORD as a source of regenerative medicine products serving for profit companies that conduct regenerative medicine and other forms of cell therapy. We also examine issues regarding the social acceptability of MSCs, including ethical con-

siderations and placenta disposal laws, in supplying umbilical cord-derived MSCs.

Visit our website: http://plaza.umin.ac.jp/~imsutcord/



IMSUT Hospital

Department of Nursing
看護部

Director	Koji Kobayashi, RN, Ph.D.
Deputy Director	Minayo Hisahara, RN.
Deputy Director	Fumiko Kasuya, RN, CNA.
Nurse Manager	Mayumi Tanii, RN, MSN, CNA.
Nurse Manager	Hatsuko Narita, RN.
Nurse Manager	Mika Kogayu, RN, MSN.
Nurse Manager	Tomoko Sato, RN.
Nurse Manager	Masako Ozawa, RN.
Nurse Manager	Hiromi Isshiki, RN.

看護部長	博士(保健学)	小林康司
副看護部長		久原みな代
副看護部長	認定看護管理者	粕谷文子
看護師長	修士(看護学)・認定看護管理者	谷井真弓
看護師長		成田初子
看護師長	修士(看護学)	小粥美香
看護師長		佐藤朋子
看護師長		小澤昌子
看護師長		一色裕美

Department of Nursing seeks to provide high-quality nursing care and contribute to the team approach to patient centered care to meet diversified needs, along with changes in social circumstances and with the progress of medical science.

One of our missions is "Making a difference in patient outcome provided by nursing care." As nurses, we provide optimal care so that patients may receive quality treatment. Patients should be able to live valuable and meaningful life. As health-care providers, we make an effort to prevent infection, pressure ulcer and other complications. We also do our best for patient safety and their high quality of life.

In 2011, we introduced the Career Ladder System to support active learning and development of nurses, it keeps nurses motivated to continue learning and fulfill their career development as a nurse. Nursing skills based on good knowledge and evidence is also very important in patient care. The online training tool "Nursing Skills Japan" was also launched in 2011 to enhance nurses' learning and to brush up their skills.

In 2012, we promote that nurses can get nursing specialty training and the certification of their field. And we empowered them for role expansion of nurses. Furthermore, we are actively engaged in a discharge nursing and ethical conference.

In 2013, we introduced the Pair System as nursing delivery system to improve the quality of nursing, the effect of OJT (on the job training), and the efficiency of nursing service.

In 2014, we organized some working groups to develop clinical nurse leaders for quality assurance, cancer nursing, clinical research/ translational research nursing.

From 2015, we accelerate utilizing competency model for developing nurse manager. Nurse Managers cooperate with the competency training courses held at various places in Japan many times as facilitator.

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IMSUT Hospital

Department of Pharmacy
薬剤部

Director	Seiichiro Kuroda
Vice director	Takeo Yasu
Pharmacist	Kenji Momo

薬剤部長	黒田誠一郎
副薬剤部長	安武夫
薬剤師	百賢二

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.

1. 論文

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IMSUT Hospital

Department of AIDS Vaccine Development
エイズワクチン開発担当

Invited Professor Tetsuro Matano, M.D., D.M.Sc.
Visiting Associate Professor Ai Kawana-Tachikawa, D.M.Sc.

教授(委嘱) 博士(医学) 俣野哲朗
客員准教授 博士(医学) 立川(川名)愛

We are working on Microbiology and Immunology to elucidate the immune mechanism for viral control in vivo. For development of an effective AIDS vaccine, we established an AIDS model using groups of rhesus macaques sharing individual MHC-I haplotypes and are studying virus-host immune interaction. We are developing vaccines using Sendai virus vectors eliciting antibody and/or cytotoxic T lymphocyte responses. We are also studying how HIVs evolve in human populations.

1. Human leukocyte antigen-associated *gag* and *nef* polymorphisms in HIV-1 subtype A/E-infected individuals in Vietnam.

Naofumi Takahashi[1], Saori Matsuoka[1], Tam Tran Thi Minh[2], Hien Pham Ba[3], Taeko K. Naruse[4], Akinori Kimura[4], Teiichiro Shiino[1], Ai Kawana-Tachikawa, Koichi Ishikawa[1], Tetsuro Matano, Lan Anh Nguyen Thi[2]: [1]AIDS Research Center, National Institute of Infectious Diseases, Tokyo, Japan, [2]Center of BioMedical Research, National Institute of Hygiene and Epidemiology (NIHE), Hanoi, Vietnam, [3]Dong Da General hospital, Hanoi, Vietnam, [4]Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan

Numbers of human leukocyte antigen (HLA)-associated polymorphisms have been reported on human immunodeficiency virus type 1 (HIV-1) subtypes B and C, but few on other subtypes. We have been working on HIV-1 and HLA genotypes in HIV-1 infected individuals in Vietnam in collaboration with NIHE. In this study, we have analyzed HLA class I-associated *gag* and *nef* polymorphisms in HIV-1 subtype A/E prevalent in Vietnam. We have determined HLA-A, B and C genotypes in 179 HIV-1-infected Vietnamese by next generation sequencing and analyzed proviral genome sequences in 144 of them, showing that 142 of the 144 were subtype A/E. Analysis revealed HLA-associated subtype A/E *gag* and *nef* polymorphisms at nineteen residues including those newly determined. Accumulation of these data would contribute to our understanding of HIV-1 subtype A/E and host immune interaction.

2. $CD8^+$ cytotoxic T lymphocyte breadth could facilitate early immune detection of immunodeficiency virus-derived epitopes with limited expression levels.

Tetsuo Tsukamoto[5], Hiroyuki Yamamoto[1], Tetsuro Matano: [5]Department of Immunology, Kindai University Faculty of Medicine, Osaka, Japan

Cytotoxic T lymphocyte (CTL) responses are important to control the replication of HIV and simian immunodeficiency virus (SIV). Accumulating evidence suggests that the ability of a few immunodominant T-cell populations to detect and kill HIV/SIV-infected cells is important in individuals with a protective major histocompatibility complex class I (MHC-I) allele. On the other hand, immunization with live(-attenuated) viruses may be effective against superinfection of virulent viral strains regardless of the host's MHC-I haplotypes, although

the underlining mechanisms have not been fully documented. In this study, we have proposed a hypothesis that the early detection of infected cells in superinfected individuals may be partly facilitated by recognition of diverse CTL epitopes with limited expression levels. We have further explained the hypothesis using simple mathematics that was written based on previous *in vitro* viral suppression assay results and by considering the physical contact of infected cells with CTLs.

3. Generation of HIV-resistant macrophages from IPSCs by using transcriptional gene silencing and promoter-target RNA.

Higaki K[6,10], Hirao M[6,10], Kawana-Tachikawa A, Iriguchi S[6], Kumagai A[6], Ueda N[6], Bo W[6], Kamibayashi S[6], Watanabe A[7], Nakauchi H[8,9], Suzuki K[9], Kaneko S[6]: [6]Department of Cell Growth and Differentiation, Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan, [7]Department of Life Science Frontier, CiRA, Kyoto University, Kyoto, Japan, [8]Division of Stem Cell Therapy, Institute of Medical Science, University of Tokyo, Tokyo, Japan, [9]Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA, USA, [10]St Vincent's Centre for Applied Medical Research (AMR), St Vincent's Hospital, Melbourne, Australia

Highly active antiretroviral therapy (HAART) has markedly prolonged the prognosis of HIV-1 patients. However, lifelong dependency on HAART is a continuing challenge, and an effective therapeutic is much desired. Recently, introduction of short hairpin RNA (shRNA) targeting the HIV-1 promoter was found to suppress HIV-1 replication via transcriptional gene silencing (TGS). The technology is expected to be applied with hemato-lymphopoietic cell transplantation of HIV patients to suppress HIV transcription in transplanted hemato-lymphopoietic cells. Combination of the TGS technology with new cell transplantation strategy with induced pluripotent stem cell (iPSC)-derived hematolymphopoietic cells might contribute to new gene therapy in the HIV field. In this study, we have evaluated iPSC-derived macrophage functions and feasibility of TGS technology in macrophages. Human iPSCs were transduced with shRNAs targeting the HIV-1 promoter region (shPromA) by using a lentiviral vector. The shPromA-transfected iPSCs were successfully differentiated into functional macrophages, and they exhibited strong protection against HIV-1 replication with alteration in the histone structure of the HIV-1 promoter region to induce heterochromatin formation. These results indicated that iPS-derived macrophage is a useful tool to investigate HIV infection and protection, and that the TGS technology targeting the HIV promoter is a potential candidate of new gene therapy.

4. Generation of multivirus-specific T cells by a single stimulation of peripheral blood mononuclear cells with a peptide mixture using serum-free medium.

Nishiyama-Fujita Y[11], Kawana-Tachikawa A, Ono T[12], Tanaka Y[11], Kato T[12], Heslop HE[13], Morio T[12], Takahashi S[11]: [11]Division of Molecular Therapy, Advanced Clinical Research Center, Institute of Medical Science, University of Tokyo, Tokyo, Japan, [12]Department of Pediatrics and Developmental Biology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, [13]Center for Cell and Gene Therapy, Baylor College of Medicine, Houston Methodist Hospital and Texas Children's Hospital, Houston, TX, USA

Restoration of virus-specific immunity by virus specific T cells (VSTs) offers an attractive alternative to conventional drugs, and can be highly effective in immunocompromised patients, including hematopoietic stem cell transplant (HSCT) recipients. However, conventional VSTs manufacture requires preparation of specialized antigen-presenting cells (APCs), prolonged ex vivo culture in serum-containing medium and antigen re-stimulation with viruses or viral vectors to provide viral antigens for presentation on APCs. To simplify this complex process, we have developed a method to generate multiple VSTs by direct stimulation of peripheral blood mononuclear cells (PBMCs) with overlapping peptide libraries in serum-free medium. We have generated VSTs that targeted seven viruses (cytomegalovirus [CMV], Epstein-Barr virus [EBV], adenovirus [AdV], human herpesvirus 6 [HHV-6], BK virus [BKV], JC virus [JCV] and Varicella Zoster virus [VZV]) in a single line. The phenotype, growth and specificity of multiple VSTs produced in serum-free medium were equivalent to those generated in conventional serum-containing medium. The use of serum-free medium allows this approach to be readily introduced to clinical practice with lower cost, greater reproducibility due to the absence of batch-to-batch variability in serum and without concerns for infectious agents in the serum used. This simplified approach will now be tested in recipients of Human Leukocyte Antigen (HLA)-matched sibling HSCT.

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