IMSUT Hospital

Department of Advanced Medical Science
先端診療部

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Department of Advanced Medical Science was established in September 1997. Our aim is to contribute to the performance and the development of advanced therapeutic approach to the diseases. We have been participating in the potentially important clinical trials and the several projects in line with our principles. Our research projects are (1) H. pylori in HIV-infected patients, (2) Early diagnosis of cardiotoxicity in chemotherapy-treated patients, (3) Analysis of the potential therapeutic advantages of cell lysate from human placenta in promoting impaired cutaneous wound healing, (4) Establishment of GMP-compliant large-scale DC vaccines loaded with cytoplasmic transduction peptide-fused protein tumor antigens, (5) Safety test of 5-aminolevulinic acid with ferrous ions in diabetic patients treated with oral hypoglycemic agents.

1. *H. pylori* in HIV-infected patients.

Matsubara Y. et al.

The prevalence of *H. pylori* infection in the HIV-infected patients is to be elucidated. Some studies showed higher rates in HIV-negative than HIV-positive. One of hypotheses is an appropriate amount of $CD4^+$ cells is needed for colonization of *H. pylori*. We investigated *H. pylori* in HIV-infected patients using biopsy specimens taken by upper gastrointestinal endoscopy. Rate of *H. pylori* infection diagnosed by light microscopy was lower in HIV-positive subjects. There was not significant relation between blood CD4 counts and *H. pylori* infection.

2. Early diagnosis of cardiotoxicity in chemotherapy-treated patients.

Watanabe A. et al.

Cardiotoxicity due to chemotherapy may occur acutely or even several years after completion of the treatment for cancer. Since cancer patients survive longer than the past due to the advances of anti-cancer drugs, cardiotoxicity associated with chemotherapeutic regimens such as anthracyclines becomes a more significant issue in these days. Once chemotherapy-induced cardiotoxicity is established, its recognition is easy. However, methods for detection of potentially high risk patients with normal cardiac function have not been established yet. The objective of this study is to determine whether echocardiographic measurements of myocardial deformation induced by increased preload, i.e. stress echocardiography, could predict the development of chemotherapy-induced cardiotoxicity in patients with hematologic malignancy.

3. Analysis of the potential therapeutic advantages of cell lysate from human placenta in promoting impaired cutaneous wound healing

Zhang X. et al

One of the major factors responsible for appearance of chronic wounds is the impairment of cytokine released by local fibroblasts and inflammatory cells, which can result in reduced angiogenesis. We explored whether the lysate of human placenta-derived mesenchymal cells (hPDMSc) can be used for this purpose because placenta is very rich in vessels. A high amount of VEGF and bFGF were detected in the lysate of hPDMSc which were comparable to that of Hela cell and human dermis fibroblast, angiogenic factor, Ang-1, EGF and IL-8 were also detectable. The lysate of hPDMSc stimulated proliferation and migration of hUVECs and fibroblast, indicating its biological activity. Full-thickness wounds were created in normal female mice, following by treatment of lysate of hPDMCs and bFGF that served as control. The stimulatory effect of lysate of hPDMSc on wound healing was indicated by the thick granulation tissue formation and epithelialization responded to lysate-treatment. By comparison, bFGF-treatments had little stimulatory effect. Our result indicated that the application of lysate of hPDMCs could potentially be a promising treatment for human chronic wound healing

4. Establishment of GMP-compliant large-scale DC vaccines loaded with cytoplasmic transduction peptide-fused protein tumor antigens.

Kimura Y. et al.

Compared to peptide vaccines depending upon internal dendritic cells (DCs), ex vivo cultured DCs are a promising vaccine strategy for cancer. Accumulating evidence showed that DC vaccines induced potent anti-tumor immune responses, compared to peptide vaccines. A novel antigen delivery technology, named as cytoplasmic transduction peptide (CTP), has been developed by JW Creazen, in order to improve antigen presentation and induction of anti-tumor immune responses by DCs. CTP delivers high polymer materials such as protein antigens into cytoplasmic compartment and retains them in the cytosol. Thus, the CTP-fused tumor antigens are taken up and presented efficiently to lymphocytes in theory. Using this system, we investigate whether our DCs are able to efficiently present the CTP-fused proteins to T-cells in vitro. The DCs loaded with the CTP-fused AFP, GPC-3, and MAGE-A1 proteins were produced in the cell processing center (CPC) from peripheral blood mononuclear cells (PBMCs) derived from normal healthy volunteers. After stimulating the PBMCs with the DCs several times, AFP and MAGE-A1 specific IFN-gamma production from cytotoxic T lymphocytes (CTLs) and helper T-cells were detected by ELISA. As the result, they could be induced in vitro from 2 and 1 among 3 volunteers respectively, but not GPC-3 specific T-cells. The present study demonstrates the potential of the CTP-fused proteins for efficient cancer immunotherapy when loaded in DCs.

5. Safety test of 5-aminolevulinic acid with sodium ferrous ions in diabetic patients treated with oral hypoglycemic agents.

Yamashita N. et al.

Recent intervention studies performed in the USA and Japan have shown that a nutritional supplement of 5-aminolevulinic acid (5-ALA) with sodium ferrous ions (SFC) efficiently reduced blood glucose levels in pre-diabetic population without any adverse events. Thus, 5-ALA with SFC is expected to be taken as a beneficial supplement by diabetic patients under OHA therapy. Its safety and efficacy should be examined in diabetic population. Thus the study was designed as a prospective single-blinded, randomized, placebo-controlled, parallel-group comparison study. Medically treated diabetic patients between 30 and 75 years old were recruited from the Tokyo metropolitan area of Japan and 45 subjects were selected after screening. These subjects were randomly assigned to three groups: daily intake of 15mg 5-ALA, 50mg 5-ALA, and a placebo (n=15, respectively). The supplement or placebo was administered for 12 weeks followed by a four week washout period. The primary endpoint was safety and occurrence of hypoglycemic attack. The secondary endpoint was changes of fasting blood glucose (FBG) and hemoglobin A1c (HbA1c). Adverse events related to 5-ALA with SFC were not observed in all groups. Abnormalities in blood and urine tests were neither observed. Significant decrease of FBG was not detected in all groups. However, there was a small but significant decrease of HbA1c at 4 and 8 week in the 15 mg 5-ALA group. A significant decrease of HbA1c was not observed in the 50 mg 5-ALA group, although there was a tendency to decrease after 4 weeks. It was concluded that 5-ALA with SFC is a safe supplement if taken by diabetic patients treated with OHAs, and may be beneficial for them. A similar study increasing the dose of ALA is carried out in Bahrain to examine the difference between races. This study is just finished and the data are going to be analyzed.

Publications

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IMSUT Hospital

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

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（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 2015, 22 new patients with HIV infection have visited to our hospital and 536 patients in total are currently under our clinical management. The total number of in-patients with HIV-infection during 2015 was 65, and 4 or 5 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], Eisuke Adachi, Tadashi Kikuchi[1], Hitomi Nakamura, Toshiyuki Miura, Takashi Odawara: [1]Division of Infectious Diseases, The Advanced Clinical Research Center

22 new patients with HIV-1 infection visited to our hospital this year (from January 1 to December 31, 2015), and 536 patients in total are under medical management in our outpatient clinic. The total number of HIV-infected in-patients during 2015 was 65. 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 512 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 50 copies/ml in 98.5% of HIV-infected patients in our outpatient clinic. Consequently, the patients are able to maintain good condition as long as they keep excellent drug adherence rates. The clinical management of HIV-in-

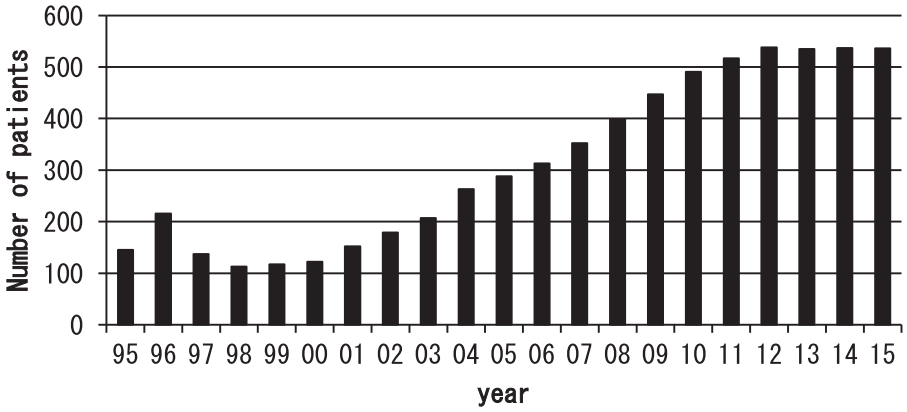

Figure 1. Number of HIV-infected outpatients in IMSUT Hospital

fected 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], Eisuke Adachi, Tadashi Kikuchi[1], Hitomi Nakamura, Toshiyuki Miura, Takashi Odawara: [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. It has been downloaded more than 10,000 times in 2015. 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. *Helicobacter pylori* gastritis in patients with HIV infection

Eisuke Adachi, Tomohiko Koibuchi, Michiko Koga[1], Tadashi Kikuchi[1], Hitomi Nakamura, Toshiyuki Miura, Takashi Odawara: [1]Division of Infectious Diseases, The Advanced Clinical Research Center

Epidemiologic studies have detected a lower prevalence of *H. pylori* in patients with HIV infection and the association between higher CD4+ cell counts and lower HIV-1 viral loads and *H. pylori* infection, with the underlying mechanisms being unknown. Several mechanisms have been proposed to explain this association. Recently, a study reported that *H. pylori* infection itself could affect the progression of, or the susceptibility to, HIV infection. *H. pylori* needs a functional immune system to colonize the human gastric mucosa persistently and a complex interaction of various helper T-cell subtypes. However, no data on associations between *H. pylori* and the breakdown of gastric mucosal immunity caused by HIV infection has been published to date. We obtained the gastric mucosa specimens and the peripheral blood mononuclear cells from HIV infected patients in IMSUT hospital. A total of 52 HIV infected patients were recruited by the end of June, 2015 and we reported that the *H. pylori* co-infection was associated with the past history of AIDS in HIV infected patients (odds ratio 0.20, P= 0.024) in the 29th annual meeting of the Japanese Society for AIDS Research. This work was supported by JSPS KAKENHI Grant Number 15K19584.

4. Methemoglobinemia in an HIV-Infected Patient Treated with Primaquine for *Pneumocystis jirovecii* Pneumonia

Ryutaro Furukawa, Eisuke Adachi, Tadashi Kikuchi[1], Michiko Koga[1], Tomohiko Koibuchi: [1]Division of Infectious Diseases, The Advanced Clinical Research Center

Pneumocystis jirovecii pneumonia (PCP) is common in patients with acquired immunodeficiency syndrome (AIDS). Trimethoprim-sulfamethoxazole (TMP-SMX) is the first choice for treating PCP; the alternatives are pentamidine and atovaquone. Primaquine combined with clindamycin is another choice when patients respond poorly or have toxic reactions to other agents. We experienced a case of an HIV-positive male patient who developed a decline in his oxygen saturation by pulse oximeter (SpO_2) during treatment for PCP and was diag-

nosed with primaquine-induced methemoglobinemia.

A 38-year-old male patient with HIV infection developed dyspnea and cyanosis during the treatment for PCP with primaquine. The methemoglobin level of the patient's blood was as high as 11.3 %. Ten days after the cessation of primaquine treatment, the patient's methemoglobin level successfully fell to 1.1%. We published a case report of methemoglobinemia in an HIV-infected patient treated with primaquine for PCP in The Journal of AIDS Research. Our case indicates that iatrogenic methemoglobinemia can confound the diagnosis of diseases that cause dyspnea and cyanosis such as PCP.

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

Tomohiko Koibuchi, Michiko Koga[1], Eisuke Adachi, Tadashi Kikuchi[1], Hitomi Nakamura, Toshiyuki Miura, Takashi Odawara: [1]Division of Infectious Diseases, The Advanced Clinical Research Center

Dozens of important medicines essential for treatment 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 fifty 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
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Our department is founded in 2001 to tackle systemic autoimmune inflammatory diseases including rheumatoid arthritis, systemic lupus erythematosus and vasculitic syndromes. We provide patients personalized and evidence-based medical service. We also challenge cutting edge science of autoimmune, rheumatic and allergic diseases and novel treatments for patients with these disorders.

1. Clinical activities in IMSUT Hospital

Osamu Hosono, Noritada Yoshikawa, Hiroshi Kobayashi, Aya Oda, Masaaki Uehara, Erika Matsubara, Hiroyuki Baba, Hirotoshi Tanaka

Rheumatologists at our division provide state-of-the-art diagnosis and treatment for diseases that affect the body's connective tissue. Physicians in the specialty see nearly 5,000 patients each year. Our physicians have active basic and clinical research projects and also are involved in training of rheumatology specialists. Our rheumatologists treat many types of arthritis, including common diseases such as rheumatoid arthritis and osteoarthritis, and collagen vascular diseases including rheumatoid arthritis, systemic lupus erythematosus and vasculitic syndromes.

Rheumatologic services offered at IMSUT include:

- Outpatient consultations
- Outpatient specialty care for patients with chronic rheumatic diseases
- Hospital consultations
- Diagnostic and therapeutic intra-articular and soft tissue injections and aspirations
- Diagnostic ultrasonography
- Education on rheumatologic diseases and treatments
- Clinical trials

Our physicians have active basic and clinical research projects and also are involved in training of rheumatology specialists.

2. Development of novel therapy to overcome intractable disorders in rheumatic diseases via targeting transcriptional apparatus

Hirotoshi Tanaka, Noritada Yoshikawa, Noriaki Shimizu, Naoki Ito, Takako Maruyama, Akiko Souta-Kuribara, Yanxia Ma, Ryo Matsumiya, Yuki Tasaka, Tsutomu Murakami, Aya Oda, Masaaki Uehara, Hiroshi Kobayashi, Osamu Hosono

We are interested in the mechanism of eukaryotic gene expression and development of novel therapy and/or drugs that target transcriptional machineries. For this purpose, our recent work is mainly focused on conditional regulation of transcription factors including the glucocorticoid receptor (GR) and inhibitory components of transcription elongation machinery including HEXIM1. Our recent achievement is now being applied in clinical settings in

IMSUT Hospital.

(i) Development of novel GR regulators

Despite the established role of glucocorticoids (GC) in controlling short-term inflammation, and despite emerging evidence supporting a disease modifying role in various autoimmune disorders, concern for adverse events associated with GCs often limits their use. Activation of the GR by GC regulates hundreds of genes expression both positively and negatively. It has become quite widely accepted that transrepression accounts for the majority of therapeutic, anti-inflammatory effects of GC, whereas transactivation is responsible for most side effects. This "transrepression hypothesis" has arisen a set of ideas about how to discover novel anti-inflammatory drugs that do not carry the same burden of side effects as GC. We have explored unique GR regulators that have a different mode of action from classical GC. Recently we have demonstrated that certain ligands can modulate interdomain communication of the GR, which will eventually contribute to isolation of novel category of ligands.

(ii) Clarification of tissue-specific effects of GC and the development of molecular basis of novel GC therapy

We have developed an efficient system to screen out the target genes of GR in glucocorticoid-responsive tissues, and are working with clarification of tissue-specific effects of GC in skeletal muscles. Skeletal muscle comprises ～40% of body mass and contributes not only to the structure and movement of the body but also to nutrient storage and supply. Excessive loss of muscle mass is associated with poor prognosis in several diseases, including myopathies and muscular dystrophies, as well as in systemic disorders such as cancer, diabetes, sepsis, heart failure, and glucocorticoid excess. Muscle atrophy also occurs in aging that is called sarcopenia and recently thought to be one of core features of "Locomotive Syndrome". The maintenance of healthy muscles is crucial for preventing metabolic disorders, maintaining healthy aging and providing energy to vital organs during stress conditions. We investigated how GR-mediated gene expression coordinately modulates anti-anabolic and catabolic actions to understand the functional coupling of metabolism and volume regulation in muscle. We identified REDD1 and KLF15 genes as direct targets of GR. We here demonstrated that KLF15 participates in muscle catabolism via the transcriptional regulation of atrogin-1 and MuRF1. Moreover, KLF15 affects mTOR through BCAA degradation and negatively modulates myofiber size. mTOR activation inhibits GR-mediated transcription by suppressing GR recruitment onto target genes, strongly suggesting a mutually exclusive crosstalk between mTOR and GR. Pharmacological activation of mTOR with BCAA attenuated GR-mediated gene expression, leading to the substantial restoration of muscle in glucocorticoid-treated rats. We, therefore, indicate 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. Given this, we have been working with the clinical trial in IMSUT hospital to verify our scenario in glucocorticoid-treated patients. In addition, we unraveled the physiological significance of muscle proteolysis using mGRKO. 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. 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.

(iii) Development of novel therapeutic strategies for fatal complications associated with rheumatic diseases

Pulmonary hypertension (PH) is a severe complication of rheumatic diseases and ultimately leads to right ventricular (RV) hypertrophy (RVH) and failure and death. Recent progress of pharmaceutical strategies has improved the prognosis of PH patients associated with rheumatic diseases, however, those treatments are neither universally available nor always effective, thus, development of novel therapeutic strategies is anticipated. We hypothesized that direct interruption of fatal and irreversible RVH/RV remodeling improves their prognosis. We have shown that overexpression of HEXIM1, which is a candidate of suppressor protein of left ventricular hypertrophy by blunting positive transcription elongation factor b (P-TEFb)/RNA polymerase II (RNAPII)-dependent transcription, prevents endothelin-1-induced cardiomyocyte hypertrophy and hypertrophic genes expression, and that cardiomyocyte-specific HEXIM1 transgenic mice ameliorates RV hypertrophy in hypoxia-induced PH model. Moreover, we revealed that overexpression of HEXIM1 prevented hypoxia-induced expression of hypoxia inducible factor 1α (HIF-1α) protein and its target genes including vascular endothelial growth factor (VEGF) in the cultured cardiac myocytes and fibroblasts, and that cardiomyocyte-specific HEXIM 1 transgenic mice repressed RV myocardial angiogenesis in hypoxia-induced PH model. Thus, we

proposed that HEXIM1 could prevent RV hypertrophy in PH via suppression of 1) myocardial angiogenesis through down-regulation of HIF-1α and VEGF, 2) P-TEFb/RNAPII-dependent transcriptional regulation, in the myocardium under hypoxic condition. HEXIM1-dependent transcriptional regulation may play a pathophysiological role in RVH and be a novel therapeutic target for mitigating RVH/RV remodeling in PH.

(iv) Development of novel therapeutics targeting innate immunity in interstitial lung disease associated with connective tissue disease.

Interstitial lung disease (ILD) associated with connective tissue disease (CTD), which is one of the fatal organ damage in rheumatoid arthritis and other collagen diseases, affects the patient's prognosis. And its treatment strategy with satisfactory effect has not yet fully established. Recently, we have discovered a novel alveolar macrophage activation mechanism through Caspase-6 activation following interleukine-1 receptor associated kinase M (IRAKM) proteolysis. In its activation mechanism in innate immunity, alveolar macrophages in response to adhesion with activated neutrophils, can modulate inflammatory cytokine production by activating NF-kB. We have analyzed details of the signaling mechanism and clarified its involvement in the pathophysiology of ILD with CTD using brochoalveolar lavage fluid from patients with ILD. In this study we are aiming at establishment of new diagnostic and therapeutic methods for them.

3. Clinicopathological study of IgG4-related diseases

Osamu Hosono, Hiroshi Kobayashi, Masaaki Uehara, Aya Oda, Erika Matsubara, Hiroyuki Baba, Naoki Ito, Yuki Tasaka, Tsutomu Murakami, Takako Maruyama, Akiko Kuribara, Ryo Matsumiya, Yanxia Ma, Noriaki Shimizu, Noritada Yoshikawa, Hirotoshi Tanaka

Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized syndrome with a presumed autoimmune pathogenesis comprised of a collection of disorders that share features including tumor-like swelling of involved organs, lymphoplasmacytic infiltrates enriched in IgG4-positive plasma cells, variable degrees of fibrosis with a characteristic storiform pattern, and elevated levels of serum IgG4. IgG4-RD affects multiple organs, such as pancreas, lacrimal and salivary glands, kidney, lung, retroperitoneum, aorta, and lymph nodes. We recently experienced two IgG4-RD patients with atypical presentation, pericarditis and normal pressure hydrocephalus, respectively. The patients raised several important questions in the diagnosis and management of IgG4-RD. One is the requirement of typical fibrotic pathology for the diagnosis of this disease. Second question is the relevance of the application of the diagnostic algorism of IgG4-RD in patients with pericardial or central nervous system involvement. Pathological confirmation is essential to fulfill the recently raised diagnostic criteria, however, such invasive procedure might not always be indicated in high-risk patients. We are going to analyze the IgG4-RD with atypical presentation experienced in our department for clinical, immunological, and pathological aspects. These studies could contribute to clarification of the clinical spectrum of IgG4-related diseases for their optimal treatment.

4. Clinical research for developing a novel therapy preventing glucocorticoid-induced muscle atrophy in patients with rheumatic diseases

Noritada Yoshikawa, Osamu Hosono, Hiroshi Kobayashi, Masaaki Uehara, Aya Oda, Erika Matsubara, Hiroyuki Baba, Naoki Ito, Yuki Tasaka, Takako Maruyama, Akiko Kuribara, Ryo Matsumiya, Yanxia Ma, Tsutomu Murakami, Noriaki Shimizu, Hirotoshi Tanaka

Either as drugs used to treat several medical conditions or as endocrine hormones released in response to many stress situations (e.g., sepsis, cachexia, starvation, and metabolic acidosis), excess of glucocorticoids (GC) induce skeletal muscle atrophy. The resulting weakness of peripheral and respiratory muscles causes further clinical problems such as fatigue, frailty, impaired wound healing, compromised lung function, immunosuppression, and altered their quality of life. However, skeletal muscle atrophy pose unmet needs for specific and effective treatments. 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. Several clinical studies are ongoing to develop novel therapy for this condition, however, even accurate and reliable measurements of muscle volume are less understood. At first, we evaluated the availability of bioelectrical impedance analysis (BIA), computed tomography (CT), and magnetic resonance imaging (MRI) for measurement of skeletal muscle mass in patients with rheumatic diseases and quantitatively assessed skeletal muscle loss after GC treatment. We clearly documented that GC-related skeletal muscle loss could be quantitatively assessed with BIA, CT, or MRI in patients with rheumatic diseases, and CT and MRI appeared to be more accurate than BIA. CT could discriminate muscles with abnormal lipid accumulation accord-

ing to radiation attenuation. More sensitive and quantitative methods for not only quantity but also quality of skeletal muscle might help to design such novel therapies preventing glucocorticoid-induced muscle atrophy in patients with rheumatic diseases.

Based on this research, we conducted a clinical trial in IMSUT hospital (See below).

5. Clinical Trial; Effect of branched-chain amino acid-enriched beverage "Amino-Value [CONC.]" supplementation in patients with glucocorticoid-induced muscle atrophy (UMIN000006972)

Hirotoshi Tanaka, Noritada Yoshikawa, Ryo Matsumiya, Erika Matsubara, Hiroyuki Baba, Akiko Souta-Kuribara, Masaaki Uehara, Aya Oda, Hiroshi Kobayashi, Osamu Hosono, Shigeru Kiryu[1], Fumitaka Nagamura[2]: [1]Department of Radiology, IMSUT Hospital, [2]Division of Advanced Medicine Promotion, Advanced Clinical Research Center, IMSUT

Skeletal muscle atrophy is induced by muscle denervation and disuse, and it is also the key component of cachexia, a catabolic, debilitating response to several diseases and one of the undesirable effects of glucocorticoid treatment. Patients in such medical conditions not only sustain a decreased quality of life, but also face a worse prognosis of the underlying pathology, making it an important treatment target, however, skeletal muscle atrophy pose unmet needs for specific and effective treatments. To overcome this issue, we have studied precise mechanisms of glucocorticoid-induced skeletal muscle atrophy, and based on our investigation described above section, we have just started a clinical trial in IMSUT hospital. The objective of this 3-month, open label, randomized, parallel group, Phase I, II clinical trial is to test the effect of commercially available BCAA-enriched beverage "Amino-Value [CONC.]" in patients with rheumatic diseases taking glucocorticoids and to explore the diagnostic and evaluation procedures for skeletal muscle atrophy in those patients. Primary outcomes of this trial are evaluation of muscle volume and strength using manual muscle test, bioimpedance, CT and MRI imaging. Key secondary outcomes are Performance Status, evaluation of daily living activity, squatting, blood and urine biochemistry. This study was conducted from May 2012 to January 2015. Oral BCAA supplementation did not exacerbate disease activity and was almost well tolerated in those patients. Moreover, the effects of BCAA supplementation on recovery of skeletal muscle mass, strength, and function were evident in not all but particular muscles.

6. Clinical Trial: A phase I clinical trial of rice-based oral cholera vaccine IMSUT-MR1501 in healthy volunteers. (UMIN000018001)

(Collaborative project of IMSUT and IMSUT Hospital)

The team of Professor Hiroshi Kiyono (Divisionof Mucosal Immunology, IMSUT) succeeded in developing a molecularly uniform rice-based oral cholera vaccine (MucoRice-CTB) by using an overexpression system for modified cholera toxin B subunit, and confirmed that orally administered rice-based vaccine effectively inhibited cholera toxin-induced diarrhea in mice. To establish MucoRice-CTB for human use, hygromycin phosphotransferase selection marker-free MucoRice-CTB line 51A was developed. MucoRice-CTB was new generation of mucosal vaccine, "Cold-chain- and Needle-free Rice-based Vaccines", which is promising especially in developing countries.

For clinical trials, they established a prototype of a closed MucoRice hydroponic factory at the Institute of Medical Science, the University of Tokyo, Japan, which was approved as GMP (Good Manufacturing Practices) factory by the Japanese Ministry of Health, Labour and Welfare in 2014. Osamu Hosono (Department of Rheumatology and Allergy, IMSUT Hospital), PI of this clinical trial, and collaborators prepared a "First-in-man" clinical trial phase I study of MucoRice-CTB in cooperation of many departments of the hospital. After the consultation with PMDA (Pharmaceuticals and Medical Devices Agency) in January 2015, this clinical trial was registered at UMIN Clinical Trial Registry (UMIN000018001) and approved by the Institutional Review Board of the Institute of Medical Science, the University of Tokyo (26-55) in March 2015. The randomized, double-blind, dose-escalation, placebo-controlled study was launched in June 2015 and will be analyzed for the safety and immunological effects of IMSUT-MR1501 in near future.

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We have been challenging to cure intractable hematological disorders such as leukemia and lymphoma mainly with the aid of hematopoietic stem cell transplantation (HSCT). Since 1998 we have been conducting cord blood transplantation (CBT) for adult patients and now CB is a majority of the stem cell source for SCT in our department. The achievement of our department in the field of HSCT is described elsewhere.
We are especially focusing on two most intractable hematological diseases, Lagerhans cell histiocytosis (LCH) and adult T-cell leukemia (ATL). Our department is one of the hub facilities for the treatment and research of these diseases. The standard strategy for the treatment of LCH has not been established because of rarity of the disease. We are treating many referred LCH patients and trying to reveal the pathophysiology of the disease. ATL is one of the most incurable hematological malignancies which occurs about 5% of HTLV-1 asymptomatic carriers. The results of chemotherapies for aggressive ATL have been quite poor and long term survive can be acquired in no more than 10% of the patients. We initiate to search donors in HSCT when starting chemotherapies for aggressive ATL patients simultaneously and achieved about 40% of long term survival rate for this intractable disease. Along with the treatment of ATL, we are analyzing the mechanism of oncogenesis of HTLV-1 infected cells into ATL and revealed phenotypical changes of the cells. Our study enables identification of high risk group for development of ATL in HTLV-1 asymptomatic carriers.

1. Advanced HTLV-1 carriers and early-stage indolent ATLs are indistinguishable based on the CADM1 positivity in flow cytometry.

Seiichro Kobayashi, Nobuhiro Ohno, Arinobu Tojo, Kaoru Uchimaru

We previously reported that the cell adhesion

molecule 1 (CADM1) vs. CD7 plot in flow cytometry reflects disease progression in human T-cell leukemia virus type 1 (HTLV-1) infection. In $CD4^+$ cells from peripheral blood, $CADM1^-CD7^+$ (P), $CADM1^+CD7^{dim}$ (D) and $CADM1^+CD7^-$ (N) subpopulations are observed. The D and N subpopulations increase as asymptomatic HTLV-1 carriers (ACs) progress to indolent adult T-cell leukemia-lymphoma (ATL), and the N subpopulation then expands in aggressive ATL. In this study we examined whether the analysis can estimate risk of developing ATL in advanced ACs. Peripheral blood samples from ACs (N=41) and indolent ATL patients (N=19) were analyzed by flow cytometry using the CADM1 vs. CD7 plot for $CD4^+$ cells and inverse long PCR (clonality analysis) of FACS-sorted subpopulations. Almost all ACs with a high HTLV-1 proviral load (> 4 copies/100 cells) had a $CADM1^+$ (D + N) frequency of > 10%. ACs with 25% < $CADM1^+$ ≤ 50% contained expanded clones similar to smoldering-type ATLs. In many patients in the 25% < $CADM1^+$ ≤ 50% group, the proportion of abnormal lymphocytes was distributed around the 5% line which divides ACs and smoldering-type ATL in Shimoyama's classification. In conclusion, the CADM1 vs. CD7 plot is useful for selection of putative high-risk ACs. Some ACs and smoldering ATLs are considered to have similar characteristics, although long-term follow up and clinical outcome (*e.g.* rate of transformation) of these cases are required to conclude if they should be included into same clinical category.

2. Formation of segmental rounded nodules during the infiltration of adult T-cell leukemia cells into ocular mucous membrane.

Koju Kamoi[1], Kaoru Uchimaru, Arinobu Tojo: [1]Department of Ophthalmology and Visual Science, Graduate school of Medical and Dental Science, Tokyo Medical and Dental University.

We documented a case of adult T-cell leukemia cell infiltration into the ocular mucous membrane that presented with rounded nodule formation. A 36-year-old woman presented with bilateral conjunctival hyperemia and small rashes on the legs and face. After complaining of significant fatigue at 6 months, she was diagnosed with the acute type of adult T-cell leukemia (ATL). Ophthalmic examination revealed the formation of bilateral segmental rounded nodules all over her ocular surface. The nodules were located both at the bulbar conjunctiva around the corneal limbs and the palpebral conjunctiva around each lacrimal punctum. Although cellular infiltrations were also seen at the corneal subepithelium and stoma, no cellular infiltrations were observed in the anterior chamber, vitreous, or retina. A biopsy was performed in order to examine the contents of the rounded nodules. Quantitative real-time polymerase chain reaction (PCR) assay detected 7.7×10^4 copies/μg and 4.6×10^4 copies/μg of HTLV-1 proviral DNA at the bulbar and palpebral conjunctivas, respectively. Monoclonal T-cell receptor γ chain gene rearrangement was detected in both samples. Pathological evaluations identified atypical lymphoid cells with scanty cytoplasm and multilobed nuclei. These analyses confirmed that the rounded nodules were formed in conjunction with the infiltration of the ATL cells. These nodules and infiltrations disappeared after starting chemotherapy. In conclusion, the formation of multiple rounded nodules during ATL cell infiltration into the ocular mucous membrane, especially at the palpebral conjunctiva around the lacrimal punctum, is a distinguishing ocular manifestation of ATL.

3. Polycomb-dependent epigenetic landscape in adult T-cell leukemia

Dai Fujikawa[1], Seiichirou Kobayashi, Kaoru Uchimaru, Makoto Yamagishi[1], Toshiki Watanabe[1]: [1]Graduate School of Frontier Sciences, Department of Computational Biology and Medical Sciences, The University of Tokyo

Adult T-cell leukemia/lymphoma (ATL) shows global gene expression alterations that confer cellular characteristics and unfavorable prognosis. However, it has been largely unknown the mechanisms of the sustained expression changes, because there is no study addressing the relationship between landscapes of the gene expression and epigenetic modifications. Here, we performed integrative analyses of epigenome (n=3) and transcriptome (n=58) from primary ATL patient cells and those from corresponding normal CD4 + T cells to decipher the ATL-specific 'epigenetic-code' that was critical in ATL pathogenesis. We found that polycomb repressive complex 2 (PRC2)-mediated tri-methylation at histone H3Lys27 (H3K27me3) was significantly and frequently reprogrammed at over half of genes in ATL cells. Large proportion of the abnormal gene downregulation was detected at early stage of disease progression and was explained by the H3K27 me3 accumulation. The global H3K27me3 alterations were involved in determination of ATL-specific gene expression program that included several tumor suppressors, unknown transcription factors, epigenetic modifiers, miRNAs, and developmental genes, suggesting that PRC2 generates diverse outcomes by the remote regulation of a broad spectrum of gene regulators. Interestingly, the key enzyme EZH2 was sensitive to promiscuous signaling network including NF-B pathway and was functionally affected by HTLV-1 Tax. The Tax-dependent immortalized cells showed H3K27me3 repro-

gramming that was significantly similar to that of ATL cells. Of note, the majority of epigenetic silencing was occurred in indolent type ATL and also in HTLV-1 infected populations from asymptomatic HTLV-1 carriers. Since pharmacological inhibition of EZH2 reversed the epigenetic disruption and selectively eliminated leukemic and HTLV-1-infected cells, targeting the epigenetic elements will hold great promise in treatment and prevention of ATL and HTLV-1-related diseases onset.

4. Transition of ATL/L cell clones can be observed during the clinical course.

Sakura Aoki[1], Kaoru Uchimaru, Toshiki Watanabe[1]: [1]Graduate School of Frontier Sciences, Department of Computational Biology and Medical Sciences, The University of Tokyo

Adult T-cell leukemia/lymphoma (ATL/L) is a peripheral T-cell neoplasm caused by transformation of the HTLV-1infected T-cells. ATL/L, specifically its aggressive type, is known for its poor prognosis even with an intensive chemotherapy. Although ATL/L cells are considered to be monoclonal, there are case reports suggesting multiclonal proliferation within a patient or proliferation of another clone depending on the time course based on Southern blot analysis, although direct molecular evidence has not been provided. Furthermore, it has been suspected that quick acquisition of drug resistance by ATL/L cells might be a result of clonal exchange. To directly analyze possible clonal change of ATL/L tumor cells during the clinical course, we employed the inverse PCR method to detect the integration sites, and analyzed and compared the clonality of ATL/L cells collected at different time points of the clinical course of patients. The results indicated that in three patients out of 19 the major clone has changed in the observation period. These results provide direct evidence that clonal transition of ATL/L cells can take place in the clinical course or in response to chemotherapy. They also indicated importance of clonality analysis for understanding the mechanism for ATL/L development and drug resistance.

5. Treatment of chronic lymphocytic leukemia with bendamustine in an HIV-infected patient on antiretroviral therapy: a case report and review of the literature.

Naoki Shimada[1], Nobuhiro Ohno, Tomohiko Koibuchi[2], Kaoru Uchimaru, Arinobu Tojo: [1]Promotion Plan for the Platform of Human Resource Development for Cancer, Research Hospital of the Institute of Medical Science, the University of Tokyo, [2]Department of Infectious Diseases and Applied Immunology, Research Hospital of the Institute of Medical Science, The University of Tokyo

Few reports have described the coincidence of chronic lymphocytic leukemia (CLL) and HIV. We administered bendamustine in refractory B-CLL accompanied by HIV infection and observed a significant objective response with concurrent ART. Although myelosuppression was a major problem, no lethal opportunistic infection occurred because the patient was given standard prophylaxis. In future, the number of CLL/SLL patients with HIV infection will increase because of the widespread use of ART. Thus, further evaluation of the safety and efficacy of bendamustine against CLL/SLL with HIV infection is necessary. Our results indicate that bendamustine can be used in HIV-infected CLL patients. We also reviewed twelve cases of CLL with HIV infection.

6. An adult case of biphenotypic acute leukemia with t(6;14)(q25;q32).

Kawamata T, Takei T, Takeda R, Ochi K, Yokoyama K, Fukuyama T, Ohno N, Uchimaru K, Tojo A.

We presented an adult case of biphenotypic acute leukemia with t(6;14)(q25;q32). Chromosome translocations involving 14q32 are generally represented by B cell neoplasms, because the immunoglobulin heavy chain (IgH) gene is located in this region. However, BCL11B gene also located in 14q32 was shown to be involved in this translocation (Bezrookove et al., 2004). BCL11B, a member of the Kruppel family of zinc finger trascription factors, plays a critical role in T cell development and functions as a tumor suppressor (Wakabayashi et al., 2003). The partner gene of this translocation is unknown. The 28S ribosomal DNA (RN28S1) was reported as a candidate fusion partner (Kobayashi et al., 2014), but this gene is not located in 6q25. The phenotype of haematological malignancies with t(6;14)(q25; q32) is variable. These include acute lymphoblastic leukemia (ALL) (Heerema et al., 2002), mixed phenotype acute leukemia (Hayashi et al., 1990, Batanian et al., 1996, Georgy et al., 2008, Kobayashi et al., 2014), acute myeloid leukaemia (AML) (Raimondi et al., 1989, Bezrookove et al., 2004), chronic T cell neoplasm (Inwards et al., 1990) and chronic lymphocytic leukaemia (CLL) (Mayr et al., 2006). In 7 of 9 acute leukaemia cases with this translocation, both myeloid and T-cell lineage markers were detected. No immunophenotype was described in the remaining two cases. This translocation may affect expression of T-cell lineage marker, but the role of BCL11B is unclear.

7. Reversible Pulmonary Arterial Hypertension Induced by Dasatinib in a Patient with Chronic Myeloid Leukemia

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We report a rare case of dasatinib-induced pulmonary arterial hypertension (PAH) in a patient with chronic myeloid leukemia that reversed completely in the short term (within 2 months) after drug discontinuation. Detailed transthoracic echocardiography (TTE) parameters were obtained throughout the recovery process. After 30 months of dasatinib treatment (100 mg/day), a 37-year-old female developed orthopnea and signs of right heart failure (leg edema, hepatomegaly, and weight gain). TTE indicated elevated mean pulmonary artery (PA) pressure, severely impaired systolic and diastolic right ventricular function, and dilated right ventricle and right atrium. After dasatinib discontinuation, clinical symptoms improved rapidly and follow-up TTE 2 months after dasatinib discontinuation showed normal right heart function. Treatment with an alternative tyrosine kinase inhibitor was initiated and has been continued without recurrence of PAH. This report suggests that dasatinib, which inhibits a large number of tyrosine kinases, can cause reversible PAH; therefore, careful cardiopulmonary evaluation by TTE is necessary during dasatinib treatment.

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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 sequence 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 2015, a total of 572 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, Reiko Sada, Shifumi Watase, Mitsuko Nakazawa, Momoyo Ohki[1], Yoshinari Miyamoto[2], Masae Ono[3], Masahiko Suzuki[4], Toshihiro Tanaka[5], Shiro Ikegawa[6], Mayumi Tamari[6], Hidewaki Nakagawa[6], Natsuko Watanabe[7], Ai Yoshihara[7]: [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

We provided genetic counseling and genetic tests to clients who visited our counseling clinic. In 2015, we had a total of 28 counseling cases including familial breast cancer, Lynch syndrome, familial polyposis of the colon, spinocerebellar ataxia, and myotonic dystrophy. 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 three 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. Elucidation of genetic characteristics of human tumors and mechanisms of their development

Kiyoshi Yamaguchi[1], Tsuneo Ikenoue, Yoichi Furukawa: [1]Division of Clinical Genome Research, Advanced Clinical Research Center

We analyzed genetic alterations in Japanese extrahepatic biliary tract cancer (BTC) and pseudomyxoma peritonei of the colon (PMP) using multiplex PCR-based targeted enrichment and next-gen-

eration sequencing (NGS).

In the genetic analysis of BTC, we analyzed a total of 27 tumors and their matched non-cancerous tissues, and identified frequent mutations in *TP53* (14/27), *KRAS* (6/27), *PIK3CA* (6/27), and *SMAD4* (6/27). Interestingly, the frequency of the *PIK3CA* mutation was higher compared with Caucasian BTC cases. This result may suggest that activation of the PI3K-AKT pathway in addition to the abrogation of p53, SMAD4, and RAS-MAPK pathways may play a crucial role in the carcinogenesis of Japanese BTC.

In the PMP study, we analyzed 18 PMPs containing 10 low-grade tumors (DPAMs) and 8 high-grade tumors (PMCAs). As a result, a total of 35 somatic mutations were identified. Frequent mutations were identified in *KRAS* (14/18) and *GNAS* (8/18), but their frequencies were not significantly different between DPAMs and PMCAs. On the other hand, *TP53* mutations were found in PMCAs (3/8), but not in the DPAMs. *PIK3CA* and *AKT1* mutations were also identified in two PMCAs, but not in the DPAMs. These results suggest that *KRAS* and/or *GNAS* mutations are common genetic features of PMP, and that mutations in *TP53* and/or genes related to the PI3K-AKT pathway may render malignant properties to PMP. These data may be useful for the understanding of tumor characteristics, and may facilitate the development of personalized medicine to PMP.

4. Clinical sequence 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

Next-generation sequencing (NGS) has enabled 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 following projects; 1) the determination of germline mutations in patients suspected of hereditary colon tumor, 2) application of a cognitive computing system, namely IBM Watson Genomic Analytics (WGA), 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 carried out three different NGS, namely targeted sequencing, whole exome sequencing, or whole genome sequencing for ten patients with colonic polyposis. In the patients, we previously failed to identify pathological mutations within the 5′ two-thirds region of the *APC* gene by Sanger sequencing. However, NGS successfully identified pathological mutations in three of the ten patients; two were mosaic mutations of *APC*, and the other was a very rare mutation in the 3′ terminal region of *APC*. These data have corroborated the usefulness of NGS in genetic diagnosis.

In the second project, we generated a pipeline to apply genomic data to IBM WGA. After written informed consent was obtained from the patients with pseudomyxoma peritonei (PMP), they were enrolled in this study. Genetic alterations in their tumor were determined by NGS and the data were subsequently analyzed by WGA. The results of WGA including predicted driver mutations and suggestion of actionable drugs were discussed in Tumor Board meeting of this project, which is held every two weeks. Evaluation of the results is now ongoing.

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The Department of Radiology works in general diagnostic radiology, neuroradiology, clinical nuclear medicine, and radiation therapy. For clinical imaging, we have a multi-detector row CT scanner, high-field MRI unit, and hybrid gamma camera system. We perform all examinations of CT, MRI, angiography, and nuclear medicine, and official reports on all the examinations are made by board-certified radiologists. Clinical studies are conducted in collaboration with other departments and other institutions. We also investigate the technical aspects of molecular imaging in intact small animals for its application to preclinical studies using optical imaging system and MRI.

Evaluation of polymeric micelle MR contrast agent for mice MR imaging: comparison with gadofluorine M

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Due to its high structural stability in the blood, polymeric micelles are expected to stay in the blood for a long period of time. The self-assembling property in a selective solvent makes polymeric micelles be comprehensively used as nano-sized drug carriers for drug targeting. The purpose of this study is to evaluate the potential of polymeric micelle contrast agent, a new PEG-poly(L-lysine)-based gadolinium magnetic resonance contrast agent, compared with gadofluorine M.

MR imaging was performed before and after intravenous injection of polymeric micelle contrast agent or gadofluorine M in mice using 1-Tesla permanent magnet compact MR system. The kinetics of both agents were assessed. The visualization of the blood vessels in maximum intensity projection images was also assessed.

In comparison with gadofluorine M, contrast enhancement in the blood was more remarkable for polymeric micelle contrast agent. According to the P-interaction analysis, the enhancement in the liver was similar between two contrast agents, and it differed significantly in the vein, kidney and spleen. In MIP images, prominent enhancement was demonstrated in the blood 24 hours after delivery of polymeric micelle contrast agent, while only slight enhancement was visible 1 hour after the injection of gadofluorine M. The degree of enhancement of the aorta and intrahepatic vein was significantly higher in polymeric micelle contrast agent until 24 hours after injection of it.

The enhancement of the blood was strong and lasted long after the injection of polymeric micelle

contrast agent. This contrast agent appears promise as both blood pool imaging agent and drug-delivery system.

Natural history of nonalcoholic steatohepatitis model mouse examined by Gd-EOB-DTPA-enhanced MRI: comparison with fatty liver model mouse.

Akai H, Nakano Y, Kiryu S

We performed this experiment aiming to clarify the natural history of nonalcoholic steatohepatitis (NASH) model mouse using Gd-EOB-DTPA-enhanced MRI. Six NASH model mice and six fatty liver model mice were used. NASH model mouse was obtained by injecting streptozotocin (200 μg per mouse) to one-week-old mouse and feeding a high fat diet from the age of 4 weeks. Fatty liver mouse was obtained by feeding a high fat diet from the age of 4 weeks. MRI studies were performed at the age of 8, 10, 12, 14 and 16 weeks. We performed two-point Dixon technique to determine the hepatic fat fraction, and contrast-to-noise ratio (CNR) of the liver was evaluated 10 minutes after injection of Gd-EOB-DTPA via retro-orbital injection. Four NASH model mice died during this study period at the age of 62, 104, 108 and 116 days. At the age of 8 weeks, the hepatic fat fraction was apparently higher in NASH model mouse (0.19 for NASH and 0.05 for fatty liver). The hepatic fat fraction of NASH model mouse slightly decreased along the time course, in contrast, that of fatty liver model mouse increased dramatically (0.12 for NASH and 0.27 for fatty liver at the age of 16 weeks). NASH model mouse showed lower CNR at the age of 8weeks (39.1 for NASH and 46.0 for fatty liver), and CNR of NASH model mouse was consistent during the study period while that of fatty liver model mouse decreased along the time course. Of the five mice that lived longer than 100days, four mice demonstrated hepatocellular carcinoma and its appearance was detected by MRI at the age of 10 weeks.

Imaging findings of histiocytic sarcoma in the liver

Takatoshi Kubo[5], Shigeru Kiryu, Hiroyuki Akai, Yasunori Ota[6], Arinobu Tojo[7], Hideo Yoshida[8], Naoya Kato[9], Yoshiyasu Nakano, Kuni Ohtomo[5]: [6]Department of Pathology, Institute of Medical Science, University of Tokyo, [7]Department of Hematology/Oncology, Institute of Medical Science, University of Tokyo, [8]Department of Gastroenterology, Japanese Red Cross Medical Center, [9]Department of Advanced Medical Science, Institute of Medical Science, University of Tokyo.

Histiocytic sarcoma in the liver is an extremely rare hematological malignancy. Here, we report the case of a 68-year-old woman who presented with characteristic wedge-shaped abnormal findings on computed tomography and magnetic resonance imaging of the liver. A liver biopsy was performed, and histiocytic sarcoma was confirmed histopathologically. In the wedge-shaped area, decreased portal flow and the deposition of iron were observed. These imaging findings are supposedly caused by intrasinusoidal tumor cell infiltration.

Source analysis of stimulus-preceding negativity constrained by functional magnetic resonance imaging.

Kotani Y[10], Ohgami Y[10], Ishiwata T[11], Arai J[12], Kiryu S, Inoue Y[4]: [10]Department of Human System Science, Tokyo Institute of Technology, [11]Department of Sport and Wellness, Rikkyo University, [12]Technology and Innovation Center Preparation Office, Daikin Industries, Ltd.

The stimulus-preceding negativity (SPN) is an event-related potential (ERP) reflecting anticipation. The anterior insular cortex is assumed to be one of the physiological sources of the SPN. However, the precise neural substrates of the SPN have yet to be confirmed. We therefore performed separate functional magnetic resonance imaging (fMRI) and ERP studies using the same time estimation task, followed by fMRI-constrained ERP source analysis. Dipole locations were determined by the fMRI results, while the time courses of dipole activities were modeled by the ERP data. Analysis revealed that the right anterior insula was significantly activated before delivery of the feedback stimulus, whereas the left anterior insula was not, and that the SPN mainly arose from four groups of brain regions related to, respectively: (1) the salience network, (2) reward expectation, (3) perceptual anticipation, and (4) arousal. The results suggest that the SPN pertains to multiple brain functions with complex interactions.

Publications

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IMSUT Hospital

Department of Diagnostic Pathology/Department of Pathology
病理診断科／病理部

Senior Assistant Professor Yasunori Ota, M.D., Ph.D. 講 師 医学博士 大 田 泰 徳

Our mission
1. *We provide an accurate and high-quality pathological diagnosis to the patient in this research hospital, The Institute of Medical Science, The University Of Tokyo.*
2. *Make diagnosis by morphological approach using microscope to the laboratory materials.*

Overview
We study about the hematological malignancy and transplantation pathology. We emphasize many clinical cases and write case reports about human diseases.

1. Effusion lymphoma in Japan.

Effusion lymphoma is found in pleura or ascites and usually lack of evidence for nodular lesion. Conventional findings about effusion lymphoma are bad clinical course and many patients are infected by HIV. However, some of Japanese patients were not infected HIV and good clinical course. We reported some case reports about effusion lymphoma in Japan and are going to promote multi-institutional joint research in Japan.

2. Follicular lymphoma and transformation.

Follicular lymphoma (FL) is a common subtype of indolent B-cell lymphoma and characterized by the translocation t(14;18)(q32;q21) and BCL2 gene rearrangements in cytogenetic studies. FL is an indolent lymphoma, but about 10% of FL was transformed to diffuse large B-cell lymphoma. MYC gene played an important role in transformation. We found the utility of immunohistochemistry with an antibody against MYC at the initial diagnosis of follicular lymphoma, grade 3A, for predicting a more aggressive clinical course

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IMSUT Hospital

Department of Surgery
外科

Associate Professor	Masaru Shinozaki, M.D., Ph.D.		准教授	医学博士	篠崎　大
Senior Assistant Professor	Giichiro Tsurita, M.D., Ph.D.		講師	医学博士	釣田義一郎
Assistant Professor	Kentaro Yazawa, M.D., Ph.D.		助教	医学博士	谷澤健太郎

The mission of our department is to provide surgical service for patients with surgical or gastrointestinal disease, such as malignancy or inflammatory bowel disease (IBD), and to develop and conduct clinical research and clinical trials in early stages (mainly, Phase I and II) on patients at the IMSUT Hospital. We have also been offering diagnostic and therapeutic endoscopy, including upper and lower gastrointestinal endoscopic examinations. Novel therapies are under way.

1. Surgical treatment in 2014

Masaru Shinozaki, Giichiro Tsurita, Kentaro Yazawa, Tomohiro Kurokawa, Yoko Tateno

In July, Dr. Kurokawa joined us from Tsukuba University. Dr. Tateno is willing to assist to perform operations at our department. We are consolidated, and performed more operations. Dr. Sameshima and Dr. Kawamura have been unstinting in their support for our operations, especially in the technical field of laparoscopic colorectal surgery. Our target organs are stomach, intestine, anus, gallbladder, liver, biliary tract, pancreas, and spleen, as well as abdominal wall.

Recently, breast cancer has become a particular field only for highly specialized physicians bearing knowledge in this field. Dr. Iwase started supporting our out-patient clinic.

2. Endoscopic examination in 2014

Giichiro Tsurita, Kentaro Yazawa, Masaru Shinozaki, Yoko Tateno, Tomohiro Kurokawa

Under cooperation with Department of Advanced Medical Science, we performed 700 upper gastrointestinal endoscopies and 1011 colonoscopies without major complications. Dr. Tsurita has been the chief of Division of Endoscopy and played a crucial role in examinations. For the patients' satisfaction, we aggressively perform endoscopic resection of colorectal neoplasms and avoid operation as much as possible. Our fellows (Y.T. and T.K.) have learned gastrointestinal endoscopic technique and have made great progress.

3. Clinical Research.

A. Clinicopathological characteristics of lower gastrointestinal cancer associated with Crohn's disease

Masaru Shinozaki, Giichiro Tsurita, Kentaro Yazawa, Yoko Tateno

In Japan, cancer in small bowel and/or large bowel associated with Crohn's disease is rapidly increasing in number. In Western countries, the distribution of cancer is similar to that of ulcerative colitis, and surveillance colonoscopy is performed just like ulcerative colitis. However, in Japan, significant proportion of such cancer is located at perianal region, and the similar methodology of sur-

veillance does not seem to be sufficient for early detection of cancer. We believe that the first step to solve this problem is accumulation and analysis of such tumors. Therefore, we prepared to make questionnaire and send to hospitals to clarify the clinicopathlogical characteristics.

B. Surveillance colonoscopy for ulcerative colitis

Masaru Shinozaki, Kiyonori Kobayashi (Kitasato University), Reiko Kunisaki (Yokomaha City University), Makoto Naganuma (Keio University), Tadakazu Hisamatsu (Kyorin University), Kennichi Takahashi (Tohoku Rosai Hospital)

Patients with ulcerative colitis have increased risk of colorectal cancer, and surveillance colonoscopy (sCS) is recommended for early detection. The concrete method of sCS has not been established. We studied actual sCS style through questionnaire. We are analyzing the data and preparing for publication.

C. Evaluation of Clinical Guidelines

Masaru Shinozaki, Hajime Sato (National Institute of Public Health)

Clinical guidelines are created to improve clinical practice, mainly from the results of trials. However, there have been few studies to evaluate them. We have investigated current guidelines, especially in the field of IBD.

D. Genome Study for colorectal Neoplasm

Masaru Shinozaki, Yoko Tateno

Recent studies revealed the molecular biological aspects of colorectal cancer carcinogenesis. Some pathways are believed to exist, and we are seeking for the molecular basis of colorectal cancer carcinogenesis.

E. Fluid factors of inflammatory bowel disease

Masaru Shinozaki, Yoko Tateno

Although C-reactive protein has been proved to be of some value in the assessment of the severity in IBD, the efficacy is limited. Cooperation with a venture company, we have been trying to develop a novel biomarker for IBD.

4. Basic research

Yoko Tateno, Tomoki Todo (Department of Advanced Cancer Therapy), Masaru Shinozaki:

Under Professor Todo's supervision, we are developing a novel genetically modified virus therapy against cancer. After this preclinical ascertainment, we strongly wish to execute a clinical trial for gastrointestinal cancer.

5. Clinical research under development

Yoko Tateno, Masaru Shinozaki, Giichiro Tsurita, Kentaro Yazawa, and investigators in other departments

Novel therapies are under investigation to apply for a clinical trial of gastrointestinal malignancy. We are preparing for the trial and various preclinical studies have been executed.

6. Ongoing Clinical trials

A. Survivin peptide vaccine for pancreatic cancer

Giichiro Tsurita, Masaru Shinozaki, Kentaro Yazawa, Yoko Tateno, Hiroshi Yasui (Antibody and Vaccine Center), Tomohiro Kurokawa

Survivin is an inhibitor of apoptosis protein, and is highly expressed in most cancers and associated with chemotherapy resistance, increased tumor recurrence, and shorter patient survival. Survivin is expressed at most of malignancy cells, while it is rarely expressed at most of the mature non-cancer cells. Therefore, anti-survivin treatment is expected to have not only tumor apoptosis but also resumption of chemotherapy sensitivity without major side effects. We have been executing a phase II clinical trial using a novel anti-survivin peptide therapy for pancreatic cancer.

B. BK-UM for gastric cancer

Masaru Shinozaki, Hiroshi Yasui (Antibody and Vaccine Center), Giichiro Tsurita, Kentaro Yazawa, Yoko Tateno, Tomohiro Kurokawa

BK-UM has been developed at Professor Mekada's laboratory, Osaka University. It was derived from diphtheria toxin, and it exerts anti-cancer effect through heparin binding epithelial growth factor receptors. BK-UM is known to have anti-tumor effect not only on ovarian cancer but also on gastric cancer, and is a candidate of the second line therapy. This time, BK-UM is given together with paclitaxel. We accepted the Institutional Review Board approval, and we intend to start the trial in 2016.

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IMSUT Hospital

Department of Anesthesia/Surgical Center
麻酔科／手術部

Associate Professor Mieko Chinzei, M.D., M.D.Sc.
(Clinical Professor)
Assistant Professor Reiko Shibata, M.D.

准教授 医学博士 鎮 西 美栄子
（病院教授）
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) management of chronic intractable pain or improving the quality of life of patients with life-threatening illness (3) assessment of the impact of anesthesia and surgery on autonomic nervous activity, and (4) risk management of medical electronic devices in Research Hospital.

1. Safety in anesthetic management, especially focusing on prevention of deep vein thrombosis during total hip arthroplasty in hemophilia patients.

Management of bleeding in patients with hemophilia has improved since the development of coagulation factor substitution therapy. In almost all of the hip or knee arthroplasty, intraoperative embolism has been detected with transesophageal echocardiography (TEE). But there may have been no report on TEE findings during arthroplastic surgery in hemophilia patients. We find TEE detected variable degree of echogenic materials in right atrium (RA) during THA in hemophilia patients under continuous infusion of coagulation factor. This may suggest that we need to consider risks not only on the side of hemorrhage but embolic events for perioperative management of hemophilia patients.

2. Management of chronic intractable pain.

Since 2008, we've provided a palliative care support service in Research Hospital for the patients suffering with intractable physical and mental pain caused by life-threatening illness and/or complications of the treatments. In patients of hematological malignancy with long treatment history, many of their illness have been diagnosed as reaction to severe stress and adjustment disorder, especially prolonged depressive reaction (F43, the ICD-10 classification of mental and behavioral disorders)

3. Assessment of the impact of anesthesia and surgery on autonomic nervous activity.

It is generally accepted that the parameters derived from power spectral analysis (PSA) of heart rate variability (HRV) can provide a non invasive measure of autonomic nervous activity. We have published several works on assessment of the impact of anesthetics on autonomic nervous activity during perioperative period using real time monitor for PSA of HRV.

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 on malfunctions or incidents of the rest of medical electronic devices in this hospital in collaboration with the Division of Clinical Trial Safety Management.

Publications

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IMSUT Hospital

Department of Joint Surgery
関節外科

Senior Assistant Professor Hideyuki Takedani, M.D. D.M.Sc.
Project Assistant Professor Hirose Jun, M.D. D.M.Sc.

講　師　医学博士　竹　谷　英　之
特任助教　医学博士　廣　瀬　　旬

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 2015, more than 180 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.

In 2014, we were performed 17 surgical treatments (11 total joint arthroplasties, 4 arthroscopic synovectomies and 2 other surgical treatments).

Publications

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IMSUT Hospital

Department of Surgical Neuro-Oncology
脳腫瘍外科

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Associate Professor	Yasushi Ino, M.D., Ph.D.	准教授	医学博士	稲　生　　靖
Project Associate Professor	Minoru Tanaka, M.D., Ph.D.	特任准教授	医学博士	田　中　　実
Senior Assistant Professor	Hiroyuki Momota, M.D., Ph.D.	講　師	医学博士	百　田　洋　之
Assistant Professor	Seisaku Kanayama, M.D.	助　教		金　山　政　作

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.

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.

Surgical treatment of brain tumor 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.

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.

Outpatient clinic

The outpatient clinic of the Department of Surgical Neuro-Oncology opened in October 2011. Patients with newly diagnosed malignant glioma have been treated with high dose or standard dose radiation therapy and concomitant chemotherapy. Recurrent malignant glioma patients are treated with innovative non-standard therapies whenever possible including oncolytic virus therapy.

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
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Project Assistant Professor	Hiroto Ishiki M.D.	特任助教	医学士	石　木　寛　人
Assistant Professor	Naoki Shimada, M.D., PhD.	助　教	農学博士	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.

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IMSUT Hospital

Department of Medical Informatics
医療情報部

Associate Professor	Shigeru Kiryu, M.D., D.M.Sc.		准教授	医学博士	桐生　茂
Senior Assistant Professor	Hiroyuki Akai, M.D., D.M.Sc.		講師	医学博士	赤井宏行
Assistant Professor	Yohiyasu Nakano, M.D.		助教	医学博士	中埜良康

Department of Medical informatics is mainly engaged in information technology of infrastructure and operation for medical service and research in the Institute of Medical Science (IMSUT) Hospital. IMSUT Hospital has introduced a state-of-the-art hospital information system, and every patient can receive better medical care. In addition, we play a leading role in creating infrastructure of regional medical co-operation beyond the framework of the hospital in recent years, and we are also planning support for the operation of the hospital.

Management and operation of hospital information system and network

Shigeru Kiryu, Hiroyuki Akai, Yohiyasu Nakano

We have engaged in the management and operation of the hospital information system in the IMSUT hospital. We are appropriately working with IT service room of IMSUT, and Information Technology Center of the University of Tokyo. We are obligated to maintain service of hospital information system and network for better medical care, and to ensure the generality and compatibility of patient medical information inside and outside of hospitals. Our missions are as follows:

- Operational guidance, supervision, development, operation, and management of hospital information system.
- Creation and management of the network infrastructure and environment handling the necessary information, along with the adherence of information security.
- General day-to-day management on the operation of hospital information system and network.
- Work on the review of hospital information system specification.
- General office work concerning the operation of hospital information system and network.

Study of the development and introduction of next-generation electronic health record system and network

Shigeru Kiryu, Hiroyuki Akai, Yohiyasu Nakano

We aim to reform hospital information system and to introduce electronic health record system in IMSUT hospital.

We are also going to interconnect two hospital information networks in the IMSUT hospital and the University of Tokyo Hospital, under the cooperation with Department of Medical Informatics and Economics, Graduate School of Medicine, the University of Tokyo. For the future development of translational research, the mutual use of medical information is essential between the two hospitals.

Regional medical support through the development and construction of community health information network

Shigeru Kiryu, Hiroyuki Akai, Yohiyasu Nakano

Regional medical cooperation is very important

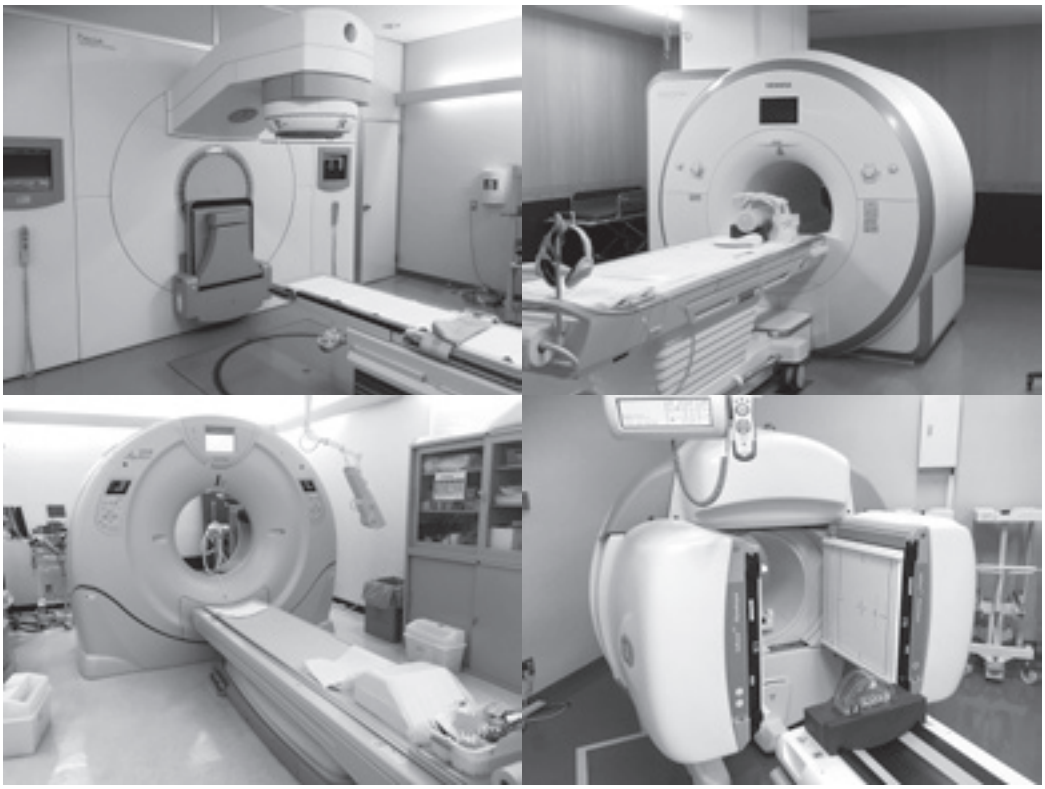
for the future evolution of the IMSUT hospital. We play a leading role in creating infrastructure of regional medical cooperation beyond the framework of the IMSUT hospital in recent years, and we are also planning support for the operation of the hospital. We are considering that introduction of the electronic health record network will be able to improve to introduce among regional clinic, hospital, and the IMSUT hospital in the regional medical cooperation.

IMSUT Hospital

Department of Radiological Technology
放射線部

Associate Professor	Shigeru Kiryu, M.D., D.M.Sc.	准教授　医学博士	桐　生　　茂
Head Radiologic Technologist	Yoshirou Satake, RT	放射線技師長	佐　竹　芳　朗

In our department, we perform radiological diagnosis of a variety of diseases and evaluate the pathophysiology using advanced imaging modalities such as multi-slice CT, high field strength MRI and hybrid SPECT-CT.
Another important role of our department is radiation therapy, which provides treatment for various tumors with relatively low burden on patients. In addition to usual radiation therapy, total body irradiation for hematopoietic stem cell transplantation is also important role of our department.



IMSUT Hospital

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

Professor	Arinobu Tojo, M.D., Ph.D.	教　授　医学博士	東　條　有　伸
Associate Professor	Tokiko Nagamura-Inoue, M.D., D.M.Sc.	准教授　医学博士	長　村　登紀子
Assistant Profissor	Toyotaka Kawamata, M.D., D.M.Sc.	助　教　医学博士	川　俣　豊　隆

Our department was established in 1990, to manage the transfusion medicine and the cell processing for hematopoietic stem cell transplantation. Beside the transfusion medicine and testing in the hospital, our department has supported translational research and managed IMSUT-Cell Resource Center (IMSUT-CRC), which has been established in 1997. Recent our projects include Research CB Stem Cells Bank as National Bioresource Project (NBRP) supported by MEXT and CB and umbilical cord (UC)-derived mesenchymal stem/stromal cell (MSCs) banking for clinical use supported by MHLW. And we are exploring the immunosuppressive therapy for severe GVHD after hematopoietic stem cell transplantation and regenerative medicine for cerebral palsy using UC-MSCs.

1. Umbilical Cord-derived mesenchymal stromal cells banking (IMSUT-CORD):

Nagamura-Inoue T, Mori Y, Takahashi A, Shimazu T, Mukai T, Tojo A.

Umbilical cord (UC) is a rich source of mesenchymal stem cells (MSCs). The UC is normally discarded after birth and its collection does not require an invasive procedure with ethical concerns. Moreover, UC-derived MSCs (UC-MSCs) possess many advantageous features, namely high frequency, pluripotency, high proliferation capacity, immunomodulatory properties and no donor age-dependent variations. We have studied these characteristics and efficient expansion system of UC-MSCs, in order to apply the regenerative medicine and immunotherapy, supported by MHLW. The UC-MSCs have the potential to inhibit the activated T cell proliferation upon the allogeneic stimulations, suggesting the clinical possibility to apply those for the GVHD treatment. Our final goal is to establish the CB and UC-MSCs banking for clinical use.

2. Therapeutic application of Umbilical cord-derived mesenchymal stromal cells for the cerebral palsy.

Mukai T, Shimazu T, Mori Y, Takahashi A, Nagamura-Inoue T.

Previous studies have been reported that MSCs have self-renewal capacity, multi-lineage differentiation potential and the ability to migrate toward sites of inflammation or injury. The potential of MSCs for transdifferentiating into not only mesoderm lineage but also endoderm and ectoderm, including the neural lineage, has enhanced the clinical application of MSCs for regenerative medicine including neurological disorders. We reported here that the umbilical cord-derived mesenchymal stromal cells (UC-MSCs) had the potential of neurogenic differentiation. Furthermore, the neurogenic lineage genes expressed more in differentiation via neurosphere formation with higher expresion of ES markers. The migration ability to damaged cells was not influenced by the neurosphere formation with or without differentiationinto neurogenic cells.

Now newborn mice models mimicking cerebral palsy is under investigation. in vivo.

3. Expansion of regulatory T cell therapy for GVHD, transplantation, and autoimmune diseases.

Nagamura-Inoue T, Ichimura S, Ogami K, Tojo A.

Regulatory T cells harbored the immunosuppressive effects and were related to the pathogenesis of graft-versus-host disease (GVHD), rejection of organ transplantation and autoimmune disease. We developed the system of *ex vivo* expansion of $CD25^{+}FOXP3^{+}$regulatory T cells using mTOR inhibitor, from the small amount of $CD4^{+}$peripheral blood and also cord blood (CB), to apply the immunological therapy.

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

Nagamura-Inoue T, Ichimura S, Takahashi A. Ueda M.

"Research Cord Blood Stem Cell Bank" (former named 'Research Stem Cell Resource Bank') was established supported by MEXT for the development of the medicine including Regenerative Medicine and drug discovery in Japan since 2004. Since 2012, July, this project has been incorporated in National BioResouce Project (NBRP). The research CB bank provides processed and cryopreserved CB units which are non-conforming for clinical use, to world-wide researchers via RIKEN Bioresource Center. Visit our website http://www.nbrp.jp/.

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

Nagamura-Inoue T, Takahashi A., Shimazu T., Ogami K, Tojo A

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 implemented; 1) CB cell processing for banking (for Tokyo Cord Blood Bank, Research cord blood stem cell bank, and related sibling donors), 2) Dendritic cell therapies, 3) Regenerative therapy of alveolar bone derived from bone marrow mesenchymal cells, 4) Gene therapy for renal cancer, 5) CB and UC-MSCs banking (IMSUT-CORD).

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IMSUT Hospital

Core Facility for Therapeutic Vectors
治療ベクター開発室

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

The Core Facility for Therapeutic Vectors (CFTV) 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 CFTV 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 CFTV, quality management system has been assessed by a third party. It was qualified to be in accordance with the requirements of the quality standards detailed ISO9001: 2008; in the scope of development and manufacture of cell and gene therapy products.

Validation of CFTV

The CFTV, 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 equipments in CFTV, has been performed to ensure cGMP compliance.

Production of clinical grade oncolytic HSV-1

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

Radiation Control Office
放射線管理室

Associate Professor	Shigeru Kiryu, M.D., D.M.Sc.	准教授　医学博士	桐　生　　茂
Senior Assistant Professor	Hiroyuki Akai, M.D., D.M.Sc.	講　師　医学博士	赤　井　宏　行
Head Radiologic Technologist	Yoshirou Satake, RT	放射線技師長	佐　竹　芳　朗

Our division has three major missions.

1. *For the safe radiation medical works, we perform the regular voluntary inspection of X-ray equipment and radiation facilities and manage the radiation control area by performing dosimetry, enviromental measurements and regular voluntary inspection.*
2. *For the prevention of radiation hazards of medical radiation workers, we manage radiation medical workers by registering the individuals, check the individual radiation exposure level, and perform yearly special health examination and the radiation safety education.*
3. *In order to ensure comprehensive radiation protection, we evaluate, in advance, radiation exposure and contamination caused by the work, and expected abnormal situations and accidents. In the basis of this evaluation, we determine the appropriate protective action. We also make advice and technical assistance as an expert of radiation protection.*

IMSUT Hospital

Center for Translational Research
TR・治験センター

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Center for Translational Research was reorganized from Division of Clinical Trial Safety Management in 2014. The 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 Research Hospital

Minako Kouno, Erika Horibe, Mashiho Yanagi, Riyo Ohwada, Saori Minote, Makiko Karasawa, Sumimasa Nagai, Hiroshi Nojima, Hiroshi Yasui, Fumitaka Nagamura.

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 Namai, Mitsumi Tokunaga, Fumitaka Nagamura

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

Hiroshi Yasui, Noriko Fujiwara, Makiko Karasawa, Fumitaka Nagamura

We supported four investigator-initiated clinical trials under an Investigational New Drug Application for the development of the academia-oriented innovative drug. Our missions on clinical trials are: coordination as the site management by secretariat, clinical research associate, translational research coordinator, and so on. We have studied approaches to support clinical trials more efficiently by extracting problems through the investigations.

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 planed 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 Institutional Review Board 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 research including clinical research, basic medical/biological research. We have collaborated with other members (listed below) in IMSUT through the consulting.

- Departments and divisions of collaborators (alphabetical order)
- Department of Hematology/Oncology, Research Hospital
- Department of Joint Surgery
- Department of Nursing, Research Hospital
- Department of Palliative Medicine, Research Hospital
- Department of Radiology, Research Hospital
- Department of Rheumatology and Allergy, Research Hospital
- Division of Genetics, Department of Cancer Biology
- Division of Mucosal Immunology, Department of Microbiology and Immunology
- Laboratory of Stem Cell Regulation, Center for Stem Cell Biology and Regenerative Medicine
- Stem Cell Bank and Division of Stem Cell Therapy, Center for Stem Cell Biology and Regenerative Medicine
- The Section of Antibody, Vaccine & Molecular Targeted Therapy Research

Publications

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IMSUT Hospital

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

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Project Senior Assistant Professor	Atsushi Takano M.D., D.M.Sc.	特任講師	医学博士	高　野　　淳
Clinical Senior Assistant Professor	Noritada Yoshikawa, M.D., D.M.Sc.	病院講師（兼任）	医学博士	吉　川　賢　忠

This 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 cancers and autoimmune diseases. Moreover, attractive clinical trials are also ongoing in collaboration with research groups in IMSUT. Part of the funding for this center was supported by the special grant from the Ministry of Education, Culture, Sports, Science and Technology, Japan from 2013-2017.

1. Clinical activities of Division of Rheumatology in IMSUT Hospital

Osamu Hosono, Noritada Yoshikawa, Hiroshi Kobayashi[1], Aya Oda[1], Masaaki Uehara[1], Erika Matsubara[1], Hiroyuki Baba[1], Hirotoshi Tanaka: [1]Department of Rheumatology and Allergy, IMSUT Hospital

Rheumatologists at our division provide state-of-the-art diagnosis and treatment for diseases that affect the body's connective tissue. Physicians in the specialty see nearly 5,000 patients each year. Our physicians have active basic and clinical research projects and also are involved in training of rheumatology specialists. Our rheumatologists treat many types of arthritis, including common diseases such as rheumatoid arthritis and osteoarthritis, and collagen vascular diseases including rheumatoid arthritis, systemic lupus erythematosus and vasculitic syndromes.

Rheumatologic services offered at IMSUT include:

- Outpatient consultations
- Outpatient specialty care for patients with chronic rheumatic diseases
- Hospital consultations
- Diagnostic and therapeutic intra-articular and soft tissue injections and aspirations
- Diagnostic ultrasonography
- Education on rheumatologic diseases and treatments
- Clinical trials

Our physicians have active basic and clinical research projects and also are involved in training of rheumatology specialists.

2. Translational Research of Division of Rheumatology

See the section of Department of Rheumatology and Allergy, IMSUT Hospital.

3. Clinical Trial of Division of Rheumatology

(i) Effect of branched-chain amino acid-enriched beverage "Amino-Value [CONC.]" supplementation in patients with glucocorticoid-induced muscle atrophy (UMIN000006972)

Hirotoshi Tanaka, Noritada Yoshikawa, Ryo Matsumiya[1], Erika Matsubara[1], Hiroyuki Baba[1], Akiko Souta-Kuribara[1], Masaaki Uehara[1], Aya Oda[1], Hiroshi Kobayashi[1], Osamu Hosono, Shigeru Kiryu[2], Fumitaka Nagamura[3]: [1]Department of Rheumatology and Allergy, IMSUT Hospital, [2]Department of Radiology, IMSUT Hospital, [3]Division of Advanced Medicine Promotion, Advanced Clinical Research Center, IMSUT

Skeletal muscle atrophy is induced by muscle denervation and disuse, and it is also the key component of cachexia, a catabolic, debilitating response to several diseases and one of the undesirable effects of glucocorticoid treatment. Patients in such medical conditions not only sustain a decreased quality of life, but also face a worse prognosis of the underlying pathology, making it an important treatment target, however, skeletal muscle atrophy pose unmet needs for specific and effective treatments. To overcome this issue, we have studied precise mechanisms of glucocorticoid-induced skeletal muscle atrophy, and based on our investigation described above section, we have just started a clinical trial in IMSUT hospital. The objective of this 3-month, open label, randomized, parallel group, Phase I, II clinical trial is to test the effect of commercially available BCAA-enriched beverage "Amino-Value [CONC.]" in patients with rheumatic diseases taking glucocorticoids and to explore the diagnostic and evaluation procedures for skeletal muscle atrophy in those patients. Primary outcomes of this trial are evaluation of muscle volume and strength using manual muscle test, bioimpedance, CT and MRI imaging. Key secondary outcomes are Performance Status, evaluation of daily living activity, squatting, blood and urine biochemistry. This study was conducted from May 2012 to January 2015. Oral BCAA supplementation did not exacerbate disease activity and was almost well tolerated in those patients. Moreover, the effects of BCAA supplementation on recovery of skeletal muscle mass, strength, and function were evident in not all but particular muscles.

(ii) A phase I clinical trial of rice-based oral cholera vaccine IMSUT-MR1501 in healthy volunteers. (UMIN000018001)

(Collaborative project of IMSUT and IMSUT Hospital)

The team of Professor Hiroshi Kiyono (Divisionof Mucosal Immunology, IMSUT) succeeded in developing a molecularly uniform rice-based oral cholera vaccine (MucoRice-CTB) by using an overexpression system for modified cholera toxin B subunit, and confirmed that orally administered rice-based vaccine effectively inhibited cholera toxin-induced diarrhea in mice. To establish MucoRice-CTB for human use, hygromycin phosphotransferase selection marker-free MucoRice-CTB line 51A was developed. MucoRice-CTB was new generation of mucosal vaccine, "Cold-chain- and Needle-free Rice-based Vaccines", which is promising especially in developing countries.

For clinical trials, they established a prototype of a closed MucoRice hydroponic factory at the Institute of Medical Science, the University of Tokyo, Japan, which was approved as GMP (Good Manufacturing Practices) factory by the Japanese Ministry of Health, Labour and Welfare in 2014. Osamu Hosono (Department of Rheumatology and Allergy, IMSUT Hospital), PI of this clinical trial, and collaborators prepared a "First-in-man" clinical trial phase I study of MucoRice-CTB in cooperation of many departments of the hospital. After the consultation with PMDA (Pharmaceuticals and Medical Devices Agency) in January 2015, this clinical trial was registered at UMIN Clinical Trial Registry (UMIN000018001) and approved by the Institutional Review Board of the Institute of Medical Science, the University of Tokyo (26-55) in March 2015. The randomized, double-blind, dose-escalation, placebo-controlled study was launched in June 2015 and will be analyzed for the safety and immunological effects of IMSUT-MR1501 after May 2016, termination of the trial.

4. Novel therapeutic target discovery for solid cancers

Yataro Daigo, Atsushi Takano, Koji Teramoto, Phung Manh Thang, Kayo Daigo, Masako Nakamura, Nguyen Duc Bach, Tomoyuki Igarashi

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 en-

richment 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 hundreds 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, the histone methyltransferase SUV39H2 was found to be activated in lung cancers, and was suggested to methylate histone H2AX on lysine 134 in cancer cells.

5. Screening of small-molecular compounds for cancer therapy

Yataro Daigo, Atsushi Takano, Koji Teramoto

Through the gene expression profile analysis of lung cancers, we identified that TTK (TTK therine threonine kinase; alias monopolar spindle 1 (Mps1)) was overexpressed in the majority of lung cancers, but its expression was hardly detectable in normal tissues except testis. As TTK kinase is an attractive cancer drug target due to the important role in the centrosome duplication, the spindle assembly checkpoint and the maintenance of chromosomal stability, we performed high throughput screening and found various lead compounds that could inhibit the TTK kinase activity as follows.

(1) Aminopyridine-based Mps1 (TTK) kinase inhibitors

Starting from an aminopyridine-based lead 3a that binds to a flipped-peptide conformation at the hinge region in Mps1, elaboration of the aminopyridine scaffold at the 2- and 6-positions led to the discovery of 19c that exhibited no significant inhibition for 287 kinases as well as improved cellular Mps1 and antiproliferative activities in A549 lung carcinoma cells (cellular Mps1 IC_{50}=5.3 nM, A549 IC_{50}=26 nM). A clear correlation between cellular Mps1 and antiproliferative IC_{50} values indicated that the antiproliferative activity observed in A549 cells would be responsible for the cellular inhibition of Mps1. The X-ray structure of 19c in complex with Mps1 revealed that this compound retains the ability to bind to the peptide flip conformation. Finally, comparative analysis of the X-ray structures of 19c, a deamino analogue 33, and a known Mps1 inhibitor bound to Mps1 provided insights into the unique binding mode at the hinge region.

(2) Imidazo[1,2-b]pyridazine derivatives-based Mps 1 (TTK) kinase inhibitors

An imidazo[1,2-a]pyrazine 10a was identified during an HTS campaign. Although 10a exhibited good biochemical activity, its moderate cellular as well as antiproliferative activities needed to be improved. The cocrystal structure of an analogue of 10a guided our lead optimization to introduce substituents at the 6-position of the scaffold, giving the 6-aryl substituted 21b which had improved cellular activity but no oral bioavailability in rat. Property-based optimization at the 6-position and a scaffold change led to the discovery of the imidazo[1,2-b] pyridazine-based 27f, an extremely potent (cellular Mps1 IC_{50} = 0.70 nM, A549 IC_{50} = 6.0 nM), selective Mps1 inhibitor over 192 kinases, which could be orally administered and was active *in vivo*. This 27f demonstrated remarkable antiproliferative activity in the nanomolar range against various tissue cancer cell lines.

6. Development of therapeutic cancer vaccine

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

Using the systematic screening system shown above, we identified concoantigens which were overexpressed in the majority of lung cancers 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 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.

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

Yataro Daigo, Atsushi Takano, Koji Teramoto, Koichiro Yuji, Hiroshi Yasui, Giichiro Tsurita, Yoshihide Fujiyama, 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 T cell receptor (TCR) repertoire by sequencing millions of cDNA of TCR α and β chains in combination with a newly-developed algorithm. Using samples from lung cancer patients treated with cancer peptide vaccines as a model, we demonstrated that detailed information of the V-(D)-J combination along with complementary determining region 3 (CDR3) sequences can be determined. We identified extensive abnormal splicing of TCR transcripts in lung cancer samples, indicating the dysfunctional splicing machinery in T lymphocytes by prior chemotherapy. In addition, we found three potentially novel TCR exons that have not been described previously in the reference genome. This newly developed TCR NGS platform can be applied to better understand immune responses in many disease areas including immune disorders, allergies, and organ transplantations.

8. Scientific support programs for cancer diagnostics and therapeutics

Yataro Daigo, Atsushi Takano, Koji Teramoto

To support cancer researchers in the field of cancer diagnostics and therapeutics, we are collecting cancer tissue, serum, plasma, and peripheral blood mononuclear cell (PBMC) from about 6500 patients with solid cancers originated from 13 organs. 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 cancer biomarkers as requested by cancer researchers and contributed to their clinical application and publications in international journals.

9. Targetting of stemness factor inhibites the growth of tumors and the formation of metastases in solid tumor.

Hiroaki Taniguchi

Tumors contain a small population of putative cancer stem cells (CSC), which possess unique self-renewal properties, and survive in a quiescent state for many years after remission and result in later relapse and metastasis. Therefore, it is conceivable that targeting CSCs will eradicate tumor-initiating cells, whereas conventional chemotherapies will only eradicate the bulk of a tumor.

Cancer stem cells and normal tissue stem cells utilize the same self-renewal pathway. However, researchers characterize some of changes, which occur in cancer stem cells, not in normal tissue stem cells. The design of new therapeutic agents should be aimed at targeting these unique molecular changes.

We have currently focused on studying these unique molecular changes, which occur in cancer stem cells, not in normal tissue stem cells. This could be a new therapeutic target against solid tumors.

A) Zinc-finger-containing transcriptional factor, Kruppel-like factor 2 (KLF2)

The Kruppel-like factor (KLF) proteins are multitasked transcriptional regulators with an expanding tumor suppressor function. KLF2 is a member of the KLF family of zinc-finger transcription factors and is involved in maintaining T-cell quiescence, regulating preadipocyte differentiation, endothelial cell function, lung development and the self-renewal of ES cells. Furthermore, KLF2 is one of the prominent members of the family because of its diminished expression in malignancies and its growth-inhibitory, pro-apoptotic and anti-angiogenic roles.

We indicate that epigenetic silencing of KLF2 occurs in cancer cells through direct transcriptional repression mediated by the Polycomb group protein Enhancer of Zeste Homolog 2 (EZH2). Binding of EZH2 to the 5′-end of KLF2 is also associated with a gain of trimethylated lysine 27 histone H3 and a depletion of phosphorylated serine 2 of RNA polymerase.

Upon depletion of EZH2 by RNA interference, short hairpin RNA or use of the small molecule 3-Deazaneplanocin A, the expression of KLF2 is restored. The transfection of KLF2 in cells with EZH 2-associated silencing showed a significant anti-tumoral effect, both in culture and in xenografted nude mice.

In this last setting, KLF2 transfection was also associated with decreased dissemination and lower mortality rate. In EZH2-depleted cells, which char-

acteristically have lower tumorigenicity, the induction of KLF2 depletion `rescued' partially the oncogenic phenotype, suggesting that KLF2 repression has an important role in EZH2 oncogenesis.

Most importantly, the translation of the described results to human primary samples demonstrated that patients with prostate or breast tumors with low levels of KLF2 and high expression of EZH2 had a shorter overall survival.

B) PR domain-containing protein, PRDM14

PRDM have been linked to human cancers. To explore the role of the PR domain family genes in breast carcinogenesis, we examined the expression profiles of 16 members of the PRDM gene family in a panel of breast cancer cell lines and primary breast cancer specimens using semiquantitative real-time PCR.

We found that PRDM14 mRNA is overexpressed in about two thirds of breast cancers. Moreover, immunohistochemical analysis showed that expression of PRDM14 protein is also up-regulated. PRDM14 are known as a key transcription factor required for the maintenance of hESC identity and the reacquisition of pluripotency in human somatic cells.

Introduction of PRDM14 into cancer cells reduced their sensitivity to chemotherapeutic drugs. Conversely, knockdown of PRDM14 by siRNA induced apoptosis in breast cancer cells and increased their sensitivity to chemotherapeutic drugs. Moreover, PRDM14 regulated cancer metastasis, angiogenesis, and stemness of cancer cells.

That little or no expression of PRDM14 is seen in noncancerous tissues suggests that PRDM14 could be an ideal therapeutic target for the treatment of breast cancer. Now, we also develop new methodology with nuclear acid medicine and modified antibody drug against PRDM14.

10. Management and enforcement of investigator-initiated clinical trials under an Investigational New Drug Application for the development of academic-oriented innovative cancer therapeutics

Hiroshi Yasui, Giichiro Tsurita[1], Masaru Shinozaki[1], Fumitaka Nagamura[2], Kohzoh Imai: [1]Department of Surgery, IMSUT Hospital, [2]Center for Translational Research, IMSUT Hospital

We are conducting three investigator-initiated clinical trials under an Investigational New Drug Application for the development of academic-oriented innovative anticancer therapeutics. The first trial is "the phase II trial of BK-UM against HB-EGF in combination with gemcitabine in patients with advanced or recurrent ovarian cancer". The second is "the multi-center double-blind parallel-group placebo-control Phase II study on the efficacy of survivin-2B peptide vaccine therapy for patients with advanced or recurrent pancreatic cancer, and for which there is no effective treatment". The third is "Phase I/II study of HB-EGF-specific inhibitor BK-UM plus weekly paclitaxel therapy in gastric cancer with peritoneal metastasis after failure of first-line treatment." We along with the Center for Translation Research are involved in site management; we also have role in enforcement in association with the department of surgery, radiology, laboratory medicine, and cell processing and transfusion. We study to conduct clinical trials to promote translational research more efficiently at IMSUT hospital through these investigations.

Publications

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IMSUT Hospital

Department of Nursing
看護部

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Deputy Director	Minayo Hisahara, RN, CNJRF.
Nurse Manager	Masako Ozawa, RN.
	Tomoko Sato, RN.
	Hatsuko Narita, RN.
	Mika Kogayu, RN, PNIPC.
	Hisako Suyama, RN.
	Mayumi Tanii, RN.
	Satomi Kiriyama, RN.

看護部長	博士(保健学)	小林康司
副看護部長	リウマチケア看護師	久原みな代
看護師長		小澤昌子
看護師長		佐藤朋子
看護師長		成田初子
看護師長	感染制御実践看護師	小粥美香
看護師長		須山寿子
看護師長		谷井真弓
看護師長		桐山里美

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 Nursing 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, chemotherapy nursing, clinical research/ translational research nursing and palliative care.

In 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　Yosuke Kurokawa

薬剤部長　　黒　川　陽　介

The Department of Pharmacy provides pharmaceutical care services. The present staff (14 pharmacists) provides a drug distribution service, complete IV admixture hyperalimentation and chemotherapy preparation services, inpatient pharmaceutical services and adequately pursues management and supply of drugs.
We are also trying to contribute to propel the right use of medicines for patients.

IMSUT Hospital

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

Professor Tetsuro Matano, M.D., D.M.Sc.

教授（委嘱） 医学博士 俣 野 哲 朗

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 are studying virus-host interaction in non-human primate AIDS models. We developed a recombinant Sendai virus vector vaccine system eliciting cytotoxic T lymphocyte responses. An international collaborative clinical trial phase I of an AIDS vaccine using this system has started in Rwanda, Kenya, and U.K.

1. Broadening of virus-specific CD8$^+$ T-cell responses is indicative of residual viral replication in aviremic SIV controllers

Takushi Nomura[1], Hiroyuki Yamamoto[1], Hiroshi Ishii[1], Hirofumi Akari[2] Taeko K. Naruse[3], Akinori Kimura[3], and Tetsuro Matano: [1]AIDS Research Center, National Institute of Infectious Diseases; [2]Primate Research Institute, Kyoto University; [3]Medical Research Institute, Tokyo Medical and Dental University

Human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) infection induces chronic, persistent viral replication leading to AIDS onset in humans and rhesus macaques, respectively. Control of HIV/SIV replication is a rare immunological event, providing clues to understand the viral control mechanism. CD8$^+$ T-cell responses are crucial for virus control, but it is unclear whether lasting HIV/SIV containment can be achieved after establishment of infection. In this study, we showed lasting SIV containment in a macaque AIDS model. Analysis of ten rhesus macaques that controlled viremia for 2 years post-infection found accumulation of proviral *gag* and *nef* CD8$^+$ T-cell escape mutations in four of them. These four controllers mounted CD8$^+$ T cells targeting Gag, Nef, and other viral proteins at 4 months, suggesting that broadening of CD8$^+$ T-cell targets can be an indicator of the beginning of viral control failure. The remaining six aviremic SIV controllers, however, harbored proviruses without mutations and showed no or little broadening of their CD8$^+$ T-cell responses in the chronic phase. Indeed, three of the latter six exhibiting no change in CD8$^+$ T-cell targets showed gradual decreases in SIV-specific CD8$^+$ T-cell frequencies, implying a concomitant reduction in viral replication. Broadly-reactive CD8$^+$ T-cell responses may be crucial for HIV control, but our results suggest that if the host could achieve the conditions in which CD8$^+$ T cells overwhelm HIV replication, stability of the breadth of virus-specific CD8$^+$ T-cell responses represents a status of lasting HIV containment by CD8$^+$ T cells. This study presents a model of stable SIV containment, contributing to elucidation of the requisites for lasting HIV control.

These studies were performed with the help of National Institute of Infectious Diseases, Tsukuba Primate Research Center in National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN), Institute for Virus Research in Kyoto University, and Medical Research Institute in Tokyo Medical and Dental University.

A project for a clinical trial of an AIDS vaccine using Sendai virus vectors is proceeding in collaboration with ID Pharma (DNAVEC Corp.) and Inter-

national AIDS Vaccine Initiative (IAVI). A phase I trial (S001) has started in Rwanda, Kenya, and U.K.
➢http://www.iavi.org/press-releases/2013/97-iavi-and-partners-initiate-phase-i-trial-of-a-novel-aids-vaccine-regimen
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