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) Antigen-specific induction of allogeneic umbilical cord or peripheral blood-derived cytotoxic T lymphocytes, (2) Treatment of drug-resistant H. pylori infection, (3) Understanding the pathophysiology of leptin in hematological malignancies and exploration of therapeutic alternatives for hematological malignancies using umbilical cord blood-derived cytotoxic T lymphocytes., (4) Early diagnosis of cardiotoxicity in chemotherapy-treated patients, (5) Analysis of the potential therapeutic advantages of cell lysate from human placenta in promoting impaired cutaneous wound healing, (6) Establishment of GMP-compliant large-scale DC vaccines pulsed with cytoplasmic transduction peptide-fused protein tumor antigens and (7) Safety test of 5-aminolevulinic acid with ferrous ions in diabetic patients treated with oral hypoglycemic agents.

1. Antigen-specific induction of allogeneic umbilical cord or peripheral blood-derived cytotoxic T lymphocytes

Fujita S. et al.

We have focused our effort on exploring the feasibility of a new immunotherapy against solid tumors using cytotoxic T lymphocytes (CTLs). We used cryopreserved umbilical cord blood or peripheral blood as the source of lymphocytes and successfully induced tumor antigen-specific CTLs in the presence of certain T cell growth factors under repetitive tumor antigenic stimulations. Furthermore we developed a new protocol to efficiently induce HLA-restricted tumor antigen-specific CTLs using modified bead-based artificial antigen presenting cell (aAPC) system that presents the molecules of MHC class I and anti-CD28 antibody.

2. Treatment of drug-resistant *H. pylori infection*

Matsubara Y. et al.

The number of patients who failed to respond first- and second-line *H. pylori* eradication therapy is gradually increasing because of drug resistance in Japan. However, there is currently no standard third-line eradication therapy. We are investigating various third-line regimens to establish effective *H. pylori* eradication therapy.

3. Understanding the pathophysiology of leptin in hematological malignancies and exploration of therapeutic alternatives for hematological malignancies using umbilical cord blood-derived cytotoxic T lymphocytes.

Lam Q.L.K. et al.

The objectives of our research were to study the role of leptin in the survival and activity of multiple myeloma as well as to explore therapeutic alternatives for hematological malignancies. We have employed available resources in our laboratory including umbilical cord blood and relevant reagents to perform experiments in order to understand more about hematological malignancies. In this regard we have successfully developed methods to isolate and expand cytotoxic T lymphocytes from either cryopreserved or fresh umbilical cord blood, and we have examined the feasibility of different strategies to derive tumor-specific cytotoxic T lymphocytes. Continuation of our study in the future will potentially benefit the existing cancer therapies.

4. 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.

5. 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. A high level amount of VEGF secreted by human placenta-derived cell is discovered in our previous study. Currently, we are examining therapeutic effects of the cell lysate from placenta on excisional skin wound healing. The objective of this study is to determine whether we can use the cell lysate for treatment of non-healing chronic wounds in clinic. First, cell proliferation growth factors and angiogenic cytokine included in the cell lysate were measured by ELISA. Our result showed that a great number of bFGF, VEGF were included in the cell lysate, and angiogenic cytokine, such as Ang-1, IL-8, EGF were also detectable. In addition, the cell lysate was functional in promoting proliferation and migration of fibroblast and HUVEC, and enhancing tube formation of HUVEC and wound closure in vitro. Second, the cell lysate was applied in mice skin excisional wound model and showed to enhance the formation of fibroblastic tissue. Currently, this study is still underway.

6. Establishment of GMP-compliant large-scale DC vaccines pulsed 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 DC vaccines are a promising vaccine strategy for cancer. Accumulating evidence showed that DC vaccines induced potent anti-tumor immune responses. JW Creazen developed a novel cell-penetrating peptide which is named as cytoplasmic transduction peptide (CTP). 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 DC vaccines are able to efficiently present the CTP-fused proteins to T-cells. Last year, we produced the DC vaccines with the CTP-fused AFP, GPC-3, and MAGE-A1 proteins in the CPC, cell processing center, from PBMCs (peripheral blood mononuclear cells) obtained from normal healthy volunteers. We are planning to test if these DCs are able to induce antigen specific cytotoxic T lymphocytes (CTLs) *in vitro*. In addition, we compare T cell responses induced by DCs pulsed with peptides and proteins. The present study allows us to translate our DC vaccine strategy to clinical trials in future.

7. 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 sup-

plement 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.

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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 2014, 26 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 2014 was 59, and about 6 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[2], Toshiyuki Miura, Takashi Odawara, and Aikichi Iwamoto[1]: [1]Division of Infectious Diseases, The Advanced Clinical Research Center, [2]International Research Center for Infectious Diseases,

26 new patients with HIV-1 infection visited to our hospital this year (from January 1 to December 31, 2014), and 536 patients in total are under medical management in our outpatient clinic. The total number of HIV-infected in-patients during 2014 was 59. 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 around 498 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

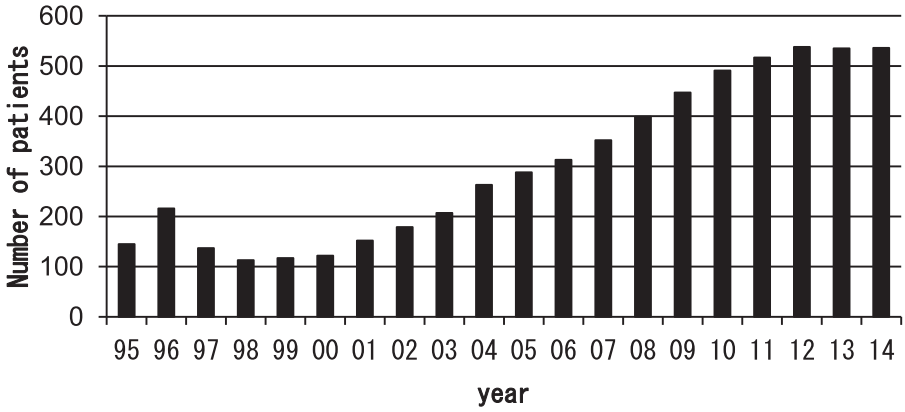

Figure 1. Number of HIV-infected outpatients in IMSUT Hospita

in 98.3% 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-infected patients have been changing from how to treat opportunistic infections into how to control patients with ART.

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

Tomohiko Koibuchi, Michiko Koga[1], Eisuke Adachi, Tadashi Kikuchi[1], Hitomi Nakamura[2], Toshiyuki Miura, Takashi Odawara and Aikichi Iwamoto[1]: [1]Division of Infectious Diseases, The Advanced Clinical Research Center, [2]International Research Center for Infectious Diseases

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 about 12,000 times in 2014, which was 2,000 times over than 2013. In Japan, where the number of HIV-experts are limited compared to other countries, the practice guidelines have substantially improved the standard of care for the HIV-infected patients in our country.

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

Tomohiko Koibuchi, Michiko Koga[1], Eisuke Adachi, Tadashi Kikuchi[1], Hitomi Nakamura[2], Toshiyuki Miura, Takashi Odawara, and Aikichi Iwamoto[1]: [1]Division of Infectious Diseases, The Advanced Clinical Research Center, [2]International Research Center for Infectious Diseases

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 collecting clinical data. Also we have clinics for overseas travelers. This year, 76 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 (6 patients), dengue fever (one patient who has no foreign travel history), post-exposure prophylaxis of rabies (9 patients) and so on. Ten patients were admitted because of their critical condition.

4. Complete Regression of Early-Stage Gastric Diffuse Large B-Cell Lymphoma in an HIV-1-Infected Patient Following Helicobacter pylori Eradication Therapy

Michio Okame, Saho Takaya, Hidenori Sato, Eisuke Adachi, Nobuhiro Ohno[2], Tadashi Kikuchi[1], Michiko Koga[1], Naoki Oyaizu[3], Yasunori Ota[3], Takeshi Fujii[4], Aikichi Iwamoto[1], and Tomohiko Koibuchi: [1]Division of Infectious Diseases, The Advanced Clinical Research Center, [2]Hematology and Oncology, IMSUT Hospital of the Institute of Medical Science, [3]Pathology, IMSUT Hospital of the Institute of Medical Science, [4]Division of Infectious Disease, Tokyo Medical University Hachioji Medical Center,

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype in HIV-1-infected patients, for which a combination of antiretroviral therapy (ART) and chemotherapy remain the mainstay of treatment. In HIV-negative patients, complete regression of the *Helicobacter pylori* (HP)-positive gastric DLBCL with stage IE/IIE resulting from HP eradication (HPE) therapy alone has been reported. In our patient, a reduction in lesion size of DLBCL was seen 3 weeks after HPE therapy. We published a rare case report of AIDS-related gastric DLBCL with stage IE that responded to HPE therapy. Our observation suggests that HPE therapy could be a first-line treatment for controlling HP-positive early-stage AIDS-related gastric DLBCL.

5. Deployment of Dr Tomohiko Koibuchi to Sierra Leone to support the Emergency Response on Ebola Virus Disease (EVD) Outbreak

Tomohiko Koibuchi

The Ebola Virus Disease (EVD) Outbreak in Western Africa was considered a Public Health Emergency for International Concern (PHEIC) by the Emergency Committee of the Member States of World Health Organization (WHO) and its advisors. This calls for a coordinated international response to contain disease and prevent the spread in international scale. Dr Koibuchi was called for this mission as the infectious disease specialist by WHO from 28 December 2014 to 30 January 2015. His main duty is to control the infection of EVD in Sierra Leone where outbreak of EVD is not yet under control. He has ten missions; First is to coordinate surveillance activities in the affected district and neighbouring districts. Second is to contribute to the training of health personnel and community sensitization. Third is to coordinate outbreak data (cases, contacts, deaths, laboratory results, actions) management and dissemination. And so on. He has fulfilled the duties in PHEIC as one of the WHO members.

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IMSUT Hospital

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Our department is founded in 2001 to tackle systemic autoimmune inflammatory diseases including rheumatoid arthritis, systemic lupus erythematosus and vasculitic syndoromes. 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, 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 rare diseases such as relapsing polychondritis and multicentric reticulohistiocytosis, as well as 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, Takako Maruyama, Akiko Souta-Kuribara, Yanxia Ma, Ryo Matsumiya, Yuki Tasaka, 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, mGRKO has unraveled a novel muscle-liver-fat axis that might be essential in regulation of adaptive adipose tissue remodeling.

(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 HEXIM1 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 (IRAK-M) 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, Yuki Tasaka, 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, a lymphoplasmacytic infiltrate 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 atypical presentation of IgG4-RD involving pericardium. This patient 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 involvement. 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, Yuki Tasaka, Takako Maruyama, Akiko Kuribara, Ryo Matsumiya, Yanxia Ma, 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 assess 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. Based on this research, we started 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)

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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. From May/2012 to Dec/2014, 20 patients have been registered in this trial, which will be terminated at Feb/2015 and immediately analyzed.

6. Clinical Trial: Investigator initiated phase 1 clinical trial of rice-based oral vaccine, MucoRice-CTB powder in healthy adults.

(Collaborative project of IMSUT and IMSUT Hospital)

The team of Professor Hiroshi Kiyono (Division of 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 are preparing 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, we are going to submit an application of the clinical trial. The clinical trial will launch in July 2015.

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Our major goal is to cure children suffering from a variety of life-threatening hematological disorders. Attempting to achieve it, we continue the commitment to treatment and follow-up care of such children, and to clinical and laboratory researches that ultimately will help us devise better therapeutic approaches to the diseases. Currently efforts are directed toward treatment of acute leukemia in adolescence and young adults, establishment of novel therapies using hematopoietic or mesenchymal stem cells (HSC or MSC, respectively), and analysis of pathogenesis of hematopoietic disorders, especially pediatric myelodysplastic syndrome (MDS).

1. Hematopoietic stem cell transplantation for children with high-risk leukemia

Yasuhiro Ebihara, Shinji Mochizuki[1], Makoto Otsu; [1]Division of Stem Cell Processing, Center for Stem Cell Biology and Regenerative Medicine

Although a standard regimen in hematopoietic stem cell transplantation (HSCT) has been available for children with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), it has not been standardized for those with rare diseases including congenital bone marrow failure syndrome (CBMFS) and natural killer (NK) cell leukemia. A multi-institutional trial using regimens with a rationale should be proposed in a prospective manner. For CBMFS, we conducted *in vitro* and *in vivo* assays to assess the sensitivity of granulocyte colony-stimulating factor (G-CSF), and transplanted the patients whose leukemic cells had a high sensitivity to G-CSF using a regime including G-CSF. Thus, we could avoid intensive chemotherapy before HSCT for patients with a vulnerable normal bone marrow reserve. For patients with Fanconi anemia, in particular, we employed a regimen containing fludarabine to reduce the dose of alkylating agents and irradiation to avoid the toxicity, which was otherwise likely to occur in those patients. For patients with NK cell disease, we used a regimen combining alkylating agents (cyclophosphamide and thiotepa) and total body irradiation based on the results that NK leukemic cells strongly expressed multidrug-resistant genes. Now we plan to extend our experience in nationwide collaborative studies.

2. International cooperative clinical study for pediatric relapsed ALL, IntReALL 2010

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Though survival of children with ALL has considerably improved over the past few decades, relapsed ALL remains a leading cause of mortality in children with cancer. Given the rarity of the disease, international collaboration is needed to recruit enough patients for studying standard and innovative treatment strategies within this specific patient

group. On behalf of the relapsed ALL committee of the Japanese Pediatric Leukemia and Lymphoma Study Group (JPLSG), we began the discussion for the collaboration between 20 national study groups including the relevant groups from Europe and selected non-European countries. in 2010. IntReALL 2010 organizes the worldwide largest international clinical trial on childhood relapsed ALL, establishing the best standard treatment strategies and investigating innovative therapies, by establishing standardized high quality diagnostics and a comprehensive research program on refractory ALL. IntReALL2010 study has started in 2014 first in Europe and will start from this April here in Japan.

3. Analysis of the pathophysiology and drug sensitivity of refractory leukemia, 8p11 myeloproliferative syndrome (EMS) by using human iPS cells

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Using developmental technics regarding to human pluripotent stem (iPS) cells, disease-specific iPS cells are generating from patients with a variety of disease. We have generated some disease-specific iPS cells, Down Syndrome, Severe Congenital Neutropenia and so on. Another is from a patient with acute myeloid leukemia (AML) developed from 8p11 myeloproliferative syndrome (EMS). EMS is an aggressive chronic myeloproliferative disorder frequently accompanies with T or B lymphoblastic lymphoma, and rapidly transforms into AML. Fibroblast growth factor receptor 1 (FGFR1) has critical role in the pathogenesis of EMS. We produced hiPS cells derived from this patient (EMS-hiPS cells). One EMS-hiPS cell lines was created from bone marrow cells fibroblasts and reprogrammed by the defined 4 reprogramming factors (OCT3/4, KLF4, SOX2, and c-MYC). We generated blood cells from EMS-hiPS cells with coculture system using AGMS-3 cells. EMS-iPS cells produced five-fold more hematopoietic colonies (especially monocyte and erythroid lineage) than control iPS cells. When some of FGFR1 signal inhibitor was added to the hematopoietic culture, colony formation was suppressed with dose increase at 1/7 level. These results indicated that EMS-iPS cells might reflect the pathophysiology of EMS, and EMS-iPS cells might be useful for drug sensitivity test for treatment of EMS.

4. Establishment of therapy for acute leukemia in adolescence and young adults

Yasuhiro Ebihara, Shinji Mochizuki[1], Satoshi Takahashi[6], Arinobu Tojo[6], Makoto Otsu: [6]Division of Molecular Therapy, Advanced Clinical Research Center

In many areas of medicine adolescents and young adults are regarded as a discrete group with specific therapeutic, psychological, educational, and resource needs. In acute leukemia age is a predictor of response. Thus, in ALL there is a clearly poorer treatment outcome after puberty, while in AML, which is more common in older adults, age is a continuous variable with poorer outcomes in each successive decade. Much is known about other prognostic factors and their relative incidence in each age stratum. Although there is some segregation of favorable factors with relative youth, age usually remains an independent factor with respect to prognosis. So far, adolescents and young adults are included in pediatric or adult-oriented treatment protocols, but it has been controversial which protocol is superior to acute leukemia in adolescence and young adults. We are now searching the most suitable therapy for them.

5. Unrelated cord blood transplantation after myeloablative conditioning regimen in adolescent and young adult patients with hematologic malignancies

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As mentioned above, adolescents and young adults with hematologic malignancies are distinct in terms of their therapeutic requirements compared to adults or children. However, there have been no data that define adolescent and young adult patients for cord blood transplantation (CBT) after conventional myeloablative conditioning regimen. We then reported the results of unrelated CBT after myeloablative conditioning regimen in patients with hematologic malignancies from 15 to 20 years old. The median times of myeloid and platelet engraftment were 21 and 38 days, respectively. The cumulative incidences of acute graft-*versus*-host disease (GVHD) was 62.0% , all of which were grade I or II, and that of extensive-type chronic GVHD was 12.5%. The probabilities of overall and disease-free survival at 3 years were 68.2% and 48.6% , respectively, comparable to adult or childhood cases. Therefore, adolescents and young adult patients with hematologic malignancies who have no human leukocyte antigen (HLA)-matched adult donors could be considered as candidates for CBT.

6. Establishment of human BM-derived MSC for the treatment of hemophilic arthropathy

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Hemophilia is a congenital disease with a lack of coagulation factors. Arthropathy is a major cause of morbidity in the patients with hemophilia. Approximately one third of the patients need the mobility assistance. Although the pathogenesis of hemophilic arthropathy (HA) still has not been precisely clarified, the destruction of articular cartilage is the most prominent event in HA. Most surgical treatments for HA, such as synovectomy or total joint arthroplasty, are performed by Department of Joint Surgery in our hospital. So far, however, the efficacy of the treatment has been insufficient. Recently it has been shown that BM contains MSC, which can differentiate into various mesenchymal tissue cells, osteocytes, adipocytes and chondrocytes. Although the mechanism by which MSC are committed to differentiate into each mesenchymal tissue, the environment surrounding MSC plays an important role in the commitment. We are then preparing for the clinical trial of the transplantation of autologous culture-expanded BM-derived MSC into the articular cartilage defect in the HA patients.

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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). No less than 30 patients per year receive allogeneic HSCT in our facilities. In recent years, unrelated cord blood has been our major stem cell source for recipients who have no suitable family donors in HSCT. Since 1998 we have performed over 390 cases of cord blood transplantation (CBT) for adult patients, which appears a distinguished experience in the world. Recent advance in identification of signaling molecules activated in a tumor-specific manner or associated with tumor-specific genomic recombination have disclosed many candidate therapeutic targets in tumors. In the field of hematological malignancies, we have already experienced remarkable clinical efficacies of novel therapeutic agents including tyrosine kinase inhibitors for Philadelphia-chromosome positive leukemias, RI-conjugated or non-conjugated anti-CD20 monoclonal antibodies for B cell lymphoma, and proteasome inhibitors as well as immunomodulatory drugs for multiple myeloma. We extensively apply these molecular targeted therapies for in- and outpatients. Furthermore, in recent years, our department has been a hub facility in the greater Tokyo area for treating patients with intractable adult T-cell leukemia/lymphoma, for which a novel anti-CCR4 monoclonal antibody was just introduced into clinical practice.

1. Impact of upfront hematopoietic stem cell transplantation for aggressive adult T cell leukemia/lymphoma

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Adult T-cell leukemia-lymphoma (ATL) is an aggressive peripheral T-cell neoplasm caused by human T-cell lymphotropic virus type I infection. Aggressive ATL (acute, lymphoma, unfavorable chronic type) has a poor prognosis. Recently, allo-

geneic hematopoietic stem cell transplantation (alloSCT) has been reported as a curative treatment for aggressive ATL. However, the optimal timing for alloSCT has not yet established. We performed alloSCT after remission (CR or PR) had achieved as soon as possible when stem cell donor was available. In this report, we retrospectively analyzed patients treated with initial chemotherapy in our hospital, in cases younger than 70 years (n=45, median age 57.5 years). All patients started SCT donor coordination for alloSCT soon after start of chemotherapy. Thirty two patients received alloSCT (71.1 %) and twenty eight of those received reduced-intensity conditioning. Disease status at transplantation of those were as follows; 2 in complete remission (CR), 18 in partial remission (PR), 7 in stable disease (SD) and 4 in progressive disease (PD). The median of the days from start of chemotherapy to transplant is 166 days (62-438 days). The 3-year OS rate was 60.0% (95%CI 41.4-78.6%) in all patients who received alloSCT. The 3-year OS rate was 76.5 % (95%CI 56.3-96.7%) in CR and PR group, in contrast, 0.0% (95%CI 0.0-41.0%) in SD and PD group. Good disease control and durable chemosensitivity at the time of the transplant were regarded as important factor. On the other hand, 13 cases could not achieve alloSCT. The primary reason was relapse of ATL. These results strongly suggest that early alloSCT may improve the survival in aggressive ATL.

2. Quantification of adult T-cell leukemia/lymphoma cells using simple four-color flow cytometry

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The absolute number of adult T-cell leukemia/lymphoma (ATL) cells in peripheral blood is an essential indicator to evaluate disease status. However, microscopically counting ATL cells based on morphology requires experience and tends to be inaccurate due to the rarity of ATL. Based on our research showing that acute type ATL cells are specifically enriched in the CD4+ /CD7− (CD7N) fraction, a new analytical method to accurately quantify ATL cells was established using an internal bead standard and simple four-color flow cytometry. This method was verified by comparison with microscopic examination of 49 peripheral blood samples and used tofollow up patients.

A strong correlation was observed between the number of CD7N cells measured by flow cytometry and the number of abnormal lymphocytes measured microscopically by experienced technicians [Pearson's R, 0.963; Spearman's rho, 0.921; intercorrelation coefficient, 0.962]. The linear regression coefficient was close to 1 (β=1.013). Our method could detect 1 cell/μL, and the limit of quantitation was between 2.9 and 9.8 cells/μL. The frequency of CD7N cells among CD4+ cells changed during chemotherapy, which reflected differences between chemosensitive and chemoresistant cases. Kaplan-Meier analysis with a log-rank test showed that patients with decreased CD7N proportion after chemotherapy had significantly longer disease-specific survival (p=0.003). Our newly established method quantified tumor cells in patients with acute-type ATL. Furthermore, this method was useful for assessing the efficacy of chemo therapy, and the change of the CD7N proportion could be more important to predict prognosis.

3. Myelopathy similar to but distinct from human T-cell leukemia virus type I (HTLV-I) - associated myelopathy (HAM) following allogeneic PBSCT for adult T-cell leukemia/lymphoma presenting.

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Adult T-cell leukemia/lymphoma (ATL) responds poorly to conventional chemotherapy, but allogeneic stem cell transplantation (allo-SCT) may improve disease prognosis. Herein, we report a female patient with human T-cell leukemia virus type I (HTLV-I)-associated myelopathy (HAM)-like myelopathy following allo-SCT for ATL. She developed crural paresis 14 months after allo-SCT. Initially, she was diagnosed with central nervous system (CNS) relapse of ATL and treated with intrathecal injection and whole brain and spine irradiation. Her symptoms recurred 5 months later, when a cerebrospinal fluid (CSF) specimen showed increased CD4+ CXCR3+ CCR4+ cell numbers and levels of neopterin and CXCL10 (IP-10). These results suggest the possible involvement of a certain immunological mechanism such as HAM in her symptoms, irrespective of the lack of anti-HTLV-I antibody in her CSF. Because a definitive diagnosis

of CNS manifestation of ATL is sometimes difficult, multimodal laboratory data are required for differential diagnosis.

4. Rapid increase of adult T-cell leukemia cells disrupts blood-ocular barrier

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The human T-cell lymphotropic virus type 1 (HTLV-1) is recognized as the etiologic agents of adult T-cell leukemia (ATL), HTLV-1 associated myelopathy/tropical spastic paraparesis, and HTLV-1 uveitis. The mechanism for induction of inflammation by HTLV-1 infection has not been clearly understood, especially at the eye. Here we report a case of developing ocular inflammation simultaneously after progression from smoldering type ATL to acute type ATL. This case implies that rapid increase of ATL cells contributed to the induction of ocular inflammation, which could be one of the mechanisms for disruption of blood -ocular -barrier in HTLV-1 infected patients.

5. Impact of clearance of blasts from peripheral blood during induction chemotherapy in adult acute myeloid leukemia.

Konuma T[1], Kato S[1], Yuji K[1], Ohno N[1], Uchimaru K[1], Takahashi S[1,2], Tojo A[1,2]: [1]Department of Hematology and Oncology, IMSUT Research Hospital, [2]Division of Molecular Therapy, Advanced Clinical Research Center

Early clearance of blast from peripheral blood (PB) to induction chemotherapy is one of the most useful prognostic indicators for achievement of complete remission (CR) and long-term survival in adult acute myeloid leukemia (AML) as well as childhood acute lymphoblastic leukemia. In this study, we retrospectively analyzed 34 consecutive adult patients who received cytarabine for 7 days and either idarubicin for 3 days or daunorubicin for 5 days as first induction chemotherapy for newly diagnosed AML at our institute. In univariate analysis, a lower decay constant (<1.275) was associated with a lower achievement of CR (p=0.04). The probability of overall survival (OS) at 2 years was higher in patients with a higher decay constant (>=1.275) (83%, 95% CI, 48% to 95%) compared with a lower decay constant (58%, 95% CI, 28% to 79%) (p=0.03). The probability of leukemia-free survival (LFS) at 2 years was higher in patients with a higher decay constant (58%, 95% CI, 30% to 79%) compared with a lower decay constant (31%, 95% CI, 11% to 54%) (p=0.04). Our data suggest that decay of PB blasts during the first 5 days of induction chemotherapy predicted achievement of CR, OS and LFS in newly diagnosed adult AML.

6. BRAF-V600E mutation on circulating cell-free DNA is a promising biomarker of high-risk adult Langerhans cell histiocytosis.

Kobayashi M[1], Tojo A[1,2]: [1]Division of Molecular Therapy, The Advanced Clinical Research Center, [2]Department of Hematology/Oncology, IMSUT Research Hospital

Langerhans cell histiocytosis (LCH) is a rare disorder characterized by clonal proliferation of Langerhans cells and significant infiltration of immune cells. Oncogenic BRAF-V600E mutation could be detected in LCH lesions from the majority of patients. Recently, it was found that patinets with active, high-risk LCH carried BRAF-V600E in circulating CD11c+/CD14+ cell fractions. In patients with various kinds of cancers, circulating cell-free DNA (cfDNA) in peripheral blood contains cancer-derived genomic DNA and has been applied to non-invasive diagnostic procedure, so called liquid biopsy. In this study, we evaluated BRAF mutation on cfDNA as a potential biomarker of LCH using allele-specific quantitative polymerase chain reaction (ASQ-PCR). We cloned normal and mutant BRAF alleles that include exon 15 and neighboring sequences into pCR2.1 to make the standard curve. cfDNA was prepared from plasma of adult LCH patients and was subjected to genotyping BRAF alleles by ASQ-PCR, which was specifically designed for detection of BRAF-V600E with a 3'-phosphate-modified oligonucleotide blocker according to Thierry AR, et al. Mutant BRAF load was estimated from the standard curve in each assay and was expressed as the percentage of mutant alleles to total number of alleles. Plasma cfDNA was prepared from 8 adult patients with LCH as well as normal subjects including cancer-free patients. The mean quantity of recovered cfDNA in LCH vs normal was 316.5pg/ml (median, 290.4) vs 92.0pg/ml (median, 91.8). Three high-risk patients with active multiple lesions were positive for BRAF-V600E. In these patients, the mean ratio of mutant BRAF alleles to total was 3.25% (median, 2.59%). Next, we compared the sensitivity of ASQ-PCR of BRAF-V600E between cfDNA and cellular DNA in the same blood sample, and the results suggested that LCH-derived genomes are significantly enriched in cfDNA compared with cellular DNA, and that

cfDNA is more adequate for liquid biopsy in LCH with BRAF-V600E. Then, in a BRAF-V600E-positive patient, we followed the mutant BRAF load during the course of initial chemotherapy. The ratio of mutant to total alleles was estimated as 1.00% prior to chemotherapy and not detectable after one course of chemotherapy consisting of vinblastine, prednisolone, methotrexate and 6-mercaptopurine. The validity of this ASQ-PCR data was confirmed by a series of routine imaging analysis performed at the same time. Taken together, ASQ-PCR of BRAF-V600E on cfDNA may contribute to planning of risk-based treatment as well as monitoring of treatment efficacy in LCH, especially in an active, high-risk group. A number of BRAF-targeted inhibitors have been approved or under clinical trial for various cancers with BRAF mutant, and one of those, vemurafenib is also active against LCH with BRAF-V600E (Haroche J, et al. Blood. 2013). Hereafter, the utility of BRAF-V600E in cfDNA should be validated in a large cohort of LCH patients.

7. Impact of Ph+ stem cell burden on clinical findings and molecular responses to first-line nilotinib in newly diagnosed chronic myeloid leukemia: the results from the interim analysis of N-road, a multi-center phase II study.

Tsuda M[1], Tojo A[1,2]: [1]Division of Molecular Therapy, The Advanced Clinical Research Center, [2]Department of Hematology/Oncology, IMSUT Research Hospital

We are conducting a phase II study (N-road) for newly diagnosed CML-CP pts, in which nilotinib 300mg BID is given for 24 M and is to be escalated to 400mg BID if no optimal response at any check points. The primary endpoint is CMR rate by 24 M, and secondary endpoints include $MR^{3.0}$/$MR^{4.0}$ by 12 M. In this setting, the impact of initial Ph+ stem cell burden on clinical findings and therapeutic responses has been investigated in a sub-study. By July 2014, 48 pts were enrolled and BM $CD34^+$ cell fractions could be evaluated by FACS-FISH analysis at diagnosis in 43 pts, among those 35 pts passed 3 M, 34 pts 6 M and 15 pts 12 M, respectively. MR3.0 rate was 8/35 at 3M, 23/34 at 6M and 10/15 at 12M. When 43 pts were classified into two groups (higher: H, lower: L) according to the mean $CD34^+$ cell counts at diagnosis (5995/μL of BM aspirates), there were significant differences ($p<0.05$) in BCR-ABL transcripts indicated as IS (77.66 vs 64.03%, p=0.030) and WBC count (81.3 vs 22.3/mL, p=0.012), but no differences in molecular responses at 3, 6 and 12 M between the two groups. There was a positive correlation between $CD34^+$ cell count and WBC count. The median percentage of Ph+ cells, as measured by FISH, in $CD34^+CD38^-$ fraction at diagnosis was 97.1% compared to 98.6% in $CD34^+$ $CD38^+$ fraction. The proportion of Ph+ cells in $CD34^+CD38^-$ fraction correlated with PLT count but inversely with RBC count, Hb and Ht, respectively. Between the two groups divided by the median percentage, there were significant differences in RBC count (406 vs 460×10^4/μL, p=0.046), Hb (11.7 vs 14.5 g/dL, p=0.009) and Hct (38.8 vs 44.7%, p=0.040). There were no significant differences in molecular responses at any check points. On the other hand, when divided by the mean percentage (81.1%), there was only a significant difference in PLT count (48.1 vs 27.2/μL, p=0.028). Absolute Ph+ cell counts in $CD34^+$ $CD38^-$ fraction were estimated in each patient by combining 3 parameters of $CD34^+$ cell counts/μL of BM aspirates, proportion of $CD38^-$ fraction and percentage of Ph+ cells. Ph+ $CD34^+CD38^-$ cell counts siginificantly correlated with WBC count and inversely with RBC count, Hb and percentage of lymphocytes. Between the 2 groups divided by the median cell counts (256/μL), there were significant differences in RBC (406.5 vs 472.0×10^4/μL, p=0.005), Hb (11.8 vs 14.3 g/dL, p=0.004), Hct (39.0 vs 44.6%, p=0.024). Although we could not find significant difference in molecular responses at any check points, patients with lower number of Ph+$CD34^+CD38^-$ cells tend to achieve $MR^{3.0}$ faster than those with higher number of cells (p=0.059). When divided by the mean cell counts (578/μL), there was a significant difference in WBC count (94.45 vs 22.44/mL, p=0.016). In conclusion, increased Ph+ stem cell burden apparently affects the level of leukocytosis and anemia at diagnosis, but not $MR^{3.0}$/$MR^{4.0}$ rate by 12 M on nilotinib, although it is likely to extend time to achieve $MR^{3.0}$.

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Projects

Our department has been working on the application of human genome information in clinics. In IMSUT Hospital, we provide genetic counseling, genetic tests for human malignancies such as leukemia and colon cancer, and a surveillance program for hereditary colorectal cancer. In addition to these clinical services, we have been carrying on two research projects; 1) implementation of genomic medicine, and 2) development of diagnostic systems for hereditary tumors.

1. Genetic analyses for hereditary diseases and human neoplasms

As a part of clinical service, we have performed genetic analysis of human neoplasms such as leukemia and colorectal cancer. In 2014, a total of 540 genetic analyses were performed in our department. The results were utilized for the precise classification of neoplasms, selection of therapeutic drugs, and evaluation of the response to treatment.

2. Analysis of variants in patients with hereditary tumors by next-generation sequencing

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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, we have been working on the following projects; 1) the determination of germline mutations in patients suspected for hereditary colon tumor, and 2) identification of somatic mutations in hematopoietic malignancies and solid tumors. These projects are aimed to return the data of personal genome and/or cancer genome to the patients in IMSUT Hospital, and apply the data for their diagnosis and treatment.

In the first project, we carried out whole genome sequencing of three patients who were diagnosed as familial polyposis of the colon (FAP). Since most of FAP cases are caused by a germline mutation in the *APC* gene, the three patients underwent genetic testing of *APC*. However, no pathogenic mutations were detected within the two-thirds region of the *APC* gene by conventional sequence analysis using the Sanger method. Therefore, we performed whole genome sequencing of the three patients. Consequently, we successfully identified three different types of pathogenic mutations in the patients. One of the three was a mosaic mutation of *APC* in a patient who suffered from mild type colonic polyposis without a family history. Another was a very rare mutation in the 3' terminal region of *APC* in an FAP patient with multiple desmoids. The third mutation was a structural variation lacking the pro-

moter region of *APC*. The three mutations are difficult to identify by genetic testing using the conventional sequencing method. These data have corroborated the usefulness of NGS in clinical practice.

In the second project, we analyzed genetic alterations in Japanese biliary tract cancer and pseudomyxoma peritonei of the colon (PMP) using multiplex PCR-based targeted enrichment and NGS. We have identified different mutation profiles between low-grade and high-grade PMP. The data may give us important information for the development of personalized approaches to the cancer treatment.

3. Genetic counseling and related activities.

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We provided genetic counseling and genetic tests to clients who visited our counseling clinic. In 2014, we had a total of 42 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 five cases with informed consent after thoughtful discussion about its merit and demerit.

Systematic surveillance programs are provided for the clients susceptible for hereditary tumors.

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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.

Assessment of the kinetics of an extracellular MRI contrast agent via retro-orbital injection in mice: comparison with tail vein injection

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It is not known whether administration of contrast via retro-orbital injection or the tail vein route affects the efficiency of dynamic contrast-enhanced magnetic resonance imaging (MRI). Therefore, we compared the effects of retro-orbital and tail vein injection on the kinetics of the contrast agent used for MRI in mice. The same group of nine healthy female mice received contrast via either route. An extracellular contrast agent was infused via the tail or retro-orbital vein, in random order. Serial dynamic contrast-enhanced MRI was performed before and after administering the contrast agent. The contrast effects in the liver, kidney, lung, and myocardium were assessed. The average total times of venous puncture and mounting of the injection system were about 10 and 4 min for the tail vein and retro-orbital route, respectively. For all organs assessed, the maximum contrast ratio occurred 30 s after administration and the time course of the contrast ratio was similar with either routes. For each organ, the contrast ratios correlated strongly; the contrast ratios were similar. The retro-orbital and tail vein routes afforded similar results in terms of the kinetics of the contrast agent. The retro-orbital route can be used as a simple efficient alternative to tail vein injection for dynamic contrast-enhanced MRI of mice.

Reducing CT Radiation Exposure with Organ Effective Modulation: A Clinical Study

Hiroyuki Akai, Shigeru Kiryu, Eisuke Shibata[4], Eriko Maeda[4], Jiro Sato[4], Nobuo Tomizawa[5], Masanori Nojima[2], Kuni Ohtomo[4]: [5]Department of Radiology, New Tokyo Hospital

Organ Effective Modulation (OEM) is a new automatic exposure control technique, which is focused to reduce radiation to radiosenstive organs placed in anterior part of patient such as lens of the eye, thyroid and breasts. In this clinical study, we evaluated the effects of OEM on image quality as well as the radiation dose in whole body CT. Consecutive 196 patients who were referred for enhanced whole body CT were divided into two groups whether the usage of OEM or not. Two groups were compared for CT radiation dose, objective image noise and subjective image quality. As a result, CTDIvol was reduced 8.3% in OEM group and high BMI patient tended to have higher dose reduction. Image noise showed no significant difference in thoracic level, except for ventral air space showing higher noise in OEM group. At abdominal level, OEM group showed lower noise in every region, only archiving significant difference in posterior segment of right hepatic lobe. Subjective image quality assessment showed more artifacts at thoracic ventral air space in OEM group, all other items including overall diagnostic acceptability showed no statistical differences between the two groups. In conclusion, OEM can reduce approximately 8% radiation dose without affecting the diagnostic acceptability of the image compared to angular-longitudinal modulation, especially in patient with high BMI.

Distinguishing inflamed lymph node from normal lymph node in mice by interstitial dynamic MR Lymphography.

Hiroyuki Akai, Yohiyasu Nakano, Shigeru Kiryu

We performed this experiment to determine whether interstitial dynamic MR Lymphography (MRL) using gadofluorine P and PEG-poly(L-lysine)-based gadolinium magnetic resonance contrast agent can differentiate normal to inflamed lymph node or not. Six normal mice and four inflamed lymph node model mice were used, and dynamic MRL was performed using a T1-weighted three dimensional fast low angle shot sequence on a 1T-compact permanent magnet MR system. Images were collected sequentially before and after the subcutaneous injection of contrast agent. The normal lymph nodes showed faster peak enhancement compared to the inflamed lymph nodes, and enhancement of the inflamed lymph nodes decreased faster than the normal lymph nodes. This tendency was consistent in mice with both contrast media. The enhancement in lymph modes retained slightly longer after the injection of PEG-poly(L-lysine)-based contrast agent.

Epidemiological investigation into the prevalence of TLTVs, LSTVs, and complete transitional anomalies in healthy adults.

Nakano Yoshiyasu, Hanaoka Shouhei[4], Masutani Yoshitaka[4], Hayashi Naoto[4], Ohtomo Kuni[4]

Transitional anomalies may be present at the junction between the thoracic and lumbar spinal segments as well as at the junction between the lumbar and sacral spinal segments. Incomplete transitions of those are called "Thoracolumbar transitional vertebrae (TLTVs)" and "Lumbosacral transitional vertebrae (LSTVs)", respectively. The prevalence of LSTVs is well described in the literature, and it ranges from 4 to over 35%. However, that of TLTVs or complete transitions is not well described so far. Purpose of this study is an epidemiological investigation into the prevalence of TLTVs, LSTVs, and complete transitional anomalies in healthy adults. Three hundred whole-spine CT datasets of 197 men and 103 women aged 40 to 88 years (mean age, 59.5) were used. All scans were obtained on one PET-CT scanners (Discovery STE; General Electric Medical Systems) at the health care section of Tokyo University Hospital, HIMEDIC. TLTVs were identified applying criteria of Wigh. LSTVs were classified according to Castellvi et al. Statistical analysis was performed using chi-square test. Thoracolumbar transitional anomalies were present in 55 (18.3%) of 300 subjects. Among these, TLTVs were present in 49 (16.3%) and complete transitions were present in 6 (2%). Lumbosacral transitional anomalies were present in 58 (19.3%) of 300 subjects. Among these, LSTVs were present in 38 (12.3%) and complete transitions were present in 20 (7%). Statistical association between the presence of thoracolumbar transition and that of lumbosacral transition was observed. Not only LSTVs but also TLTVs and complete transitional anomalies are relatively common anomalies, and should be paid an attention to in the clinical practice.

Automated detection of anomalous spinal segmentations: a feasibility study using 300 CT datasets.

Nakano Yoshiyasu, Hanaoka Shouhei[4], Nemoto Mitsutaka[4], Masutani Yoshitaka[4], Hayashi Naoto[4], Ohtomo Kuni[4]

Spinal transitional anomalies such as TLTVs and LSTVs may alter the number of presacral segments, normally 24, into 23 or 25. The identification of these anomalies is mandatory for the understanding of the pathological condition as well as the treating of the relevant level in the spinal disorders. Misidentification may even lead to wrong-level spine surgery. We have developed an automated computer program to estimate the number of presacral segments (PSN) from whole spine CT data. The purpose of this study is to evaluate the accuracy of our program for the feasibility in clinical

use. Three hundred whole-spine CT datasets were used. Our program estimates PSN detecting as many as 173 anatomical landmarks such as mid-posterior ends of intervertebral discs. For the Ground Truth of this study, two radiologists independently reviewed all CT datasets and determined PSN for each subject. Any disagreement was resolved through discussion. The presence of transitional anomalies was also searched for. We used Cohen's Kappa index to measure the agreement between the program results and Ground Truth. We also evaluated how the value would vary according to the presence of transitional anomalies. Kappa index for the agreement between PSN by our program and PSN by Ground truth in whole subjects, in subjects with transitional anomalies, and in subjects with LSTV; was 0.527, 0.447, and 0.215, respectively. Our feasibility study using 300 CT datasets indicates our automated computer program is potentially useful for the detection of spinal transitional anomalies.

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赤井宏行，大友邦．膵がんとの鑑別が困難であった自己免疫性膵炎．日本医師会雑誌．日本医師会．143：1718–9，2014

IMSUT Hospital

Department of Pathology
病理診断科

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.
We corrected HIV associated lymphoma in Japan and found the transition of the subtype of lymphoma. It might suggest the circumstance of the lymphomagenesis of the HIV patients.
AITL is a rare but distinct entity of malignant T-cell lymphoma. We found novel somatic mutation of this lymphoma.

1. Lymphomas associated with HIV (human immunodeficiency virus) infection.

The incidence of lymphoma is 60- to 200- fold higher in patients with HIV infection than in the general, uninfected patient population. The types of lymphoma in HIV patients are different from immunocompetent people. The introduction of combined antiretroviral therapy (ART) has reduced the mortality of patients with HIV infection worldwide. However, malignant lymphoma is a severe and frequent complication seen in patients with acquired immunodeficiency syndrome (AIDS). The diagnostic criteria for some categories of AIDS-related lymphoma were revised in the World Health Organization International Classification of Lymphoma, fourth edition. We'd like to find out the clinicopathological characteristics of Japanese patients with AIDS-related lymphoma according to the revised classification. 207 AIDS-related lymphoma cases diagnosed between 1987 and 2012 in Japan were subjected to histological subtyping and clinicopathological analyses. Diffuse large B-cell lymphoma (DLBCL) was the predominant histological subtype throughout the study period (n = 104, 50%). Among the DLBCL cases, 24% were of the germinal center (GC) type and 76% were of the non-GC type. Non-GC-type cases showed a significantly lower 1-year survival rate (43%) than the GC-type cases (82%). Cases of Burkitt lymphoma (n = 57, 28 %), plasmablastic lymphoma (n = 16, 8%), primary effusion lymphoma (n = 9, 4%), Hodgkin lymphoma (n = 8, 4%), and large B-cell lymphoma arising in Kaposi sarcoma-associated herpesvirus-associated multicentric Castleman disease (n = 2, 1%) were also observed. Hodgkin lymphoma was more common in patients receiving ART (11.1%) than in ART naıve patients (1.4%). Statistical analyses identified CD10 negativity, BCL-6 negativity, Epstein-Barr virus positivity, and Kaposi sarcoma-associated herpesvirus positivity as risk factors for poor prognosis. This information will help in the early diagnosis of lymphoma in patients with AIDS.

2. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma

Angioimmunoblastic T cell lymphoma (AITL) is a distinct subtype of peripheral T cell lymphoma characterized by generalized lymphadenopathy and frequent autoimmune-like manifestations. Although frequent mutations in TET2, IDH2 and DNMT3A, which are common to various hematologic malignancies, have been identified in AITL, the molecular pathogenesis specific to this lymphoma subtype is unknown. We report somatic RHOA mutations encoding a p.Gly17Val alteration in 68% of AITL samples. Remarkably, all cases with the mutation encoding p.Gly17Val also had TET2 mutations. The RHOA mutation encoding p.Gly17Val was specifically identified in tumor cells, whereas TET2 mutations were found in both tumor cells and non-tumor hematopoietic cells. RHOA encodes a small GTPase that regulates diverse biological processes. We demonstrated that the Gly17Val RHOA mutant did not bind GTP and also inhibited wild-type RHOA function. Our findings suggest that impaired RHOA function in cooperation with preceding loss of TET2 function contributes to AITL-specific pathogenesis.

3. We report other new findings by many case reports.

Duodenal follicular lymphoma is usually indolent even without any treatment. But we report a case of systemic dissemination with histologic diffuse large B-cell lymphoma transformation. This case suggests that the life-time follow-up that is usually done for patients with nodal follicular lymphoma should be provided to patients with duodenal follicular lymphoma.

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IMSUT Hospital

Department of Surgery (Gastrointestinal and Breast Surgery)

外科(主として，大腸・胃・食道・乳腺領域)

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, and to develop and conduct clinical research and clinical trials in early stages (mainly, Phase I and II) on patients at the Research Hospital. We have also been offering diagnostic and therapeutic endoscopy, including upper and lower gastrointestinal endoscopic examinations. Novel therapies started this year.

1. Surgical treatment in 2014

Masaru Shinozaki, Giichiro Tsurita, Kentaro Yazawa, Yoko Tateno, Yuichi Tachikawa, Akihiko, Seo, Natsumi Fukuhara, Daisuke Hojo, Takahide Shinagawa, Hiroshi Nagata

Until March, 2014, two clinical staffs worked at the Deparment: Drs. Tateno and Tachikawa. After April, 2014, clinical fellows from the Division of Colorectal Surgery and Vascular Surgery, the University of Tokyo Hospital came to join us one after another at an interval of two months. We are consolidated, and performed more operations. Dr. Sameshima and Dr. Kawamura had 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. Sanuki continued the out-patient clinic and assisted our breast cancer operations.

2. Endoscopic examination in 2014

Giichiro Tsurita, Kentaro Yazawa, Masaru Shinozaki, Yoko Tateno, Yuichi Tachikawa, Seo, Natsumi Fukuhara, Daisuke Hojo, Takahide Shinagawa, Hiroshi Nagata

Under cooperation with Department of Advanced Medical Science, we performed 720 upper gastrointestinal endoscopies and 763 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 Y.T.) have learned gastrointestinal endoscopic technique and have made great progress.

3. Clinical Research.

A. The role of micro RNA in the pathogenesis of inflammatory bowel disease

Emi Inoue, Masaru Shinozaki, Keisuke Hata (The University of Tokyo), Hideaki Kimura (Yokohama City University)

Recently, micro RNA (miRNA) had been known to play a crucial role in post-transcriptional regulation. In inflammatory bowel disease (IBD), its etiology has not been revealed yet. However, interaction between mucosa and intraluminal bacteria and immunological response are speculated to be included at least in the pathophysiology. There may be a possibility that abnormality in miRNA is involved in the pathogenesis of IBD. We established miRNA quantification system, and sought for abnormality of miRNA and its mechanism.

B. Whole genome sequencing of inflammatory bowel disease

Masaru Shinozaki, Yoichi Furukawa, Giichiro Tsurita, Kentaro Yazawa

The progress in nucleic acid sequencing technique enabled us to investigate whole genome in various fields. Like other diseases, inflammatory bowel disease is caused not only by environmental factors but also by hosts' genetic background. Although several susceptibility loci have been clarified using microsatellite difference, causative genetic changes have not been disclosed. We are studying whole genome of affected individuals.

C. Whole genome sequencing of colorectal neoplasm

Masaru Shinozaki, Yoichi Furukawa, Giichiro Tsurita

We perform whole genome sequencing for colorectal cancer under various conditions. Now, we have been accumulating specimens from cases and controls.

D. 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 surveillance 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 started to make questionnaire and send to hospitals to clarify the clinicopathlogical characteristics.

E. Evaluation of Clinical Guidelines

Emi Inoue, 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 inflammatory bowel disease.

4. Basic research-Virus therapy for gastrointestinal and hepatobiliary cancer

Yoko Tateno, Tomoki Todo (Deparment 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 the 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. BK-UM for ovarian cancer

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

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. This phase II trial has been conducted in cooperation with Osaka University and

Fukuoka University.

B. Survivin peptide vaccine for pancreatic cancer

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

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.

C. BK-UM for gastric cancer

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

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 will be given together with paclitaxel. We are preparing for the Institutional Review Board approval.

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IMSUT Hospital

Surgical Center
手術部

Associate Professor (Clinical Professor)	Mieko Chinzei, M.D., M.D.Sc.	准教授（病院教授）	鎮　西　美栄子
Assistant Professor	Reiko Shibata, M.D.	助　教	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.

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3. 鎮西美栄子，岩瀬哲，今井浩三：ホスピス緩和ケア白書：2014がんプロフェッショナル養成基盤推進プランと学会・学術団体の緩和ケアへの取り組み；分担執筆　第Ⅰ部　緩和ケアにおける専門医教育の現状と課題 4　東京大学大学院医学系研究科　緩和医療学講座　2014年3月，青海社

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 2014, there are 175 surgical treatments for hemophilia (97 for hemophilia A, 23 for hemophilia B, 1 for deficiency factor VII patient, and 1 for Von Willebrand disease). 18 of them have the deficiency factor antibody.

In 2014, we were performed 18 surgical treatments (12 for hemophilia A, 6 for hemophilia B). One of them has the deficiency factor antibody. Nine were performed total joint arthroplasties, four was arthroscopic synovectomy and five were other surgical treatments.

Publications

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IMSUT Hospital

Department of Surgical Neuro-Oncology
脳腫瘍外科

Professor	Tomoki Todo, M.D., Ph.D.	教　授	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
Project Senior Assistant Professor	Minoru Tanaka, M.D., Ph.D.	特任講師	医学博士	田　中　　実
Assistant Professor	Motokazu Ito, M.D., Ph.D.	助　教	医学博士	伊　藤　元　一
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, will be treated at our department. Malignant glioma is incurable by standard therapy alone, therefore refined, personalized treatment regimens of non-standard radiation therapy and chemotherapy will be considered. In addition, innovative therapy such as oncolytic virus therapy will be applied whenever possible. Based on scientific evidences and findings from basic research, we will conduct advanced medical practices in addition to the standard therapy.

A clinical study of a replication-competent, recombinant herpes simplex virus type 1 (G47Δ) in patients with progressive 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 I-IIa clinical trial of G47Δ in patients with progressive glioblastoma at the University of Tokyo Hospital. Patients with a single lesion of recurrent glioblastoma, age 18 or older, and with a good performance status are enrolled. The primary end point is to access the safety of G47Δ, and the secondary end point is to access the efficacy by tumor size and progression free survival. The approval to perform this study simultaneously at the IMSUT Hospital was obtained from the government in May 2013. The first patient of this study at the IMSUT Hospital enrolled in January 2014. Patient accrual for this trial was closed in November 2014 in order to advance to a phase II clinical trial.

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

A new protocol for a phase II clinical trial of G47Δ in patients with progressive or residual glioblastoma was submitted to the PMDA in July 2014. After a 30-day review, the protocol was officially accepted. 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 will be enrolled. The primary end point is a 1-year survival ratio, and the secondary end points are overall survival, progression free survival, efficacy assessed by tumor size and safety assessed by adverse events. Patient accrual has started in December 2014.

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 repeatedly 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 include an operative microscope, a 3-D neuro-navigation system, intraoperative motor evoked potential monitoring, intraoperative ultrasonography and an ultrasonic surgical aspirator.

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.

Publications

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IMSUT Hospital

Department of Palliative Medicine
緩和医療科

Professor	Arinobu Tojo, M.D., D.M.Sc.	
Associate Professor	Mieko Chinzei, M.D., D.M.Sc.	
Project Senior Assistant Professor	Satoru Iwase, M.D., D.M.Sc.	
Project Assistant Professor	Hiroto Ishiki M.D.	
Assistant Professor	Naoki Shimada, M.D., PhD.	

教　授	医学博士	東　條　有　伸
病院教授	医学博士	鎭　西　美栄子
特任講師	医学博士	岩　瀬　　哲
特任助教		石　木　寛　人
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 Cell Processing and Transfusion
セルプロセッシング・輸血部

Professor	Arinobu Tojo, M.D., D.M.Sc.	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 Professor	Toyotaka Kawamata, M.D., D.M.Sc.	助　教	医学博士	川　俣　豊　隆

Our department was established in 1990, in order to manage the transfusion medicine and the cell processing for hematopoietic stem cell transplantation. 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 banking for clinical use supported by MHLW. Furthermore, we developed immunosuppressive therapy for severe GVHD after hematopoietic stem cell transplantation using expanded regulatory T cells from CB and adult blood, and UC-MSCs.

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

Nagamura-Inoue T, Mori Y., Takahashi A., Yamamoto Y, Shimazu 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. 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. Improved Explant Method To Isolate Umbilical Cord-derived Mesenchymal Stem/Stromal Cells And Their Immunosuppressive Properties.

Mori Y, Ohshimo J, Shimazu T, He H, Takahashi A, Yamamoto Y, Tsunoda H, Tojo A, Nagamura-Inoue T.

The umbilical cord (UC) has become one of the major sources of mesenchymal stem cells (MSCs). The common explant method of isolating UC-derived MSCs (UC-MSCs) involves mincing the UCs into small fragments, which are then attached to a culture dish bottom from which the MSCs migrate. However, the fragments frequently float up from the bottom of the dish, thereby reducing the cell recovery rate. To overcome this problem, we demonstrate an improved explant method for UC-MSC isolation, which involves the use of a stainless steel mesh (Cellamigo®; Tsubakimoto Chain Co.; Japan) to protect the tissue from floating after the minced fragments are aligned at regular intervals in culture dishes. The culture medium was refreshed every 3 days and the adherent cells and tissue fragments

were harvested using trypsin. The number of UC-MSCs isolated from 1 g of UC using the explant method with Cellamigo® was $2.9 \pm 1.4 \times 106$/g, which was significantly higher than that obtained without Cellamigo®($0.66 \pm 0.53 \times 106$/g) ($n = 6$, $P < 0.01$) when cells reached 80-90% confluence. In addition, the processing time and incubation time required to reach 80-90% confluence were reduced in the improved explant method compared with the conventional method. The UC-MSCs isolated using the improved method were positive for CD105, CD73, CD90, and HLA class I expression, and were negative for CD45 and HLA class II expression. The isolated UC-MSCs efficiently inhibited the responder T cells induced by allogeneic dendritic cells in a mixed lymphocyte reaction. Conclusively, we demonstrated that the use of Cellamigo® improves the explant method for isolating UC-MSCs.

3. Stage-specific embryonic antigen 4 in Wharton's jelly-derived mesenchymal stem cells is not a marker for proliferation and multipotency.

He H, Nagamura-Inoue T, Tsunoda H, Yuzawa M, Yamamoto Y, Yorozu P, Agata H, Tojo A.

Umbilical cord Wharton's jelly (WJ) is a rich source of mesenchymal stem cells (MSCs) similar to bone marrow (BM) and adipose tissues. Stage-specific embryonic antigen (SSEA)4 has been reported as a stem cell marker in BM-derived MSCs, but whether SSEA4(+) cells have growth and differentiation advantages over SSEA4(−) cells remains controversial. To gain insight into the role of SSEA4, we studied SSEA4(+) cells in WJ-derived MSCs (WJ-MSCs). WJ-MSCs were collected by the explant (WJe-MSCs) or collagenase methods (WJc-MSCs) and analyzed by flow cytometry and reverse-transcription polymerase chain reaction (RT-PCR). To evaluate whether culture conditions influenced the SSEA4 expression, WJe-MSCs were cultured in the medium supplemented with different fetal bovine serum (FBS) concentrations. SSEA4 was expressed for a long-term culture. In contrast, SSEA3(+) disappeared rapidly in early passages of the culture. The incidence of SSEA4(+) and SSEA3(+) cells was similar between WJe-MSCs and WJc-MSCs at passages P0-P9, except for transient depletion of SSEA4 expression in early passages of WJe-MSCs. These were CD73(+)CD105(+) cells that express embryonic stem cell markers detected by RT-PCR. No differences in growth and differentiation ability of osteocytes and adipocytes were observed between the sorted SSEA4(+) cells and SSEA4(−) cells. Further, SSEA4 expression in WJe-MSCs was significantly correlated with FBS concentration in the culture medium. SSEA4, which may display altered expression profiles in response to culture conditions, may not be an essential marker of WJ-MSC multipotency.

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

Nagamura-Inoue T, Yamamoto Y, 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.

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

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

"Research Cord Blood Stem Cell Bank" (prior name., 'Research Stem Cell Resource Bank') was established supported by MEXT, to promote 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 the 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/.

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

Nagamura-Inoue T, Yamamoto Y, Takahashi A., Shimazu T., Nakai M., 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 have been 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 tissue engineering using bone marrow mesenchymal cells, 4) Gene therapy for renal cancer, 5) CB and UC-MSCs banking (IMSUT-CORD).

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IMSUT Hospital

Clinical FACS Core Laboratory
臨床検体専用FACSコアラボラトリー

Project Associate Professor Nobukazu Watanabe, M.D., Ph.D.

特任准教授 医学博士 渡 辺 信 和

Clinical FACS Core Laboratory was established in December 2011 as a sharing laboratory. Our major purpose is to conduct clinical research and develop analytical methods of pathogenic conditions during infectious disease, cancer and hematopoietic stem cell and organ transplantations. Through collaborations with hospitals in Japan, we have performed several problem-based clinical studies to tackle the issues of adult T cell leukemia (ATL) and pathogenic conditions after transplantation, e.g. cytomegalovirus infection, graft failure, acute graft versus host disease (GVHD), relapse of leukemia, and recurrence of hepatitis.

1. Phenotypic analysis of ATL cells and prediction of the onset of ATL from human T-lymphotropic virus type 1 (HTLV-1) asymptomatic carriers

Tomohiro Ishigaki, Seiichiro Kobayashi[1], Nobuhiro Ohno[2], Yuji Zaike[3], Natsuko Sato, Eri Watanabe, Kaoru Uchimaru[2] and Nobukazu Watanabe: [1]Department of Molecular Therapy, [2]Research Hospital, [3]Department of Laboratory Medicine, IMSUT

Among the one million HTLV-1 carriers in Japan, approximately one thousand progress to ATL every year. Through collaborations with the Research Hospital and two laboratories at IMSUT, we are analyzing ATL cells using a flow cytometry-based method of phenotypic analysis [HTLV-1 analysis system (HAS)-Flow] to monitor disease condition. In addition, we are analyzing peripheral blood from HTLV-1 carriers to find a predictable phenotypic change of peripheral blood cells just before ATL onset in order to begin more effective treatment.

2. Analysis of ATL cells and immune cells after hematopoietic cell transplantation, DC therapy and anti-CCR4 antibody therapy in patients with ATL.

Eri Watanabe, Natsuko Sato, Ilseung Choi[4], Yoko Suehiro[4], Nobuaki Nakano[5], Yoshitaka Inoue[6], Seiichiro Kobayashi, Kaoru Uchimaru, Atae Utsunomiya[5], Takahiro Fukuda[6], Naokuni Uike[4] and Nobukazu Watanabe: [4]Department of Hematology, National Kyushu Cancer Center, [5]Department of Hematology, Imamura-bunin Hospital, [6]Stem Cell Transplantation Division, National Cancer Center Hospital

In a Japanese study group of cell therapy for ATL, hematopoietic cell transplantation, DC therapy and anti-CCR4 antibody therapy are planned for patients with acute ATL. We are joining this study group and analyzing engraftment and ATL cells using HLA-Flow and HAS-Flow methods. In addition, we are analyzing ATL cells and normal regulatory T cells with their expression levels of CCR4 which is the target of anti-CCR4 antibody therapy using 12-color flow cytometer.

3. Studies for the mechanisms underlying persistent chimerism and late rejection after cord blood transplantation in patients with severe combined immunodeficiencies (SCID).

Eri Watanabe, Nobukazu Watanabe, Kosuke Imai[7], Tomohiro Morio[7]: [7]Department of Pediatrics, Tokyo Medical Dental University

Although T cells and NK cells are lacked in patients with SCID, persistent chimerism and late rejection sometimes occur after cord blood transplantation. We analyze subpopulation-specific chimerism using HLA-Flow method and investigate the underlying mechanisms of these pathogenic conditions.

4. Studies for the mechanisms underlying recurrence of type C hepatitis and rejection after living-donor liver transplantation

Nobukazu Watanabe, Akinobu Takaki[8], Kazuko Koike[6], Takahito Yagi[9]: [8]Department of Gastroenterology and Hepatology, [9]Department of Gastroenterological Surgery, Transplant and Surgical Oncology, Okayama University Graduate School of Medicine and Dentistry

Since the 2004 approval of insurance coverage for living-donor liver transplantations (LDLT), more than 6,000 LDLTs have been performed in Japan. Although most recipients have a good prognosis, patients with hepatitis C virus (HCV) infection still face the recurrence of hepatitis after transplantation. In addition, rejection is an important issue because immunosuppressive agents are needed to suppress anti-graft immune reactions. Long-term use of immunosuppressants, however, can worsen HCV infections and future malignancies. To understand the mechanism underlying these pathologic conditions, we are investigating the following: chimerism analysis/HLA-Flow method, detection of regulatory T cells and allospecific T cells, and identification of HCV-specific $CD8^+$ T cells using tetramers.

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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 primary function of the Core Facility for Therapeutic Vectors (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 defined by FDA of USA. In 2002, CFTV was established as the first facility in Japanese academia for the production of viral or cellular vectors of a clinical grade.

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 in progress

A new project for the production of oncolytic measles virus (MV) has been approved by the facility committee. Preparation of SOPs is in progress.

IMSUT Hospital

Center for Translational Research
TR・治験センター

Professor	Fumitaka Nagamura, M.D., D.M.Sc		教　授	医学博士	長村文孝
Project senior Assistant Professor	Masanori Nojima, M.D., D.M.Sc., M.P.H.		特任講師(兼任)	医学博士	野島正寛
Project senior Assistant Professor	Hiroshi Yasui, M.D., D.M.Sc		特任講師(兼任)	医学博士	安井　寛
Senior Assistant Professor	Sumimasa Nagai, M.D., D.M.Sc		講師(兼任)	医学博士	永井純正
Project assistant Professor	Makiko Karasawa, M.D., D.M.Sc		特任助教	医学博士	柄澤麻紀子

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

Noriko Fujiwara, Minako Kouno, Erika Horibe, Mashiho Yanagi, Riyo Ohwada, Saori Minote, Makiko Karasawa, 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 Mamai, 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 three investigator-initiated clinical trials under an Investigational New Drug Application for the development of the academia-oriented innovative drug. The first trial is "the second phase trial of BK-UM against HB-EGF in combination with gemcitabine in patients with advanced or recurrent ovarian cancer". We play the role of clinical trial coordination as the site management by secretariat, clinical research associate, and translational research coordinator.

The second trial 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". We play the role of clinical trial coordination as the site management by secretariat, project manager, and translational research coordinator.

The third is "the double-blind parallel-group placebo-control Phase II study on the efficacy of the mixed therapeutic cancer vaccines for patients with non-small cell lung cancer". We supported to submit clinical trial notification.

We study 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.

Noriko Fujiwara, Makiko Karasawa, 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 (confirmatory and exploratory), basic medical/biological research. We have collaborated with other members (listed below) in IMSUT this year through the consulting.

Departments and divisions of collaborators (alphabetical order)

- Department of Hematology/Oncology, Research Hospital
- 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 Mucosal 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

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IMSUT Hospital

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

Professor	Hirotoshi Tanaka, M.D., D.M.Sc.	教　授	医学博士	田　中	廣　壽
Project Professor	Yataro Daigo, M.D., D.M.Sc.	特任教授	医学博士	醍　醐	弥太郎
Project Associate Professor	Hiroaki Taniguchi, M.D., D.M.Sc.	特任准教授（兼任）	医学博士	谷　口	博　昭
Project Associate Professor	Koichiro Yuji, M.D., D.M.Sc.	特任准教授	医学博士	湯　地	晃一郎
Project Senior Assistant Professor	Hiroshi Yasui, M.D., D.M.Sc.	特任講師	医学博士	安　井	寛
Project Senior Assistant Professor	Atsushi Takano M.D., D.M.Sc.	特任講師	医学博士	高　野	淳

This center was established in April 1 st, 2012, in the memory of Professor Shibasaburo Kitasato, the founder and the first director of our institute, because the year 2012 was 120 th anniversary of our institute which was built in 1892. Prof Kitazato 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[1], Noritada Yoshikawa[1], Hiroshi Kobayashi[1], Aya Oda[1], Masaaki Uehara[1], Erika Matsubara[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 rare diseases such as relapsing polychondritis and multicentric reticulohistiocytosis, as well as 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 Trials 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], Akiko Souta-Kuribara[1], Masaaki Uehara, Hiroshi Kobayashi, 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. From May/2012 to Dec/2012, 7 patients have been registered in this trial and this trial is currently in progress.

(ii) Investigator initiated phase 1 clinical trial of rice-based oral vaccine, MucoRice-CTB powder in healthy adults.

(Collaborative project between IMSUT and IMSUT Hospital)

The team of Professor Kiyono (Division of 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, Hirotoshi Tanaka (Department of Rheumatology and Allergy, and Division of Rheumatology, Center for Antibody and Vaccine Therapy, IMSUT Hospital), and collaborators are preparing 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, we are going to submit an application of the clinical trial. The clinical trial will launch in July 2015.

4. Novel therapeutic target discovery for solid cancers

Yataro Daigo, Atsushi Takano, Koji Teramoto, Phung Manh Thang, Kayo Daigo, Yuichiro Yoshioka

To identify molecules involved in human carcinogenesis and those which could be applied for the development of new molecular therapies and/or biomarkers, we had established a systematic screening system as follows; i) identification of overexpressed genes in the majority of solid cancers (lung, esophagus etc.) by genome-wide screening using the expression microarray in the combination of enrichment of tumor cell populations from cancer tissues by laser microdissection, ii) verification of no or little expression of each of candidate molecules in normal tissues by northern-blot analyses, iii) validation of the clinicopathological significance of its higher expression with tissue microarray containing 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 bio-

marker 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). In fact, 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.

5. Identification of a nuclear protein, LRRC42, involved in lung carcinogenesis

Yataro Daigo, Atsushi Takano

Through the gene expression profiles of 120 lung cancer cases using a cDNA microarray containing 27,648 genes or expressed sequence tags (ESTs), we identified LRRC42 (Leucine-rich repeat containing 42) to be significantly overexpressed in the majority of lung cancers. Northern blot analysis demonstrated that LRRC42 was expressed only in testis among normal tissues. Knockdown of LRRC42 expression by siRNA against LRRC42 significantly suppressed the growth of lung cancer cells, whereas stable induction of LRRC42 expression significantly promoted cell growth. LRRC42, which was found to localize in the nucleus of mammalian cells, is likely to interact with and stabilize GATAD2B (GATA zinc finger domain-containing 2B) and MBD3 (Methyl-CpG-binding domain protein 3) proteins that could contribute to lung cancer cell proliferation partly through the regulation of p21Waf1/Cip1. LRRC42 overexpression as well as its interaction with LRRC42-GATAD2B might play essential roles in lung carcinogenesis, and be a promising molecular target for lung cancer therapy.

6. Development of therapeutic cancer vaccine

Yataro Daigo, Atsushi Takano, Koichiro Yuji, Hiroshi Yasui, Kohzoh Imai

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.

7. 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 5,000 patients with solid cancers originated from 13 organs. We also constructed tissue microarray system covering about 5,000 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. As a part of this program, we clarified clinicopathological features and EGFR gene mutation status in elderly patients with resected non-small-cell lung cancer.

8. Targeting of stemness factors inhibits the growth of tumors and the formation of metastases in solid tumor.

Hiroaki Taniguchi, Kohzoh Imai

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 EZH2-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 characteristically 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.

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

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

We are conducting two investigator-initiated clinical trials under an Investigational New Drug Application for the development of the academic-oriented innovative cancer drug. 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". We play the role of the site management with the department of clinical trial safety management, as well as the enforcement with the department of surgery, radiology, laboratory medicine, the surgical center, and the center for translational research.

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". We play the role of the site management with the department of clinical trial safety management, as well as the enforcement with the department of surgery, radiology, laboratory medicine, cell processing and transfusion, and the center for translational research. We study to conduct clinical trials to promote translational research more efficiently in IMSUT hospital through these investigations.

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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 lunched 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 Partnership 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.

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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. Identification of SIV Nef CD8$^+$ T cell epitopes restricted by a MHC class I haplotype associated with lower viral loads in a macaque AIDS model

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Virus-specific CD8$^+$ T-cell responses are crucial for the control of HIV and simian immunodeficiency virus (SIV) replication. Multiple studies on HIV-infected individuals and SIV-infected macaques have indicated association of several major histocompatibility complex class I (MHC-I) genotypes with lower viral loads and delayed AIDS progression. Understanding of the viral control mechanism associated with these MHC-I genotypes would contribute to the development of intervention strategy for HIV control. We have previously reported a rhesus MHC-I haplotype, *90-120-Ia*, associated with lower viral loads after SIVmac239 infection. $Gag_{206\text{-}216}$ and $Gag_{241\text{-}249}$ epitope-specific CD8$^+$ T-cell responses have been shown to play a central role in the reduction of viral loads, whereas the effect of Nef-specific CD8$^+$ T-cell responses induced in all the *90-120-Ia*$^+$ macaques on SIV replication remains unknown. Here, we identified three CD8$^+$ T-cell epitopes, $Nef_{9\text{-}19}$, $Nef_{89\text{-}97}$, and $Nef_{193\text{-}203}$, associated with *90-120-Ia*. $Nef_{9\text{-}19}$ and $Nef_{193\text{-}203}$ epitope specific CD8$^+$ T-cell responses frequently selected for mutations resulting in viral escape from recognition by these CD8$^+$ T cells, indicating that these CD8$^+$ T cells exert strong suppressive pressure on SIV replication. Results would be useful for elucidation of the viral control mechanism associated with *90-120-Ia*.

2. Vaccine-induced CD107a$^+$ CD4$^+$ T cells are resistant to depletion following AIDS virus infection

Kazutaka Terahara[3], Hiroshi Ishii[1], Takushi Nomura[1], Naofumi Takahashi[1], Akiko Takeda[1], Teiichiro Shiino[1], Yasuko Tsunetsugu-Yokota[3], and Tetsuro Matano: [3]Department of Immunology, National Institute of Infectious Diseases

CD4$^+$ T-cell responses are crucial for effective antibody and CD8$^+$ T-cell induction following virus infection. However, virus-specific CD4$^+$ T cells can be preferential targets for HIV infection. HIV-specific CD4$^+$ T-cell induction by vaccination may thus result in enhancement of virus replication following infection. In the present study, we show that vac-

cine-elicited $CD4^+$ T cells expressing CD107a are relatively resistant to depletion in a macaque AIDS model. Comparison of virus-specific CD107a, MIP-1β, IFN-γ, TNF-α, and IL-2 responses in $CD4^+$ T cells of vaccinated macaques pre- and 1-week post-challenge showed a significant reduction in the $CD107a^-$ but not the $CD107a^+$ subset after virus exposure. Those vaccinees that failed to control viremia showed a more marked reduction and exhibited significantly higher viral loads at week 1 than unvaccinated animals. Our results indicate that vaccine-induced $CD107a^-$ $CD4^+$ T cells are depleted following virus infection, suggesting a rationale for avoiding virus-specific $CD107a^-$ $CD4^+$ T-cell induction in HIV vaccine design.

These studies were performed with the help of National Institute of Infectious Diseases, Tsukuba Primate Research Center in National Institute of Biomedical Innovation, 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 DNAVEC Corp. and International AIDS Vaccine Initiative (IAVI). A phase I trial (S001) has started in Rwanda, Kenya, and U.K.

- http://www.iavi.org/Information-Center/Publications/Documents/IAVI_AIDS_Vaccine_in_Japan_2008_ENG.pdf
- http://www.iavi.org/Information-Center/Press-Releases/Pages/IAVI-AND-PARTNERS-INITIATE-PHASE-I-TRIAL-OF-A-NOVEL-AIDS-VACCINE-REGIMEN.aspx

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