

## IMSUT Hospital

# Department of Advanced Medical Science 先端診療部

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*Department of Advanced Medical Science was established in September 1997. Our aim is to contribute to the performance and the development of advanced therapeutic approach to the diseases. We have been participating in the potentially important clinical trials and the several projects in line with our principles. Our research projects are (1) H. pylori in HIV-infected patients, (2) Early diagnosis of cardiotoxicity in chemotherapy-treated patients, (3) Analysis of the potential therapeutic advantages of cell lysate from human placenta in promoting impaired cutaneous wound healing, (4) Establishment of GMP-compliant large-scale DC vaccines loaded with cytoplasmic transduction peptide-fused protein tumor antigens, (5) Safety test of 5-aminolevulinic acid with ferrous ions in diabetic patients treated with oral hypoglycemic agents, (6) A phase I clinical trial of RNF43 peptide-related immune cell therapy combined with low-dose cyclophosphamide in patients with advanced solid tumors.*

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

Matsubara Y. et al.

The prevalence of H.pylori infection in the HIV-infected patients is to be elucidated. Some studies showed higher rates in HIV-negative than HIV-positive. One of hypotheses is an appropriate amount of CD4<sup>+</sup> cells is needed for colonization of H. pylori. We investigated H. pylori and inflammatory cells in HIV-infected patients using biopsy specimens taken by upper gastrointestinal endoscopy.

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

Watanabe A. et al.

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

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

Zhang X. et al

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

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

Kimura Y. et al.

Compared to peptide vaccines depending upon internal dendritic cells (DCs), ex vivo cultured DCs are a promising vaccine strategy for cancer. Accumulating evidence showed that DC vaccines induced potent anti-tumor immune responses, compared to peptide vaccines. A novel antigen delivery technology, named as cytoplasmic transduction peptide (CTP), has been developed by JW Creazen, in order to improve antigen presentation and induction of anti-tumor immune responses by DCs. CTP delivers high polymer materials such as protein antigens into cytoplasmic compartment and retains them in the cytosol. Thus, the CTP-fused tumor antigens are taken up and presented efficiently to lymphocytes in theory. Using this system, we investigate whether our DCs are able to efficiently present the CTP-fused proteins to T-cells in vitro. The DCs loaded with the CTP-fused AFP, GPC-3, and MAGE-A1 proteins were produced in the cell processing center (CPC) from peripheral blood mononuclear cells (PBMCs) derived from normal healthy volunteers. After stimulating the PBMCs

with the DCs several times, AFP and MAGE-A1 specific IFN-gamma production from cytotoxic T lymphocytes (CTLs) and helper T-cells were detected by ELISA. As the result, they could be induced in vitro from 2 and 1 among 3 volunteers respectively, but not GPC-3 specific T-cells. The present study demonstrates the potential of the CTP-fused proteins for efficient cancer immunotherapy when loaded in DCs.

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

Yamashita N. et al.

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

## 6. A phase I clinical trial of RNF43 peptide-related immune cell therapy combined with low-dose cyclophosphamide in patients with advanced solid tumors.

Hijikata Y. et al.

The objective of this study was to investigate the safety and the tolerability of combined cellular immunotherapy with low-dose cyclophosphamide (CPM) in patients with advanced solid tumors. This study targeted a novel tumor-associated antigen, ring finger protein 43 (RNF43). Eligible patients were resistant to standard therapy, HLA-A\*24:02- or A\*02:01-positive and exhibiting high RNF43 expression in their tumor cells. They were administered 300 mg/m<sup>2</sup> CPM followed by autologous lymphocytes, preliminarily cultured with autologous RNF43 peptide-pulsed dendritic cells (DCs), RNF43 peptide-pulsed DCs and systemic low dose inter-

leukin-2. The primary endpoint was safety whereas the secondary endpoint was immunological and clinical response to treatment. Ten patients, in total, were enrolled in this trial. Primarily, no adverse events greater than Grade 3 were observed. Six out of 10 patients showed stable disease (SD) on day 49, while 4 other patients showed progressive disease. In addition, one patient with SD exhibited a partial response after the second trial. The frequency of regulatory T cells (Tregs) in patients with SD significantly decreased after CPM administration. The ratio of interferon- $\gamma$ -producing, tumor-reactive CD8<sup>+</sup> T cells increased with time in patients with SD. We successfully showed that the combination of immune cell therapy and CPM was safe, might induce tumor-specific immune responses and clinical efficacy, and accompanied by a decreased ratio of Tregs in patients with RNF43-positive advanced solid tumors.

## Publications

Watanabe A, Suzuki S, Kano H, Matsuno S, Takai, H, Kato Y, Otsuka T, Uejima T, Oikawa Y, Nagashima K, Kirigaya H, Kuniyama T, Sagara K, Yamashita N, Sawada H, Aizawa T, Yajima J, Yamashita T. (2016) Left atrial remodeling assessed by transthoracic echocardiography predicts left atrial appendage flow velocity in patients with paroxysmal atrial fibrillation. *Int Heart J*. 57: 177-182

Goto K, Annan DA, Morita T, Li W, Muroyama R,

Matsubara Y, Ito S, Nakagawa R, Tanoue Y, Jinushi M, Kato N. (2016) Novel chemoimmunotherapeutic strategy for hepatocellular carcinoma based on a genome-wide association study. *Sci Rep* 6: 38407

Noguchi R, Yamaguchi K, Ikenoue T, Terakado Y, Ohta Y, Yamashita N, Kainuma O, Yokoi S, Maru Y, Nagase H, Furukawa Y. (2017) Genetic alterations in Japanese extrahepatic biliary tract cancer. *Oncol Lett*, in press.

## IMSUT Hospital

# Department of Infectious Diseases and Applied Immunology

## 感染免疫内科

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### 【兼任】

<sup>\*1</sup>Division of Infectious Diseases, The Advanced Clinical Research Center  
(先端医療研究センター感染症分野)

*Founded in 1981, Department of Infectious Diseases and Applied Immunology (DIDAI) started HIV clinic in 1986. In 2016, 15 new patients with HIV infection have visited to our hospital and 532 patients in total are currently under our clinical management. The total number of in-patients with HIV-infection during 2016 was 43, and 5 or 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<sup>1</sup>, Eisuke Adachi, Tadashi Kikuchi<sup>1</sup>, Hitomi Nakamura, Takashi Odawara, Hiroshi Yotsuyanagi<sup>1</sup>: 'Division of Infectious Diseases, The Advanced Clinical Research Center

15 new patients with HIV-1 infection visited to our hospital this year (from January 1 to December 31, 2016), and 532 patients in total are under medical management in our outpatient clinic. The total

number of HIV-infected in-patients during 2016 was 43. 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 521 HIV-infected patients in our hospital, and most of their HIV viral loads have been well controlled. After one year of ART, the viral loads become less than 50 copies/ml in 96.2% of HIV-infected patients in our outpatient clinic. Con-

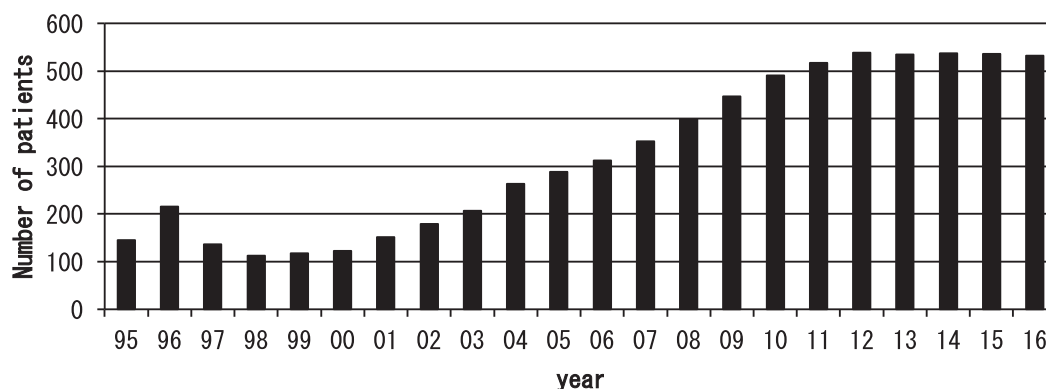


Figure 1. Number of HIV-infected outpatients in IMSUT Hospital

sequently, 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<sup>1</sup>, Eisuke Adachi, Tadashi Kikuchi<sup>1</sup>, Hitomi Nakamura, Takashi Odawara, Hiroshi Yotsuyanagi<sup>1</sup>: 'Division of Infectious Diseases, The Advanced Clinical Research Center**

The Japanese guidelines for treatment of HIV-infected patients have been established since 1998 with support from Ministry of Health, Labor and Welfare. The representatives from our department have played critical roles in development of the current practice guidelines in Japan. It is vital to create practice guidelines that are specific for the unique genetic and social backgrounds of the HIV-infected population in Japan. In collaboration with other Japanese HIV-experts, the physicians from our department update the practice guidelines annually, as we deem necessary. The guidelines are available at <http://www.haart-support.jp/guideline.htm> and used widely by Japanese clinicians. It has been downloaded more than 17,000 times in 2016. 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<sup>1</sup>, Eisuke Adachi, Tadashi Kikuchi<sup>1</sup>, Hitomi Nakamura, Takashi Odawara, Hiroshi Yotsuyanagi<sup>1</sup>: 'Division of Infectious Diseases, The Advanced Clinical Research Center**

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

## Publications

1. Adachi E, Sugiyama M, Shimizu S, Kodama K, Kikuchi T, Koga M, Mizokami M, Koibuchi T. Human immunodeficiency virus and hepatitis B genotype G/A2 recombinant co-infection: a case study. Springerplus. 2016 Sep 7; 5(1): 1502.
2. Ishizaka A, Sato H, Nakamura H, Koga M, Kikuchi T, Hosoya N, Koibuchi T, Nomoto A, Kawana-Tachikawa A, Mizutani T. Short Intra-cellular HIV-1 Transcripts as Biomarkers of Residual Immune Activation in Patients on Antiretroviral Therapy. J Virol. 2016 May 27; 90(12): 5665-76.
3. Katoh J, Kawana-Tachikawa A, Shimizu A, Zhu D, Han C, Nakamura H, Koga M, Kikuchi T, Adachi E, Koibuchi T, Gao GF, Brumme ZL, Iwamoto A. Rapid HIV-1 Disease Progression in

- 
- Individuals Infected with a Virus Adapted to Its Host Population. PLoS One. 2016 Mar 8; 11(3)
4. Adachi E, Kido Y, Ota Y, Koibuchi T. Immunostaining of Cryptosporidiosis with Human Immunodeficiency Virus Infection. Intern Med. 2016; 55(21): 3229-3230.

## IMSUT Hospital

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

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

### 1. Clinical activities in IMSUT Hospital

**Osamu Hosono, Noritada Yoshikawa, Toshiki Eri, Erika Matsubara, Hiroyuki Baba, Aya Oda, Masaaki Uehara, Hirotooshi Tanaka**

Rheumatologists at our division provide state-of-the-art diagnosis and treatment for diseases that affect the joints and connective tissues (rheumatic diseases). 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. We, as rheumatologists, treat many types of arthritis and autoimmune diseases, including rheumatoid arthritis, osteoarthritis, and collagen vascular diseases (e.g., systemic lupus erythematosus, polymyositis, and vasculitic syndromes).

Rheumatologic services offered at IMSUT Hospital include:

- Outpatient consultations
- Outpatient specialty care for patients with chronic rheumatic diseases
- Hospital consultations
- Diagnostic and therapeutic intra-articular and soft

tissue injections and aspirations

- Diagnostic ultrasonography
- Education on rheumatologic diseases and treatments
- Clinical trials

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

**Hirotooshi Tanaka, Noritada Yoshikawa, Noriaki Shimizu, Naoki Ito, Takako Maruyama, Akiko Souta-Kuribara, Yuki Tasaka, Aya Oda, Masaaki Uehara, Yuji Nakamura, Akane Fukuda, Toshiki Eri, 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 atrogen-1 and MuRF1. Moreover,

KLF15 affects mTOR through BCAA degradation and negatively modulates myofiber size. mTOR activation inhibits GR-mediated transcription by suppressing GR recruitment onto target genes, strongly suggesting a mutually exclusive crosstalk between mTOR and GR. Pharmacological activation of mTOR with BCAA attenuated GR-mediated gene expression, leading to the substantial restoration of muscle in glucocorticoid-treated rats. We, therefore, indicate the critical importance of the interaction of GR and mTOR in the regulation of metabolism-volume coupling in skeletal muscle. Recently, we have created skeletal muscle-specific GR knockout mice (mGRKO) and revealed that mGRKO show significant increase of their myofiber size and muscle mass. Given this, we have been working with the clinical trial in IMSUT hospital to verify our scenario in glucocorticoid-treated patients. In addition, we unraveled the physiological significance of muscle proteolysis using mGRKO. The resulting depletion of plasma alanine serves as a cue to increase plasma levels of fibroblast growth factor 21 (FGF21) and activates liver-fat communication, leading to the activation of lipolytic genes in adipose tissues. Targeting the skeletal muscle-liver-fat signalling axis involving glucose-alanine cycle, therefore, would be a novel approach for treatment of patients with obesity, diabetes and metabolic syndrome.

### **(iii) Clarification of functional crosstalk between GR and estrogen receptor for metabolic regulation**

Aging, in general, is associated with gradual decrements in tissue and organ functions. In women, menopause characterized by the loss of ovarian function represents an aging process that leads to changes in the systemic steroid hormone profile from a regularly fluctuating estrogen cycle to very low and constant levels. This decrease in systemic estrogen may, however, have tissue-specific effects on estrogen-responsive tissues such as adipose tissue and skeletal muscle. Recently, impaired estrogen receptor  $\alpha$  (ER $\alpha$ ) action has shown to promote obesity and metabolic dysfunction in humans and mice. On the other hand, we revealed that mGRKO shows the opposite phenotype against metabolic syndrome. Therefore, we hypothesized that clarification of functional crosstalk between GR and ER $\alpha$  in adipose tissue and skeletal muscle contributes to developing a novel therapeutic modality for metabolic syndrome. Now, we are challenging to unveil the crosstalk between GR and ER $\alpha$  by using mGRKO, mER $\alpha$ KO, mGR/ER $\alpha$  double KO mice, ovariectomized mice, and a mice model of Cushing's disease.



#### (iv) 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 1 $\alpha$  (HIF-1 $\alpha$ ) 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-1 $\alpha$  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.

#### 3. Development of novel therapeutic approach of systemic autoimmune diseases targeting intestinal microbiota

Toshiki Eri, Kimito Kawahata<sup>1</sup>, Takeyuki Kan-zaki<sup>1</sup>, Mitsuru Imamura<sup>1</sup>, Kazuya Michishita<sup>1</sup>, Lisa Aakahira<sup>1</sup>, Ei Bannai<sup>1</sup>, Takeshi Satoh<sup>2</sup>, Kimura Yasumasa<sup>2</sup>, Satoshi Uematsu<sup>2</sup>, Hirotoshi Tanaka, Kazuhiko Yamamoto<sup>1</sup>: <sup>1</sup>The Department of Allergy and Rheumatology, The University of Tokyo Hospital, <sup>2</sup>Division of Innate Immune Regulation, International Research and Development Center for Mucosal Vaccine, Institute of Medical Science, The University of Tokyo

T cell lymphopenia results in peripheral homeostatic expansion in order to maintain the T cell im-

mune system, which is termed lymphopenia-induced proliferation (LIP). LIP is a potential risk for expanding autoreactive clones to become pathogenic in human and murine autoimmune diseases. However, the ontogeny of T cells that induce autoantibody production by autoreactive B cells in LIP remains unclear. Transfer of CD4<sup>+</sup>CD25<sup>-</sup> conventional T (Tc) cells into T-cell-deficient athymic nude mice has been previously reported as a LIP-induced autoimmune model which develops organ-specific autoimmune diseases and systemic antinuclear antibodies (ANAs). We show here that via LIP in this model, Tc cells proliferated and differentiated into PD-1<sup>+</sup>CXCR5<sup>-</sup> B-helper T cells, which promoted splenic germinal center (GC) formation, provided help for autoantibody-producing B cells, and had distinctive features of follicular helper T (Tfh) cells except that they lacked CXCR5. Intestinal microbiota were essential for their generation, since depletion of intestinal microbiota in recipient mice by antibiotics resulted in a reduction of LIP-induced PD-1<sup>+</sup>CXCR5<sup>-</sup> B-helper T cells and an amelioration of autoimmune responses. Our findings will contribute to the elucidation of the mechanism of lymphopenia-induced autoimmunity and autoantibody production, and will pave the way for microbiota-targeted novel therapeutic approaches to systemic autoimmune diseases.

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

Noritada Yoshikawa, Osamu Hosono, Masaaki Uehara, Aya Oda, Erika Matsubara, Hiroyuki Baba, Naoki Ito, Yuki Tasaka, Takako Maruyama, Akiko Kuribara, Tsutomu Murakami, Yuji Nakamura, Akne Fukuda, Toshiki Eri, Noriaki Shimizu, Hirotoshi Tanaka

Reduction of skeletal muscle mass and resulting weakness of peripheral and respiratory muscles cause various clinical problems such as fatigue, frailty, compromised lung function, and worse quality of life. Maintaining skeletal muscle mass and strength, therefore, is critical to preserve full activity, prevent obesity, and decrease the risk of heart disease, diabetes, and cancer. In rheumatology field, reduction of skeletal muscle mass and strength are often critical to negatively affect prognosis of the patients. Especially, prolonged glucocorticoid (GC) treatment for rheumatic disorders accelerates skeletal muscle atrophy known as GC-induced myopathy. However, there is no standardized intervention to prevent or treat this GC side effect. To overcome this issue, we have studied precise mechanisms of GC-induced skeletal muscle atrophy and revealed that administration of branched-

chain amino acids (BCAA) ameliorates GC-induced muscle atrophy in animal model. Therapeutic effects of BCAA, however, have been reported to be controversial, most possibly because of the absence of standard protocol and evaluation procedure of treatment outcome. Given this, we precisely studied the administration procedure of BCAA in rodent model of GC-induced myopathy and found that bolus oral administration is mandatory to elicit such extent of mTOR activation that restores muscle mass. Moreover, we established the quantitative methods for assessing GC-induced skeletal muscle atrophy in patients with rheumatic disorders, compared with bioelectrical impedance analysis (BIA), computed tomography (CT), and magnetic resonance imaging (MRI). Based on this research, we conducted a clinical trial in IMSUT Hospital (See below). Moreover, we are now challenging to identify non-invasive biomarkers for detecting the subjects affected or at risk of GC-induced myopathy and various types of muscle atrophy.

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

**Hirotoishi Tanaka, Noritada Yoshikawa, Noriaki Shimizu, Erika Matsubara, Hiroyuki Baba, Akiko Souta-Kuribara, Masaaki Uehara, Aya Oda, Osamu Hosono, Shigeru Kiryu<sup>1</sup>, Fumitaka Nagamura<sup>2</sup>:** <sup>1</sup>Department of Radiology, IMSUT Hospital, <sup>2</sup>Division of Advanced Medicine Promotion, Advanced Clinical Research Center, IMSUT

To test the effects of bolus supplementation of branched-chain amino acids (BCAA) on skeletal muscle mass, strength, and function in patients with rheumatic disorders taking glucocorticoid (GC), we conducted a Phase I-II open label, randomized, and parallel group clinical trial.

Patients with rheumatic disorders treated with prednisolone ( $\geq 10\text{mg/day}$ ) were randomized to ingest additional daily 12g of BCAA ( $n=9$ ) or not ( $n=9$ ) for 12 weeks. BCAA supplementation was achieved by drinking commercially available concentrated BCAA drink Amino-value CONC<sup>®</sup> (Otsuka Pharmaceutical, Co., Ltd., Tokyo, Japan) containing BCAA in 100ml solution; valine, 500mg; leucine, 1,000mg; isoleucine, 500mg (2g as BCAA). BCAA (+) patients were designed to take 2 bottles of Amino-value CONC<sup>®</sup> three times a day after each meal. At baseline, and 4, 8, and 12 weeks, they underwent bioelectrical impedance analysis (BIA), muscle strength and functional tests, and computed tomography (CT) analysis for cross sectional area (CSA) of mid-thigh muscle.

Disease activities of the patients were well controlled and daily GC dose was similarly reduced in

both groups, indicating that bolus oral supplementation of BCAA did not exacerbate disease activity of the patients, and was almost tolerable. Limb muscle mass was recovered in both groups. Whole-body muscle mass and muscle strength and functional mobility were increased only in BCAA (+) group. The effects of BCAA supplementation on recovering skeletal muscle mass were prominent in particular muscles such as trunk muscles and biceps femoris muscle.

This trial is the first-in-man clinical trial to demonstrate that BCAA supplementation might be safe and, at least in part, improve skeletal muscle mass, strength, and function in patients with rheumatic disorders treated with GC.

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

**(Collaborative project of IMSUT and IMSUT Hospital)**

The team of Professor Hiroshi Kiyono (Division of Mucosal Immunology, IMSUT) succeeded in developing a molecularly uniform rice-based oral cholera vaccine (MucoRice-CTB) by using an over-expression 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 IMSUT, which was approved as GMP (Good Manufacturing Practices) factory by the Japanese Ministry of Health, Labour and Welfare in 2014. Osamu Hosono (Department of Rheumatology and Allergy, IMSUT Hospital), PI of this clinical trial, and collaborators prepared a "First-in-man" clinical trial phase I study of MucoRice-CTB in cooperation of many departments of the hospital. After the consultation with PMDA (Pharmaceuticals and Medical Devices Agency) in January 2015, this clinical trial was registered at UMIN Clinical Trial Registry (UMIN000018001) and approved by the Institutional Review Board of IMSUT (26-55) in March 2015. The randomized, double-blind, dose-escalation, placebo-controlled study was launched in June 2015 and the results of this clinical trial will be published in near future.

## Publications

- Ono T, Kamimura N, Matsuhashi T, Nagai T, Nishiyama T, Endo J, Hishiki T, Nakanishi T, Shimizu N, Tanaka H, Ohta S, Suematsu M, Ieda M, Sano M, Fukuda K, Kaneda R. The histone 3 lysine 9 methyltransferase inhibitor chaetocin improves prognosis in a rat model of high salt diet-induced heart failure Sci Rep 7: 39752 (2017) doi: 10.1038/srep39752
- Matsubara E, Yoshikawa N, Hosono O, Baba H, Eri T, Uehara M, Oda A, Sekita C, Taniguchi A, and Tanaka H. A rheumatoid arthritis patient complicated with adenine phosphoribosyltransferase deficiency and unilateral renal agenesis: a first case report. Mod Rheumatol Case Rep. In press.
- Yoshikawa N, Shimizu N, Uehara M, Oda A, Matsumiya R, Matsubara E, Kobayashi H, Hosono O, Kuribara-Souta A, Baba H, Nagamura F, Kiryu S, and Tanaka H. The effects of bolus supplementation of branched-chain amino acids on skeletal muscle mass, strength, and function in patients with rheumatic disorders during glucocorticoid treatment. Mod Rheumatol. In press DOI: 10.1080/14397595.2016.1213480.
- Kobayashi H, Uehara M, Oda A, Matsubara E, Baba H, Matsumiya R, Yoshikawa N, Hosono O, Tanaka H. Normal pressure hydrocephalus, a possible complication in IgG4-related disease. Interdiscip Neurosurg. 5: 1-2, 2016.
- Ishii H, Konuma T, Ohnuma K, Hosono O, Tanaka H, Kato S, Tojo A, Takahashi S. Remission of remitting seronegative symmetrical synovitis with pitting edema after unrelated cord blood transplantation for myelodysplastic syndrome. Ann Hematol. 95(3): 523-4, 2016.

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*We are challenging to cure intractable hematological disorders such as leukemia and lymphoma with the aid of hematopoietic stem cell transplantation (HSCT). Our major stem cell source for recipients without suitable family donors is unrelated cord blood, with which no less than 20 adult patients receive cord blood transplantation (CBT) annually. Since 1998, we have performed over 400 cases of CBT, which appears a distinguished experience in the world.*

*Recent advances in identification of tumor-specific therapeutic targets resulted in a series of rationally designed therapeutic agents. In the field of hematological malignancies, we have already experienced remarkable clinical efficacies of molecular targeted drugs including tyrosine kinase inhibitors for Philadelphia-chromosome positive leukemia, monoclonal antibodies for CD20<sup>+</sup> B cell lymphoma and CCR4<sup>+</sup> adult T cell leukemia/lymphoma (ATL), and proteasome inhibitors and immunomodulatory drugs for multiple myeloma, respectively. We extensively apply these molecular targeted therapies for in- and out-patients. Furthermore, our department is one of the hub facilities in Japan for clinical practice and clinical research in ATL and Langerhans cell histiocytosis (LCH), both of which are rare and intractable tumors.*

1. Exploratory introduction of cognitive computing (AI) to clinical sequencing in blood disorders.

Yokoyama K<sup>1,7</sup>, Yokoyama N<sup>2,6</sup>, Kobayashi M<sup>3</sup>, Nakamura S<sup>3</sup>, Isobe M<sup>1</sup>, Jimbo K<sup>1</sup>, Ogawa M<sup>1</sup>, Ochi K<sup>1</sup>, Hirano M<sup>1</sup>, Kawamata T<sup>1</sup>, Konuma T<sup>1</sup>, Kato S<sup>1</sup>, Ohno N<sup>1</sup>, Imai Y<sup>1</sup>, Uchimaru K<sup>1</sup>, Taka-

hashi S<sup>1,3</sup>, Shimizu E<sup>4</sup>, Yamaguchi R<sup>4</sup>, Imoto S<sup>5</sup>, Furukawa Y<sup>2,6</sup>, Miyano S<sup>4</sup>, Tojo A<sup>1,3</sup>: <sup>1</sup>Department of Hematology/Oncology, IMSUT Hospital, <sup>2</sup>Department of Applied Genomics, IMSUT Hospital, <sup>3</sup>Division of Molecular Therapy, <sup>4</sup>Laboratory of Genome Database, <sup>5</sup>Division of Health Medical Data Science, <sup>6</sup>Division of Clinical Genome Research, <sup>7</sup>Center for Gene and Cell Therapy

Next-generation sequencing (NGS) is an attractive tool for prospective use in the field of clinical oncology. However, for this purpose, further innovations are necessary including medical informatics which links somatic mutations to clinical intervention. This process is currently labor-intensive, involving experienced curators who pick up the relevant evidence among a growing body of knowledge and translate it into medical practice. We organized a clinical sequencing team, called as IMSUT Tumor Board, and have been integrating clinical and genomic information in hematological malignancies with the aid of cognitive computing or artificial intelligence (AI). Genomic DNA was prepared from malignant cell fractions and normal tissues in each patient, and subjected to comparative NGS, mainly targeted deep sequencing with ready-made panels and, on demand, whole exome sequencing and or RNA sequencing. Sequence data was analyzed using a pipeline of in-house semi-automated medical informatics. AI was used to identify candidate driver mutations and pathways in each patient, from which pathogenic information as well as applicable drug information was deduced. A summary of NGS data was reported and discussed in IMSUT Tumor Board to deliberate upon potentially actionable findings. Until Nov. 2016, we performed NGS analysis on 113 patients with AML, MDS, MPN, et al., among which actionable findings could be obtained in 27 patients. Eight patients actually received treatments motivated in IMSUT Tumor Board. Our preliminary results indicate that AI can be well suited to clinical sequencing.

## 2. Analysis of severe opportunistic infections after mogamulizumab therapy for aggressive ATL

Takei T, Ohno N, Ogawa M, Takeda R, Kawamata T, Yokoyama K, Fukuyama T, Uchimaru K, Tojo A

Mogamulizumab (MOG) is a humanized anti-CCR4 monoclonal antibody and shows significant clinical activity in adult T-cell leukemia/lymphoma (ATL). In our department, MOG is usually administered to relapsed and refractory ATL cases or older patients not eligible for allogeneic stem cell transplantation (allo-SCT), considering its unfavorable

impact on allo-SCT. In this study, we performed retrospective analysis of the clinical outcome of MOG therapy in relapsed and refractory ATL and the incidence of therapy-related severe opportunistic infection. Between June 2012 and March 2016, we administered MOG to 24 patients (M:F=12:12) containing 18 acute type, 3 lymphoma type and 3 high-risk chronic type. Overall response rate (CR+PR) was 33% in relapsed and refractory ATL cases (CR 3, PR 4, SD 3, PD 13). Twelve patients received MOG in combination with chemotherapy, and among those, the episodes of severe opportunistic infection were observed in 4 patients (33%). These include varicella, corynebacterium bacteremia/peritonitis, disseminated mucormycosis, and mycobacterium genavense infection. HBV reactivation was observed in another 1 patient. The remaining 12 patients with MOG monotherapy did not develop severe opportunistic infection. In comparative analysis, severe opportunistic infection occurred in 2 out of 34 patients (6%) treated with chemotherapy only. Our results suggest that MOG in combination with chemotherapy may be a risk factor for severe opportunistic infection in ATL cases, and that careful survey and rapid diagnosis of infection is necessary in such a situation.

## 3. Three cases of therapy-related and MLL-rearranged myeloid neoplasms following adult T-cell leukemia

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

There is a limited number of reports about secondary malignancies following adult T-cell leukemia/lymphoma (ATL). One of the reasons for this rarity may be attributable to its very poor prognosis. Here, we describe therapy-related myeloid neoplasms with the MLL gene rearrangement in 3 patients with ATL, two of which were acute type disease and treated with a VP16-containing regimen (modified LSG), followed by (Pt.2) or combined with (Pt.3) several cycles of mogamulizumab, anti-CCR4 monoclonal antibody. The remaining one (Pt.1) was chronic type and given with oral low-dose VP16. Pts. 1 and 2 developed AML after the latent periods (between exposure to cytotoxic agents and diagnosis) of 47 and 25 months, respectively. Pt.3 was complicated by CMML after only 10 months of latent periods. Cytogenetic study showed 11q23 abnormalities; t(6;11)(q27;q23) in Pt.1 and add(11)(q23)x2 in Pt.2, t(11;22)(q23;q13) in Pt.3. FISH analysis using the MLL gene probe revealed their split signals in all cases. MLL gene rearrangements in therapy-related leukemias are found mainly following a treatment with anti-topoisomerase II or an intercalating topoisomerase II inhibi-

tor, and so is the case in our patients. Curiously, it appears that development of secondary neoplasms was rather accelerated following mogamulizumab, especially in Pt.3, although it effectively eliminates not only ATL cells but also effector regulatory T cells and acts like an immune checkpoint inhibitor. Careful survey of similar events is needed in ATL patients who receive chemotherapy and mogamulizumab.

#### 4. Clinical profile and BRAF status of adult Langerhans cell histiocytosis in Japan: 10-year single institution experience

Miho Ogawa<sup>1</sup>, Kobayashi M<sup>2</sup>, Takeda R<sup>1</sup>, Ochi K<sup>1</sup>, Takei T<sup>1</sup>, Kawamata T<sup>1</sup>, Yokoyama K<sup>1,3</sup>, Ohno N<sup>1</sup>, Takahashi S<sup>1,2</sup>, Uchimaru K<sup>1</sup>, Tojo A<sup>1,2</sup>: <sup>1</sup>Department of Hematology/Oncology, IMSUT Hospital, <sup>2</sup>Division of Molecular Therapy, <sup>3</sup>Center for Gene and Cell Therapy

During the last decade, there has been a significant progress in the clinical and basic research in Langerhans Cell Histiocytosis (LCH), the latter of which includes an identification of BRAF-V600E as a major driver mutation. However, the clinical profile and treatment outcome in adult LCH is still poorly documented. We report here a single-institution analysis of the clinical features of adult LCH.

We performed retrospective analysis of 28 patients referred to our hospital since 2005. BRAF-V600E was examined by allele-specific quantitative PCR (AS-qPCR) using cell-free DNA (cfDNA) and also by immuno-histochemical staining of biopsy specimens. Patient's median age at diagnosis was 43 (range 24-66) and 50% was female. Twelve patients (43%) had a single organ disease (single-system; SS) and others had multi-organ disease (multi-system; MS). Bone (50%) and skin (25%) were main lesions in SS-LCH patients, which were younger (median 39) than MS-LCH patients (median 45). High-risk organ such as lung, liver, spleen and bone marrow was involved in 8 MS-LCH patients. AS-qPCR analysis of BRAF-V600E was performed in 21 patients, resulting in positive data in only 5 MS-LCH patients. Twenty-two patients received Japan LCH Study Group (JLSG) Special C regimen consisting of vinblastine, prednisolone and methotrexate with daily 6-mercaptopurine, and 3 refractory patients were followed by 2-CdA as a salvage therapy. During their clinical courses, two MS-LCH patients died of LCH progression and a cerebrovascular event, respectively. BRAF-V600E load in cfDNA correlated with the disease progression. Since adult LCH is quite rare, the diagnosis is generally delayed but the prognosis is rather favorable. BRAF-V600E in cfDNA may be under-esti-

mated since significant parts of patients had already received chemotherapy at the blood sampling. Recent findings of MAPK and PI3K pathway mutation in LCH will facilitate the understanding of its pathogenesis and future molecular therapy.

#### 5. MYD88 L265P Mutated Splenic Marginal Zone Lymphoma associated with Cold Agglutinin Disease.

Ochi K<sup>1</sup>, Yokoyama K<sup>1,8</sup>, Yokoyama N<sup>2,6</sup>, Kobayashi M<sup>3</sup>, Ogawa M<sup>1</sup>, Takeda R<sup>1</sup>, Takei T<sup>1</sup>, Kawamata T<sup>1</sup>, Fukuyama T<sup>1</sup>, Ohno N<sup>1</sup>, Takahashi S<sup>1,3</sup>, Uchimaru K<sup>1</sup>, Yamaguchi R<sup>4</sup>, Imoto S<sup>5</sup>, Furukawa Y<sup>2,6</sup>, Miyano S<sup>4</sup>, Ohta Y<sup>7</sup>, Tojo A<sup>1,3</sup>: <sup>1</sup>Department of Hematology/Oncology, IMSUT Hospital, <sup>2</sup>Department of Applied Genomics, IMSUT Hospital, <sup>3</sup>Division of Molecular Therapy, <sup>4</sup>Laboratory of Genome Database, <sup>5</sup>Division of Health Medical Data Science, <sup>6</sup>Division of Clinical Genome Research, <sup>7</sup>Department of Pathology, IMSUT Hospital, <sup>8</sup>Center for Gene and Cell Therapy

Splenic marginal zone lymphoma (SMZL) is a rare low-grade B cell lymphoma accounting for less than 2% of lymphoid neoplasm and often associated with autoimmune disorders, although their pathogenic correlation remains unclear. We report here a case of SMZL preceded by chronic cold agglutinin disease (CAD). A 48-year-old woman presented severe anemia due to steroid-refractory CAD, and was referred to our hospital for progressive systemic illness and high fever. On admission she showed elevated serum soluble IL-2R and mild splenomegaly. She was pathologically diagnosed as SMZL by splenectomy and received 8 cycles of rituximab every 2 weeks, resulting in marked improvement of anemia. Lymphoma cells were positive for CD5/CD11c/CD20/CD23, phenotypically compatible with SMZL. Targeted deep sequencing of spleen and bone marrow specimens identified MYD88 L265P mutation, which is a most recurrent (>90%) mutation in Waldenström macroglobulinemia /lymphoplasmacytic lymphoma (LPL) and also found in 5-15% of SMZL. MYD88 is an adaptor molecule in toll-like receptor (TLR) and IL-1R signaling, and its activating mutation such as L265P triggers IRAK-mediated NF-κB signaling essential for B cell activation. Although a strong correlation was previously indicated between the presence of MYD88 L265P and monoclonal IgM paraproteinemia, it was not evident in our case probably due to sustained prior steroid therapy. Nevertheless, the present case is categorized into a small subgroup of SMZL which shares the common pathogenic (MYD88 L265P) and clinical (CAD) features with LPL.

## Publications

- Oshima Y, Tanimoto T, Yuji K, Tojo A. Association between aortic dissection and systemic exposure of vascular endothelial growth factor receptor (VEGFR)-inhibitors in the Japanese Adverse Drug Event Report database. *Circulation* 2016 *accepted for publication*
- Shimada N, Ohno N, Tanosaki R, Yuji K, Uchimaru K, Tojo A. Therapy-related acute myeloid leukemia after the long-term administration of low-dose etoposide for chronic-type adult T-cell leukemia/lymphoma: A case report and literature review. *Int Med* 2016 Jul 13. pii: 1049909116658641. [Epub ahead of print]
- Konuma T, Kiyuna T, Miharu Y, Suzuki M, Shibata H, Kato S, Takahashi S, Tojo A. Breakthrough fungemia due to *Candida fermentati* with fks1p mutation under micafungin treatment in a cord blood transplant recipient. *Transplant Infect Dis*. 2016 Nov 15. doi: 10.1111/tid.12634. [Epub ahead of print]
- Yasu T, Konuma T, Kato S, Kurokawa Y, Takahashi S, Tojo A. Different effects of lansoprazole and rabeprazole on the plasma voriconazole trough levels in allogeneic hematopoietic cell transplant recipients. *Ann Hematol*. 95(11): 1845-91, 2016
- Kubo T, Kiryu S, Arai H, Ota Y, Tojo A, Yoshida H, Kato N, Nakano Y, Ohtomo K. Hepatic involvement of histiocytic sarcoma: CT and MR imaging findings. *Kor J Radiol*. 17(5): 758-62, 2016
- Takei T, Konuma T, Takahashi S, Miharu Y, Suzuki M, Shibata H, Ishii H, Kato S, Takahashi S, Tojo A. Multi-locus sequence analysis for identification of *Achromobacter xylosoxidans* from positive blood culture bottle in cord blood transplant recipient. *Infect Dis*. 48(11-12): 864-6, 2016
- Oshima Y, Yuji K, Tojo A. "Imatinib induced-gastric antral vascular ectasia" in a reporting system of the Japanese Adverse Drug Event Report database (JADER). *Int J Hematol*. 103(5): 596-8, 2016
- Kawamata T, Ogawa M, Takei T, Takeda R, Ochi K, Yokoyama K, Fukuyama T, Ohno N, Uchimaru K, Tojo A. An adult case of biphenotypic acute leukemia with t(6;14)(q25;q32). *Atlas Gen Cytogen Oncol Hematol*. in press 2016 On line version: <http://AtlasGeneticsOncology.org/Reports/t0614q25q32KawamataID100080.html>
- Kamoi, K, Nagata Y, Mochizuki M, Uchimaru K, Tojo A, Ohno-Matsui K. Formation of segmental rounded nodules during the infiltration of adult T-cell leukemia cells into ocular mucous membrane. *Cornea*. 35(1): 137-9, 2016

## IMSUT Hospital

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*Our department has been working on the application of human genome information in clinics. As clinical services in IMSUT Hospital, we provide genetic counseling, genetic tests for human malignancies such as leukemia and cancer, and a surveillance program for patients with hereditary colorectal cancer. In addition, we have been carrying out two research projects; 1) determination of genetic alterations in human tumors, and elucidation of the mechanisms underlying their development, and 2) clinical sequence for the implementation of genomic medicine*

### 1. Genetic test of human neoplasms

Nozomi Yusa, Yoichi Furukawa

As a part of clinical service, we have performed genetic analysis of human neoplasms such as leukemia and colorectal cancer. In 2016, a total of 595 genetic analyses were performed in our department. The results were utilized for the precise classification of neoplasms, evaluation of disease status, selection of therapeutic drugs, and evaluation of the response to treatment.

### 2. Genetic counseling and related activities

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

We provided genetic counseling and genetic tests to clients who visited our counseling clinic. In 2016, we had a total of 38 counseling cases including familial breast cancer, Lynch syndrome, familial adenomatous polyposis, Peutz-Jeghers syndrome, 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.

### 3. Elucidation of genetic characteristics of human tumors and mechanisms of their development

Kiyoshi Yamaguchi<sup>1</sup>, Tsuneo Ikenoue, Yoichi Furukawa: <sup>1</sup>Division of Clinical Genome Research, Advanced Clinical Research Center

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



eration sequencing (NGS).

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

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

#### 4. Clinical sequence for the implementation of genomic medicine

Kiyoshi Yamaguchi<sup>1</sup>, Tsuneo Ikenoue, Yoichi Furukawa, Mitsuhiro Komura<sup>2</sup>, Eigo Shimizu<sup>2</sup>, Rui Yamaguchi<sup>2</sup>, Tetsuo Shibuya<sup>3</sup>, Satoru Miyano<sup>2,3</sup>, Takanori Hasegawa<sup>4</sup>, Seiya Imoto<sup>4</sup>, Masayuki Kobayashi<sup>5</sup>, Kazuaki Yokoyama<sup>5</sup>, Arinobu Tojyo<sup>5</sup>, Koichiro Yuji<sup>6</sup>: <sup>1</sup>Division of Clinical Genome Research, Advanced Clinical Research Center, <sup>2</sup>Laboratory of DNA Information Analysis, <sup>3</sup>Laboratory of Sequence Analysis, Human Genome Center, <sup>4</sup>Di-

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NGS has enabled us to analyze the comprehensive human genome, and facilitated the identification of germline changes responsible for hereditary diseases and somatic alterations in human neoplasms. In collaboration with Human Genome Center, Health Intelligence Center, and Advanced Clinical Research Center, we have been working on the following projects; 1) the determination of germline mutations in patients suspected of hereditary colon tumor, 2) application of a cognitive computing system, namely IBM Watson Genomic Analytics (WGA), for the personalized medicine. These projects are aimed to use the information of personal genome and/or cancer genome in clinic, and apply the data for their diagnosis and treatment.

In the first project, we applied NGS technology for patients with multiple adenomatous polyps in the colon. In the patients, we previously failed to identify pathological mutations within the 5' two-thirds region of the *APC* gene by Sanger sequencing. However, NGS successfully identified pathological mutations in three of the patients; two were somatic mosaic mutations of *APC*, and the other was a very rare mutation in the 3' terminal region of *APC*. In addition, whole genome sequencing identified a promoter deletion of ~10kb encompassing promoter 1B and exon1B of the *APC* gene. These data have corroborated the usefulness of NGS in clinical diagnosis of familial cancer.

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

#### Publications

1. Noguchi, R., Yamaguchi, K., Ikenoue, T., Terakado, Y., Ohta, Y., Yamashita, N., Kainuma, O., Yokoi, S., Maru, Y., Nagase, H. and Furukawa, Y. Genetic alterations in Japanese extrahepatic biliary tract cancer. *Oncol. Lett.* 2016 in press.
2. Gohda, Y., Noguchi, R., Horie, T., Igari, T., Nakamura, H., Ohta, Y., Yamaguchi, K., Ikenoue, T., Hatakeyama, S., Yusa, N., Furukawa, Y. and Yano, H. Pseudomyxoma peritonei of a mature ovarian teratoma caused by mismatch repair deficiency in a patient with Lynch syndrome: a case report. *BMC Med. Genet.* 17(1): 94, 2016.
3. Yamaguchi, K., Nagayama, S., Shimizu, E., Komura, M., Yamaguchi, R., Shibuya, T., Arai, M., Hatakeyama, S., Ikenoue, T., Ueno, M., Miyano, S., Imoto, S. and Furukawa, Y. Reduced expression of APC-1B but not APC-1A by the deletion of promoter 1B is responsible for familial adenomatous polyposis. *Sci. Rep.* 6: 26011, 2016.
4. Ikenoue, T., Terakado, Y., Nakagawa, H., Hikiba,

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Y., Fujii, T., Matsubara, D., Noguchi, R., Zhu, C., Yamamoto, K., Kudo, Y., Asaoka, Y., Yamaguchi, K., Ijichi, H., Tateishi, K., Fukushima, N., Maeda, S., Koike, K. and Furukawa, Y. A novel mouse

model of intrahepatic cholangiocarcinoma induced by liver-specific *Kras* activation and *Pten* deletion. Sci. Rep. 6: 23899, 2016.

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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.*

### Impact of hepatocellular carcinoma heterogeneity on non-contrast-enhanced computed tomography as a prognostic indicator

Kiryu S, Akai H, Nojima M<sup>1</sup>, Hasegawa K<sup>2</sup>, Shin-kawa H<sup>2</sup>, Norihiro Kokudo<sup>2</sup>, Koichiro Yasaka, Kuni Ohtomo<sup>3</sup>: <sup>1</sup>Division of Advanced Medicine Promotion, The Advanced Clinical Research Center, The Institute of Medical Science, University of Tokyo, <sup>2</sup>Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Graduate School of Medicine, University of Tokyo, <sup>3</sup>International University of Health and Welfare

We investigated the relationship between the heterogeneity of hepatocellular carcinoma (HCC) on preoperative non-contrast-enhanced computed tomography (CT) and patient prognosis. Institutional review board waiver was obtained for this retrospective analysis. The heterogeneity of CT images from 122 patients between January 2004 and September 2009 was assessed using a Laplacian of Gaussian spatial band-pass filter, and texture feature parameters such as mean, standard deviation (SD), entropy, mean of the positive pixels (MPP),

skewness, and kurtosis were obtained at three different filter levels and without filtration. The relationship between CT texture features and 5-year overall survival (OS) or disease-free survival (DFS) was assessed. Patients were dichotomized according to the best cut-off values calculated by the log-rank test to classify the outcome of OS or DFS. The likelihood ratio test was performed to evaluate the effect of each CT texture feature on clinical parameters. The Kaplan-Meier curves for OS or DFS was significantly different between patient groups dichotomized by cut-off values for all CT texture parameters with filtration at at least one filter level. Without filtration, OS or DFS was significantly different for some CT texture parameters. Multivariate Cox proportional hazard regression analysis showed significant effects of most CT texture parameters on OS with filtration at at least one filter level and without filtration except kurtosis. SD, entropy and MPP with coarse filter, and skewness without filtration showed a significant effect on DFS. The CT texture features of non-contrast-enhanced CT images showed a relationship with HCC prognosis

## **Influence of Indocyanine Green on Hepatic Gd-EOB-DTPA Uptake: A Proof-of-Concept Study in Mice**

**Akai H, Yasaka K, Nojima M, Inoue Y<sup>4</sup>, Ohtomo K, Kiryu S:** <sup>4</sup>Department of Diagnostic Radiology, Kitasato University School of Medicine

We performed this experiment to explore whether indocyanine green (ICG) inhibits hepatic uptake of gadolinium ethoxybenzyl-diethylenetriaminepenta-acetic acid (Gd-EOB-DTPA). Groups of six female C57BL6 mice were injected with 5mg/kg ICG, 20mg/kg ICG, or phosphate-buffered saline (control group) 10 min prior to the injection of Gd-EOB-DTPA; identical three-dimensional gradient echo T1-weighted images were subsequently obtained to create time-intensity curves and to measure the peak enhancements in liver parenchyma. We studied both hypo- and normo-thermic mice. Peak enhancements for all experimental conditions were evaluated and among-group differences were assessed using two-way factorial analysis of variance with Bonferroni post hoc testing. As a result, the time-intensity curves of the three groups gradually increased from 5 to 30 min and almost plateaued after 30 min in hypothermic mice. The extent of enhancement decreased as the amount of injected ICG increased. In normothermic animals, the time-intensity curves of the control and ICG 5mg/kg groups peaked 10-15 min after injection, the peak enhancements were very similar, and the intensities thereof then gradually fell until 60 min. Compared with these groups, the ICG 20mg/kg group exhibited lower peak enhancement and a weaker decrease in intensity to 60 min. Both the amount of ICG injected ( $p < 0.001$ ) and the experimental temperature ( $p < 0.001$ ) significantly affected the measurements. In conclusion, ICG inhibits the hepatic uptake of Gd-EOB-DTPA and affects the signal intensity upon Gd-EOB-DTPA-enhanced magnetic resonance imaging. Such inhibition was more obvious in hypothermic mice.

## **Computed tomography and magnetic resonance imaging of a plexiform angiomyxoid myofibroblastic tumor: a case report**

**Akai H, Kiryu S, Shinozaki M<sup>5</sup>, Ohta Y<sup>6</sup>, Nakano Y<sup>7</sup>, Yasaka K, Ohtomo K:** <sup>5</sup>Department of Surgery, Institute of Medical Science, University of Tokyo, <sup>6</sup>Department of Pathology, Institute of Medical Science, University of Tokyo, <sup>7</sup>Department of Radiology, Graduate School of Medicine, University of Tokyo

Plexiform angiomyxoid myofibroblastic tumor (PAMT) is a very rare mesenchymal tumor of the stomach. Here we present a case of pathologically

confirmed PAMT with a unique cyst formation. A 55-year-old male with a 10-year history of a gastric submucosal tumor underwent computed tomography (CT) and magnetic resonance imaging (MRI). Two cysts were observed in the tumor, and the cyst wall showed moderately high intensity on T2-weighted images compared with the gastric wall. On dynamic study, the cyst wall showed a gradual enhancement pattern, and prominent enhancement was observed in the delayed phase. Laparoscopic partial gastric resection was performed, and a pathological diagnosis of PAMT was rendered. We present a rare case of PAMT. One of the cysts in the tumor in our case had an epithelial wall lining, which had never been reported before in gastric mesenchymal tumor. Also partial glandular structure was seen within the tumor. The cause of this unique cyst is unclear, but several hypotheses regarding its formation are posited.

## **Quantitative computed tomography texture analysis for estimating histological subtypes of thymic epithelial tumors**

**Yasaka K, Akai H, Nojima M, Shinozaki-Ushiku A<sup>8</sup>, Fukayama M<sup>8</sup>, Nakajima J<sup>9</sup>, Ohtomo K, Kiryu S:** <sup>8</sup>Department of Pathology, Graduate School of Medicine, The University of Tokyo, <sup>9</sup>Department of Thoracic Surgery, Graduate School of Medicine

We investigated whether high-risk thymic epithelial tumor (HTET) can be differentiated from low-risk thymic epithelial tumor (LTET) using computed tomography (CT) quantitative texture analysis. The data of 39 patients who underwent thymectomy for thymic epithelial tumor were retrospectively analyzed. Texture analysis was performed for images with or without a Laplacian of Gaussian filter (with various spatial scaling factors [SSFs]). Two radiologists evaluated the visual heterogeneity of TET using a 3-point scale. The texture parameter of mean in the unfiltered image (mean0u) and entropy in the filtered image featuring coarse texture (entropy6u) for UECT, and the mean in the unfiltered image (mean0c) for CECT were significant parameters for differentiating between HTET and LTET as determined by logistic regression analysis. The area under the receiver operating characteristics curve for differentiating HTET from LTET using mean0u/entropy6u/mean0u and entropy6u in combination/mean0c was 0.75/0.76/0.87/0.89. Entropy6u provided a higher diagnostic performance compared with visual heterogeneity analysis ( $p \leq 0.018$ ). In conclusion, using CT quantitative texture analysis, HTET can be differentiated from LTET with a high diagnostic performance.

## **Precision of quantitative computed tomography texture analysis using image filtering: a phantom study for scanner variability**

**Yasaka K, Akai H, Mackin D<sup>10</sup>, Court L<sup>10</sup>, Moros E<sup>11</sup>, Kuni Ohtomo:** <sup>10</sup>Department of Radiation Physics, University of Texas MD Anderson Cancer Center, <sup>11</sup>Department of Radiation Oncology, Diagnostic Imaging, and Cancer Imaging and Metabolism, H Lee Moffitt Cancer Center and Research Institute

We investigated how quantitative texture parameters using image filtering vary among different computed tomography (CT) scanners using a phantom developed for radiomics studies. A phantom, consisting of 10 different cartridges with various textures, was scanned under six different scanning protocols using four CT scanners from four different vendors. CT texture analyses were performed for both unfiltered images and filtered images (using a Laplacian of Gaussian spatial band-pass filter) featuring fine, medium, and coarse textures. Forty-five regions of interest were placed for each cartridge (x) in a specific scan image set (y), and the average of the texture values ( $T(x,y)$ ) was calculated. The interquartile range (IQR) of  $T(x,y)$  among the six scans was calculated for a specific cartridge ( $IQR(x)$ ), while the IQR of  $T(x,y)$  among the 10 cartridges was calculated for a specific scan ( $IQR(y)$ ), and the median  $IQR(y)$  was then calculated for the six scans (as the control IQR,  $IQR_c$ ). The median of their quotient ( $IQR(x)/IQR_c$ ) among the 10 cartridges was defined as the variability index (VI). The VI was relatively small for the mean in unfiltered images (0.011) and for standard deviation (0.020-0.044) and entropy (0.040-0.044) in filtered images, indicating that these parameters were relatively robust among different scanners. Skewness and kurtosis in filtered images featuring medium and coarse textures were relatively variable across different CT scanners, with VIs of 0.638-0.692 and 0.430-0.437, respectively. The behavior of these quantitative CT texture parameters should be taken into consideration in applying study results reported in articles or performing studies regarding quantitative CT texture analyses.

## **Quantitative computed tomography texture analyses for anterior mediastinal masses: differentiation between solid masses and cysts**

**Yasaka K, Akai H, Abe O<sup>7</sup>, Ohtomo K, Kiryu S**

We investigated whether solid anterior mediastinal masses could be differentiated from cysts using quantitative computed tomography (CT) texture analyses. This clinical retrospective study included 76 unenhanced CT (UECT) images and 84 contrast

enhanced CT (CECT) images of anterior mediastinal masses, which were diagnosed histopathologically or using imaging criteria. CT histogram analyses for images of masses with or without filtration were performed. In logistic regression analyses, a combination of the mean in unfiltered images (mean0; i.e., CT attenuation) and mean in filtered images featuring coarse texture for UECT (area under the receiver operator characteristics curve (AUC)=0.870) and the combination of mean0 and entropy in filtered images featuring fine texture for CECT (AUC=0.997) could predict the internal characteristics of anterior mediastinal masses. In UECT and CECT, diagnostic performance using these combinations tended to be high compared to mean0 alone (AUC=0.780 [p=0.033] and AUC=0.983 [p=0.130], respectively). Solid anterior mediastinal masses can be differentiated from cysts using quantitative CT texture analyses with moderate to high diagnostic performance.

## **Anomalous branching pattern of the portal vein**

**Yasaka K, Akai H, Kiryu S**

We reported a rare branching pattern of the portal vein with clinical relevance. The branching pattern of the main portal vein (MPV) is classified as type I (MPV bifurcates into the right portal vein and left portal vein), type II (MPV trifurcates into the right anterior portal vein, right posterior portal vein, and left portal vein), and type III (the right posterior portal vein originates from the MPV, after which the MPV ramifies into the right anterior portal vein and left portal vein). With abdominal dynamic computed tomography in a patient, we found extremely rare variant in branching pattern of MPV in which right posterior portal vein ramified from left portal vein and which cannot be classified as the patterns described above. Recognition of this variant is important prior to surgical or interventional radiological strategies.

## **Clinical applicability of new generation computed tomography image reconstruction technique**

**Yasaka K, Akai H, Kiryu S, Maeda E<sup>7</sup>, Sato J<sup>7</sup>, Kuni Ohtomo**

Computed tomography (CT) images have been reconstructed using filtered back projection (FBP) technique. Using this technique, images can be reconstructed in almost real time, however, image quality was deteriorated in several situations; when arms are not raised for scans of torso, when scanned at reduced radiation dose level, and when metal is present within the scan range. We investigated whether new generation computed tomogra-

phy image reconstruction techniques, such as full iterative reconstruction (IR) algorithms and single energy metal artifact reduction (SEMAR), are useful in these situations. And we found the followings; full IR enables artifact reduction for abdominal CT in patients scanned without arm elevation, full IR enables 28% radiation dose reduction for coronary

CT while improving image quality, full IR provides diagnostically more acceptable high-resolution CT images for the detailed analyses of lung nodules, and SEMAR enables significant metal artifact reduction and significant improvement in image quality for CT examinations of the oropharyngeal region and the pelvic region.

## Publications

- Akai H, Kiryu S, Shibata E, Maeda E, Sato J, Tomizawa N, Nojima M, Ohtomo K. Reducing CT radiation exposure with organ effective modulation: A retrospective clinical study. *Eur J Radiol.* 85(9): 1569-73, 2016.
- Yasaka K, Akai H, Kiryu S. Anomalous branching pattern of the portal vein: right posterior portal vein originating from the left portal vein. *Surg Radiol Anat.* 2016 Oct 3. [Epub ahead of print]
- Akai H, Kiryu S, Ohta Y, Yasaka K, Nakano Y, Inoue Y, Ohtomo K. The natural history of streptozotocin-stimulated non-alcoholic steatohepatitis mice followed by MRI: comparison with simple steatosis mice. *Magn Reson Imaging.* 2017 Jan 3. [Epub ahead of print]
- Akai H, Kiryu S, Shinozaki M, Ohta Y, Nakano Y, Yasaka K, Ohtomo K. Computed tomography and magnetic resonance imaging of a plexiform angiomyxoid myofibroblastic tumor: a case report *BMC Medical Imaging.* in press.
- Hagiwara A, Akai H, Kosaka T, Suyama Y, Ogura K, Kawauchi N. A Dorsal Pancreatic Artery Originating from the Right Inferior Phrenic Artery. *J Vasc Interv Radiol.* 27(1): 143-5, 2016. 17 (5): 758-62, 2016.
- Kotani Y, Ohgami Y, Yoshida N, Kiryu S, Inoue Y. Anticipation process of the human brain measured by stimulus-preceding negativity (SPN), *T J Sports Med Phys Fitness.* in press.
- Kubo T, Kiryu S, Akai H, Ota Y, Tojo A, Yoshida H, Kato N, Nakano Y, Ohtomo K. Hepatic Involvement of Histiocytic Sarcoma: CT and MRI Findings. *Korean J Radiol.*
- Maeda E, Tomizawa N, Kanno S, Yasaka K, Kubo T, Ino K, Torigoe R, Ohtomo K. Subjective and objective evaluation of 10-30% dose reduced coronary artery phantom scans reconstructed with Forward projected model-based Iterative Reconstruction SoluTion (FIRST). *Data Brief* 10: 210-214, 2016.
- Maeda E, Tomizawa N, Kanno S, Yasaka K, Kubo T, Ino K, Torigoe R, Ohtomo K. The feasibility of Forward-projected model-based Iterative Reconstruction SoluTion (FIRST) for coronary 320-row computed tomography angiography: A pilot study. *J. Cardiovasc. Comput. Tomogr.* 2016 Nov 9 [Epub ahead of print]
- Yasaka K, Furuta T, Kubo T, Maeda E, Katsura M, Sato J, Ohtomo K. Full and hybrid iterative reconstruction to reduce artifacts in abdominal CT for patients scanned without arm elevation. *Acta Radiol.* 2016 Jan 1 [Epub ahead of print]
- Yasaka K, Maeda E, Hanaoka S, Katsura M, Sato J, Ohtomo K. Single-energy metal artifact reduction for helical computed tomography of the pelvis in patients with metal hip prostheses. *Jpn. J. Radiol.* 34: 625-32, 2016.
- Yasaka K, Kamiya K, Irie R, Maeda E, Sato J, Ohtomo K. Metal artefact reduction for patients with metallic dental fillings in helical neck computed tomography: comparison of adaptive iterative dose reduction 3D (AIDR 3D), forward-projected model-based iterative reconstruction solution (FIRST) and AIDR 3D with single-energy metal artefact reduction (SEMAR). *Dentomaxillofac. Radiol.* 45: 20160114, 2016.
- Yasaka K, Katsura M, Akahane M, Sato J, Matsuda I, Ohtomo K. Model-based iterative reconstruction and adaptive statistical iterative reconstruction: dose-reduced CT for detecting pancreatic calcification. *Acta Radiol. Open.* 5: 2058460116628340, 2016.
- Yasaka K, Katsura M, Sato J, Akahane M, Matsuda I, Ohtomo K. Comparison of new and conventional versions of model-based iterative reconstruction in reduced-dose computed tomography for diagnosis of hepatic steatosis. *Jpn. J. Radiol.* 34: 339-48, 2016.
- Yasaka K, Katsura M, Hanaoka S, Sato J, Ohtomo K. High-resolution CT with new model-based iterative reconstruction with resolution preference algorithm in evaluations of lung nodules: Comparison with conventional model-based iterative reconstruction and adaptive statistical iterative reconstruction. *Eur. J. Radiol.* 85: 599-606, 2016.

## IMSUT Hospital

# Department of Surgery 外科

Associate Professor Masaru Shinozaki, M.D., Ph.D.  
Senior Assistant Professor Giichiro Tsurita, M.D., Ph.D.  
Assistant Professor Kentaro Yazawa, M.D., Ph.D.

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講師 医学博士 釣田 義一郎  
助教 医学博士 谷澤 健太郎

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

### 1. Surgical treatment in 2016

**Masaru Shinozaki, Giichiro Tsurita, Kentaro Yazawa, Tomohiro Kurokawa**

We are consolidated, and performed operations. Dr. Sameshima and Dr. Kawamura have been unstinting in their support for our operations, especially in the technical field of laparoscopic colorectal surgery. Our target organs are stomach, intestine, anus, gallbladder, liver, biliary tract, pancreas, and spleen, as well as abdominal wall. Recently, breast cancer has become a particular field only for highly specialized physicians bearing knowledge in this field. Dr. Iwase has maintained supporting our out-patient clinic.

### 2. Endoscopic examination in 2016

**Masaru Shinozaki, Giichiro Tsurita, Kentaro Yazawa, Yoko Taten, Tomohiro Kurokawa**

Under cooperation with Department of Advanced Medical Science, we performed 789 upper gastrointestinal endoscopies and 1047 colonoscopies without major complications. For the patients' satisfaction, we aggressively perform endoscopic resec-

tion of colorectal neoplasms and avoid operation as much as possible. Our fellows (Y.T. and T.K.) have learned gastrointestinal endoscopic technique and have made great progress.

### 3. Clinical Research.

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

**Masaru Shinozaki, Giichiro Tsurita, Kentaro Yazawa, Tomohiro Kurokawa**

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 the cancer is predominantly at right hemi-colon, 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 prepared to make questionnaire and send to hospitals to clarify the clini-

copathological characteristics.

## B. Surveillance colonoscopy for ulcerative colitis

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

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

## C. Evaluation of Clinical Guidelines

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

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

## D. Genome Study for colorectal Neoplasm

**Masaru Shinozaki**

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

## E. Clinicopathological studies in inflammatory bowel disease

**Masaru Shinozaki**

As an attending institute of inflammatory bowel disease group supported by the Ministry of Health, Labor and Welfare, we join the clinical projects on studies in inflammatory bowel disease.

## 4. Basic research

### A. Viral therapy against cancer

**Yoko Taten, Tomoki Todo (Department of Advanced Cancer Therapy), Masaru Shinozaki**

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

## 5. Clinical trials

### A. Survivin peptide vaccine for pancreatic cancer

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

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

## Publications

1. Shinozaki M, Kobayashi K, Kunisaki R, Hisamatsu T, Naganuma M, Takahashi K, Iwao Y, Suzuki Y, Watanabe M, Itabashi M, Torii A, Takazoe M, Sugita A. Surveillance for Dysplasia in Patients with Ulcerative Colitis: Discrepancy between Guidelines and Practice. *Digestive Endoscopy* (in press)
2. Akai H, Kiryu S, Shinozaki M, Ohta Y, Nakano Y, Ohtomo K. Computed tomography and magnetic resonance imaging of a plexiform angiomyxoid myofibroblastic tumor: a case report. *BMC medical imaging* (in press)
3. 三枝直人, 三枝純一, 横山 正, 大澤高明, 石黒成治, 篠崎 大, 菊池 学, 横山泰久. 痔瘻で初発したクローン病症例に対し“Top down療法”は有効である. *日本大腸肛門病学会雑誌* 69(8): 424-9, 2016.
4. 黒川友博, 篠崎 大. 腸炎まるわかり 回腸囊炎 (Pouchitis) 消化器内視鏡 (in press)
5. 篠崎 大. Crohn病—狭窄形成術 外科 78(12): 1407-12, 2016.



## IMSUT Hospital

# Department of Anesthesia 麻酔科

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

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*Our clinical practice and clinical studies have been focused on (1) anesthetic management in patients undergoing major surgery including joint arthroplastic surgery for hemophilia patients, variable surgical procedures for translational researches (2) assessment of reliability of cardiac output measurements (3) 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. Assessment of reliability of cardiac output measurements.

Knowing a patient's cardiac output (CO) could contribute to a safe, optimized hemodynamic control during surgery. Precise CO measurements can serve as a guide for resuscitation therapy, catecho-

lamine use, differential diagnosis, and intervention during a hemodynamic crisis. Despite its invasiveness and intermittent nature, the thermodilution technique via a pulmonary artery catheter (PAC) remains the clinical gold standard for CO measurements. LiDCOrapid™ (LiDCO, London, UK) and FloTrac/Vigileo™ (Edwards Lifesciences, Irvine, CA) are less invasive continuous CO monitors that use arterial waveform analysis.

### 3. Risk management of medical electronic devices.

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

## Publications

1. Asamoto M, Orii R, Otsuji M, Bougaki M, Imai Y, Yamada Y. Reliability of cardiac output measurements using LiDCOrapid™ and FloTrac/Vigileo™ across broad ranges of cardiac output values. J Clin Monit Comput. 2016 Jun 14.
2. Satorou I, Asamoto M, Orii R, Yamada Y. Detection of Spinal Anesthesia Effect by Measuring a Pulse Oximeter Based Toes Perfusion Index. The 16th World Congress of Anaesthesiologists, 2016. WCA16-ABS-1976
3. 赤兎真一, 折井亮, 朝元雅明, 井上哲, 山田芳嗣. PPVとSPVの関係. 日本麻酔科学会第63回学術集会, プログラム:P2-01, 2016
4. 井上哲, 朝元雅明, 折井亮, 山田芳嗣. PI(PERFUSION INDEX)を用いた脊髄くも膜下麻酔の効果推定. 日本麻酔科学会第63回学術集会, プログラム:P2-02, 2016

## IMSUT Hospital

# Department of Joint Surgery

## 関節外科

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

講師 医学博士 竹谷 英之  
助教 医学博士 大野 久美子

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

### Surgical treatment for haemophilia

From 2006 to 2016, more than 200 surgical treatments for hemophilia included other coagulation diseases such as deficiency factor VII or Von Wille-

brand disease. Some of them have the deficiency factor antibody as well.

In 2016, we were performed 15 surgical treatments (6 total joint arthroplasties, 5 arthroscopic synovectomies and 4 other surgical treatments).

### Publications

1. Goto M, Haga N, Yokota K, Takamizawa K, Takedani H. A successful physiotherapy management case of a patient with acquired haemophilia A prior to factor VIII inhibitor eradication. *Haemophilia*. 2016 May; 22(3): e228-31.
2. Goto M, Takedani H, Yokota K, Haga N. Strategies to encourage physical activity in patients with hemophilia to improve quality of life. *Journal of blood medicine*. 2016; 7: 85-98.
3. Hirose J, Takedani H, Kubota M, Kinkawa J, Noguchi M. Total hip arthroplasty and total knee arthroplasty in a patient with congenital deficiency of plasminogen activator inhibitor-1. *Haemophilia*. 2016 May; 22(3): e237-9.
4. Masaoka T, Amano K, Takedani H, Suzuki T, Otaki M, Seita I, et al. Usefulness of a simple self-administered joint condition assessment sheet to predict the need for orthopaedic intervention in the management of haemophilic arthropathy. *Haemophilia*. 2016 Dec 11.
5. Shinkoda Y, Shirahata A, Fukutake K, Takamatsu J, Shima M, Hanabusa H, et al. A phase III clinical trial of a mixture agent of plasma-derived factor VIIa and factor X (MC710) in haemophilia patients with inhibitors. *Haemophilia*. 2016 Aug 1.
6. Takedani H, Hirose J, Minamoto F, Kubota M, Kinkawa J, Noguchi M. Major orthopaedic surgery for a haemophilia patient with inhibitors using a new bypassing agent. *Haemophilia*. 2016 Sep; 22(5): e459-61.

## IMSUT Hospital

# Department of Surgical Neuro-Oncology

## 脳腫瘍外科

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Project Associate Professor	Minoru Tanaka, M.D., Ph.D.
Senior Assistant Professor	Hiroyuki Momota, M.D., Ph.D.
Assistant Professor	Seisaku Kanayama, M.D.

教授	医学博士	藤	堂	具	紀
准教授	医学博士	稲	生		靖
特任准教授	医学博士	田	中		実
講師	医学博士	百	田	洋	之
助教		金	山	政	作

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

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

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

### A clinical study of G47Δ in patients with progressive olfactory neuroblastoma

A phase I clinical trial of G47Δ in patients with progressive olfactory neuroblastoma was approved

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

### Surgical treatment of brain tumor patients

Our department started treating in-patients in April 2012. Standard craniotomies and image guided stereotactic biopsies of deep seated lesions, as well as high-tech brain tumor resections have been performed. The high-tech equipment regularly used in brain tumor resection surgeries includes an operative microscope, a 3-D neuro-navigation system, intraoperative motor evoked potential monitoring, intraoperative ultrasonography and an ultrasonic surgical aspirator.

### Treatment of primary central nervous system lymphoma

Primary central nervous system lymphoma patients will first undergo biopsy for pathological diagnosis. In addition to the standard therapy regimen using high-dose methotrexate followed by radiotherapy, an advanced treatment regimen utilizing rituximab, methotrexate, procarbazine, and vincristine (R-MPV) therapy followed by consolidation whole-brain radiation therapy has been used as a treatment option.

### **Outpatient clinic**

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

## IMSUT Hospital

# Department of Palliative Medicine

## 緩和医療科

Professor	Arinobu Tojo, M.D., D.M.S
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
特任講師	医学博士	岩	瀬		哲
特任助教	医学士	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.*

### Publications

- Mori M, Shirado AN, Morita T, Okamoto K, Matsuda Y, Iwase S. Predictors of response to corticosteroids for dyspnea in advanced cancer patients: a preliminary multicenter prospective observational study. *Support Care Cancer*. Nov 29, 2016
- Ishiki H, Iwase S. Non-surgical treatment for locally advanced head and neck squamous cell carcinoma: beyond the upper limit. *Transl. Cancer Res*. 5(2): 98-102, 2016
- Kaneishi K, Imai K, Iwase S. Use of olanzapine for the relief of nausea and vomiting in patients with advanced cancer: a multicenter survey in Japan. *Support Care Cancer*. 2016
- Iwase S, Ishiki H, Watanabe A, Shimada N, Chiba T, Kinkawa J, Tojo A. Mapisal Versus Urea Cream as Prophylaxis for Capecitabine -Associated Hand-Foot Syndrome. *J Clin Oncol*. 34: 391, 2016
- Iwase S, Kawaguchi T, Yotsumoto D, Doi T, Miyara K, Odagiri H, Kitamura K, Ariyoshi K, Miyaji T, Ishiki H, Inoue K, Tsutsumi C, Sagara Y, Yamaguchi T. Efficacy and safety of an amino acid jelly containing coenzyme Q10 and L-carnitine in controlling fatigue in breast cancer patients receiving chemotherapy: a multi-institutional, randomized, exploratory trial (JORTC-CAM01). *Support Care Cancer*. 24: 637-46, 2016
- Shinozaki T, Ebihara M, Iwase S, Yamaguchi T, Hirakawa H, Shimbashi W, Kamijo T, Okamoto M, Beppu T, Ohori J, Matsuura K, Suzuki M, Nishino H, Sato Y, Ishiki H. Quality of life and functional status of terminally ill head and neck cancer patients: a nation-wide, prospective observational study at tertiary cancer centers in Japan. *Jpn J Clin Oncol*. 2016
- Matsuo N, Morita T, Matsuda Y, Okamoto K, Matsumoto Y, Kaneishi K, Odagiri T, Sakurai H, Hiramoto S, Watanabe T, Kohara H, Shimoyama S, Aruga E, Baba M, Sumita K, Iwase S. Predictors of Responses to Corticosteroids for Cancer-Related Fatigue in Advanced Cancer Patients: A Multicenter, Prospective, Observational Study. *J Pain Symptom Manage*. 52(1): 64-72, 2016
- Matsuo N, Morita T, Matsuda Y, Okamoto K, Matsumoto Y, Kaneishi K, Odagiri T, Sakurai H, Hiramoto S, Watanabe T, Kohara H, Shimoyama S,

- Aruga E, Baba M, Sumita K, Iwase S. Predictors of responses to corticosteroids for anorexia in advanced cancer patients: a multicenter prospective observational study. *Support Care Cancer*. 2016
- Shimada N, Ishiki H, Iwase S, et al. Cancer Transitional Care for Terminally Ill Cancer Patients Can Reduce the Number of Emergency Admissions and Emergency Department Visits. *Am J Hosp Palliat Care*. 2016
- Oshima Y, Tanimoto T, Yuji K, Tojo A. Association between aortic dissection and systemic exposure of vascular endothelial growth factor receptor (VEGFR)-inhibitors in the Japanese Adverse Drug Event Report database. *Circulation* 2016
- Shimada N, Ohno N, Tanosaki R, Yuji K, Uchimaruk K, Tojo A. Therapy-related acute myeloid leukemia after the long-term administration of low-dose etoposide for chronic-type adult T-cell leukemia/lymphoma: A case report and literature review. *Int Med* 2016
- Konuma T, Kiyuna T, Mihar Y, Suzuki M, Shibata H, Kato S, Takahashi S, Tojo A. Breakthrough fungemia due to *Candida fermentati* with *fkp1* mutation under micafungin treatment in a cord blood transplant recipient. *Transplant Infect Dis*. 2016
- Tominaga K, Shimamura T, Kimura N, Murayama T, Matsubara D, Kanauchi H, Niida A, Shimizu S, Nishioka K, Tsuji E, Yano M, Sugano S, Shimono Y, Ishii H, Saya H, Mori M, Akashi K, Tada K, Ogawa T, Tojo A, Miyano S, Goto N. Addiction to the IGF2-ID1-IGF2 circuit for maintenance of the breast cancer stem-like cells. *Oncogene* 2016
- Yasu T, Konuma T, Kato S, Kurokawa Y, Takahashi S, Tojo A. Different effects of lansoprazole and rabeprazole on the plasma voriconazole trough levels in allogeneic hematopoietic cell transplant recipients. *Ann Hematol*. 95(11): 1845-91, 2016
- Kubo T, Kiryu S, Arai H, Ota Y, Tojo A, Yoshida H, Kato N, Nakano Y, Ohtomo K. Hepatic involvement of histiocytic sarcoma: CT and MR imaging findings. *Kor J Radiol*. 17(5): 758-62, 2016
- Takei T, Konuma T, Takahashi S, Mihar Y, Suzuki M, Shibata H, Ishii H, Kato S, Takahashi S, Tojo A. Multi-locus sequence analysis for identification of *Achromobacter xylosoxidans* from positive blood culture bottle in cord blood transplant recipient. *Infect Dis*. 48(11-12): 864-6, 2016
- Ishii H, Konuma T, Kato S, Oiwa-Monna M, Tojo A, Takahashi S. Impact of hematogones on the long-term outcomes of single-unit cord blood transplantation for adult patients. *Leuk lymphoma*. 58(1):118-26, 2016
- Konuma T, Kato S, Oiwa-Monna M, Ishii H, Tojo A, Takahashi S. Early phase mixed chimerism in bone marrow does not affect long-term outcomes of myeloablative single-unit cord blood transplantation for adult patients with hematological malignancies. *Leuk lymphoma*. 57(12): 2848-94, 2016
- Oshima Y, Yuji K, Tojo A. "Imatinib induced-gastric antral vascular ectasia" in a reporting system of the Japanese Adverse Drug Event Report database (JADER). *Int J Hematol*. 103(5): 596-8, 2016
- Murayama T, Nakaoku T, Nishimura T, Tominaga K, Nakata A, Tojo A, Sugano S, Kohno T, Gotoh N. Oncogenic fusion gene encodes CD74-NRG1 confers cancer stem cell-like properties in lung cancer through a IGF2 autocrine/paracrine circuit. *Cancer Res*. 76(4): 974-83, 2016
- Yamamoto H, Lu J, Oba S, Kawamata T, Yoshimi A, Kurosaki N, Yokoyama K, Matsushita H, Kurokawa M, Tojo A, Ando K, Morishita K, Katagiri K, Kotani A. miR-133 regulates *Evi1* expression in AML cells as a potential therapeutic target. *Sci Rep*. 6: 19204, 2016
- Kawamata T, Ogawa M, Takei T, Takeda R, Ochi K, Yokoyama K, Fukuyama T, Ohno N, Uchimaruk K, Tojo A. An adult case of biphenotypic acute leukemia with t(6; 14) (q25; q32). *Atlas Gen Cytogen Oncol Hematol*. in press 2016
- Konuma T, Kato S, Oiwa-Monna M, Ishii H, Tojo A, Takahashi S. Comparison of graft-versus-host disease-free, relapse free survival of transplantation using matched sibling donor, matched unrelated donor, or unrelated cord blood after myeloablative conditioning for adult patients with hematological malignancies. *Leuk Lymphoma*. 57(9): 2126-32, 2016
- Ishii H, Konuma T, Ohnuma K, Hosono O, Tanaka H, Kato S, Tojo A, Takahashi S. Remission of remitting seronegative symmetrical synovitis with pitting edema after unrelated cord blood transplantation for myelodysplastic syndrome. *Ann Hematol*. 95(3): 523-4, 2016
- Mukai T, Nagamura-Inoue T, Mori Y, Shimazu T, Takahashi A, Tsunoda H, Yamaguchi S, Tojo A. Neurosphere formation enhances the neurogenic differentiation potential and migratory ability of umbilical cord-mesenchymal stromal cells. *Cytotherapy*. 18(2): 229-41, 2016
- Hori A, Agata H, Takaoka M, Tojo A, Kagami H. Effect of cell seeding conditions on the efficiency of *in vivo* bone formation. *Int J Oral Maxillofac Implants*. 31(1): 232-9, 2016
- Kamoi K, Nagata Y, Mochizuki M, Uchimaruk K, Tojo A, Ohno-Matsui K. Formation of segmental rounded nodules during the infiltration of adult T-cell leukemia cells into ocular mucous membrane. *Cornea*. 35(1): 137-9, 2016
- Konuma T, Kato S, Ooi J, Ebihara Y, Mochizuki S, Ishii H, Takei T, Oiwa-Monna M, Tojo A, Takahashi S. Second allogeneic transplantation using unrelated cord blood for relapsed hematological malignancies after allogeneic transplantation. *Leuk Lymphoma*. 57(1): 103-9, 2016

## IMSUT Hospital

# Department of Medical Informatics

## 医療情報部

Associate Professor Shigeru Kiryu, M.D., D.M.Sc.  
 Senior Assistant Professor Hiroyuki Akai, M.D., D.M.Sc.  
 Assistant Professor Koichiro Yasaka, M.D., D.M.Sc.

准教授 医学博士 桐 生 茂  
 講師 医学博士 赤 井 宏 行  
 助教 医学博士 八 坂 耕一郎

*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 hos-

pital. We are considering that introduction of the electronic health record network will be able to improve to introduce among regional clinic, hospital, and the IMSUT hospital in the regional medical cooperation.

*IMSUT Hospital*

# Department of Radiological Technology

## 放射線部

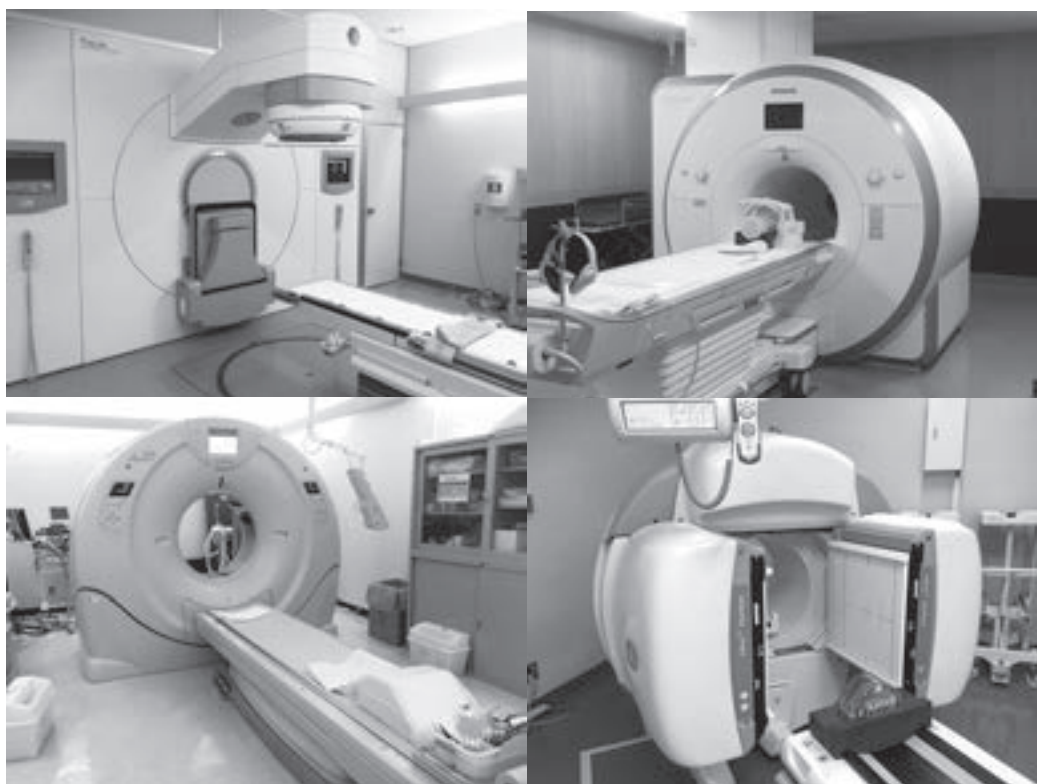
Associate Professor  
Head Radiologic Technologist

Shigeru Kiryu, M.D., D.M.Sc.  
Yoshiro Satake, RT

准教授 医学博士  
放射線技師長

桐 生 茂  
佐 竹 芳 郎

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



## IMSUT Hospital

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

Professor Arinobu Tojo, M.D., PhD.  
Associate Professor Tokiko Nagamura-Inoue, M.D., PhD.  
Assistant Professor Toyotaka Kawamata, M.D., PhD.

教授 医学博士 東 條 有 伸  
准教授 医学博士 長 村 登紀子  
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. In addition to 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 Cord Blood Bank (RCBB) Cells Bank as National Bioresource Project (NBRP) supported by AMED(MEXT) and CB and umbilical cord (UC)-derived mesenchymal stromal cell (MSC) banking for clinical use supported by AMED(MHLW). And we developed immunosuppressive therapy for severe GVHD after hematopoietic stem cell transplantation, using UC-MSCs or expanded regulatory T cells from CB and adult blood. We also explore the clinical application of UC-MSC for newborn encephalopathy, some of which develop to cerebral palsy.*

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

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

Umbilical cord (UC) is a rich source of mesenchymal stromal 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 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 AMED (MHLW). The UC-MSCs have the potential to inhibit the activated T cell proliferation upon the allogeneic stimulations, suggesting the clinical possibility to apply those for the GVHD treatment. Our final goal is to establish the CB and

UC-MSCs banking for clinical use.

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

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

Previous studies have been reported that MSCs have self-renewal capacity, multi-lineage differentiation potential and the ability to migrate toward sites of inflammation or injury. The potential of MSCs for transdifferentiating into not only mesoderm lineage but also endoderm and ectoderm, including the neural lineage, has enhanced the clinical application of MSCs for regenerative medicine including neurological disorders. We reported here that the umbilical cord-derived mesenchymal stromal cells (UC-MSCs) had the potential of neurogenic differentiation. Furthermore, the neurogenic lineage genes expressed more in differentiation via

neurosphere formation with higher expression of ES markers. The migration ability to damaged cells was not influenced by the neurosphere formation with or without differentiation into neurogenic cells. Newborn mice models mimicking intraventricular hemorrhage (IVH) which develops into cerebral palsy showed functional improvement by UC-MSCs injection. *in vivo*.

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

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

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

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

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

"Research Cord Blood Stem Cell Bank" (former

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

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

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

To promote the cell therapy in translational researches, IMSUT-Cell Resource Center (IMSUT-CRC) has been established in 1997 (originally called as Room for Clinical Cellular Technology (RCCT)). Until now, the following projects had implemented; 1) CB cell processing for banking(1997-2008) (for Tokyo Cord Blood Bank, Research cord blood stem cell bank, and related sibling donors), 2) Dendritic cell therapies (1998-2001), 3) Regenerative therapy of alveolar bone derived from bone marrow mesenchymal cells (2005-2011), 4) Gene therapy for renal cancer (1998), 5) CB and UC-MSCs banking (IMSUT-CORD) (2012-present), 6) Regenerative medicine for hemophilia arthropathy using autologous bone marrow-derived MSC (in preparation).

## Publications

- 1) Mitsuhashi K, Kako S, Shigematsu A, Atsuta Y, Doki N, Fukuda T, Kanamori H, Onizuka M, Takahashi S, Ozawa Y, Kurokawa M, Inoue Y, Nagamura-Inoue T, Morishima Y, Mizuta S, Tanaka J; Adult Acute Lymphoblastic Leukemia Working Group of the Japan Society for Hematopoietic Cell Transplantation. Comparison of Cyclophosphamide Combined with Total Body Irradiation, Oral Busulfan, or Intravenous Busulfan for Allogeneic Hematopoietic Cell Transplantation in Adults with Acute Lymphoblastic Leukemia. *Biol Blood Marrow Transplant*. 2016 Sep 13. pii: S1083-8791(16)30333-0. doi: 10.1016/j.bbmt.2016.09.007.
- 2) Ishiyama K, Yamaguchi T, Eto T, Ohashi K, Uchida N, Kanamori H, Fukuda T, Miyamura K, Inoue Y, Taguchi J, Mori T, Iwato K, Morishima Y, Nagamura-Inoue T, Atsuta Y, Sakamaki H, Takami A. Acute megakaryoblastic leukemia, unlike acute erythroid leukemia, predicts an unfavorable outcome after allogeneic HSCT. *Leuk Res*. 2016 May 12; 47: 47-53.
- 3) Sakai R, Taguri M, Oshima K, Mori T, Ago H, Adachi S, Morita S, Taniguchi S, Fukuda T, Ohashi K, Eto T, Miyamura K, Iwato K, Kobayashi N, Kanamori H, Morishima Y, Nagamura-Inoue T, Sakamaki H, Atsuta Y, Murata M. A comparison of tacrolimus and cyclosporine combined with methotrexate for graft-versus-host disease prophylaxis, stratified by stem cell source: a retrospective nationwide survey. *Int J Hematol*. 2016 Mar; 103(3): 322-33.
- 4) Mukai T, Nagamura-Inoue T, Shimazu T, Mori Y, Takahashi A, Tsunoda H, Yamaguchi S, Tojo A. Neurosphere formation enhances the neurogenic differentiation potential and migratory ability of umbilical cord-mesenchymal stromal cells. *Cytotherapy*. 18: 229-241, 2016.
- 5) Nishiwaki S, Imai K, Mizuta S, Kanamori H, Ohashi K, Fukuda T, Onishi Y, Takahashi S, Uchida N, Eto T, Nakamae H, Yujiri T, Mori S, Nagamura-Inoue T, Suzuki R, Atsuta Y, Tanaka

- J. Impact of MRD and TKI on allogeneic hematopoietic cell transplantation for Ph+ ALL: a study from the adult ALL WG of the JSHCT. *Bone Marrow Transplant.* 51: 43-50, doi: 10.1038/bmt.2015.217. 2016.
- 6) Arai Y, Kanda J, Nakasone H, Kondo T, Uchida N, Fukuda T, Ohashi K, Kaida K, Iwato K, Eto T, Kanda Y, Nakamae H, Nagamura-Inoue T, Morishima Y, Hirokawa M, Atsuta Y, Murata M. Risk factors and prognosis of hepatic acute GvHD after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant.* 51: 96-102, doi: 10.1038/bmt.2015.205. 2016.
- 7) Nagamura-Inoue T, Mukai T. Umbilical Cord is a Rich Source of Mesenchymal Stromal Cells for Cell Therapy. *Current Stem Cell Research & Therapy*, 11, 634-642, 2016

## IMSUT Hospital

# Surgical Center

## 手術部

Professor Tomoki Todo, M.D., Ph.D.  
Project Associate Professor Minoru Tanaka, M.D., Ph.D.

教授 医学博士 藤 堂 具 紀  
特任准教授 医学博士 田 中 実

*Our mission is the management and operation of the surgical center to achieve a safe and organized environment where surgical procedures can be performed in high quality. Our activities include the management of clean areas, establishment of protocols for infection control, maintenance of equipment such as astral lamps, surgical microscopes, and fiberscopes, and organizing of daily and weekly operations. Three of four operating rooms are maintained at a NASA class 10,000 clean level. One operating room is maintained at a NASA class 1,000 clean level and specifically designed for neurosurgery and joint surgery. For prompt and sustained supply of sterilized materials, we keep the surgical tools for each department in sets of designated purposes.*

### Equipment in the surgical center

The center is equipped with C-arm x-ray TV systems, surgical microscopes, ultrasonic aspirators, image guided navigation systems, intraoperative ultrasound imaging systems, intraoperative nerve simulation monitoring systems, etc. The endoscopic procedure rooms is located separately but adjacent to the surgical center.

### TV monitoring system

Each operating room is equipped with a TV camera, so that the rooms can be monitored in the control center as well as by pad devices carried by managing anesthesiologists.

### Induction of electronic ordering system

We are accelerating the induction of an electronic ordering system for the surgical center that allows a real time ordering by clinical departments and computerized management of operation schedules.

### Facts in the fiscal year 2015

Total number of operations	220
Planned operations	198
Emergency operations	12
General anesthesia	111
Spinal	120
Epidural	1
Local	35
Others	44

*IMSUT Hospital*

## Radiation control Office

### 放射線管理室

Associate Professor  
Senior Assistant Professor

Shigeru Kiryu, M.D., D.M.Sc.  
Hiroyuki Akai, M.D., D.M.Sc.

准教授 医学博士  
講師 医学博士

桐 生 茂  
赤 井 宏 行

*Our division has three major missions.*

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



## IMSUT Hospital

# Center for Translational Research

## TR・治験センター

Professor	Fumitaka Nagamura, M.D., D.M.Sc
Associate Professor	Masanori Nojima, M.D., Ph.D., M.P.H.
Project Associate Professor	Hiroshi Yasui, M.D., Ph.D.
Senior Assistant Professor	Sumimasa Nagai, M.D., Ph.D.

教授(兼任)	医学博士	長	村	文	孝
准教授(兼任)	医学博士	野	島	正	寛
特任准教授(兼任)	医学博士	安	井	寛	
講師(兼任)	医学博士	永	井	純	正

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

### 1. Promotion of Translational Research at IMSUT Research Hospital

**Minako Kouno, Erika Horibe, Mashiho Yanagi, Riyo Ohwada, Saori Minote, Sumimasa, Nagai, Hiroshi Yasui, Hiroshi Nojima, 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 Amai, Mitsumi Tokunaga, Fumitaka Nagamura**

We have planned and performed data management, monitoring, and statistical works in clinical trials.

[Data management]: Planning, EDC and CRF 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, Miwako Okada, Minako Kouno, Riyo Owada, Erika Horibe, Mashiho Yanagi, Saori Minote, Rie Arai, Eri Moriya, Miwako Mutoh, Satsuki Yonetomi, Fumitaka Nagamura**

Our research aims to develop efficient approaches for conducting investigator-initiated clinical trials under Investigational New Drug (IND) applications to promote translational research. In 2016, we were supporting by site management as well as project management for four investigator-initiated clinical trials under INDs applications for the development of academic-oriented innovative drugs. Currently, we are preparing a phase I trial of novel therapeutic cancer vaccines for hematological malignancies.

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

**Minako Kouno, Riyo owada, Fumitaka Nagamura**

TR is the early phase of clinical trials, which applied the developments of basic researches for patients with incurable and/or life-threatening diseases. Highly educated nurses are indispensable for the conducts of TRs in terms of the protection of participants in TRs and the conducts of scientifically appropriate TRs. We developed the scholastic program for the graduate students of nurses in the area of TR. We planned and implemented the one-week program to foster the expert research nurse aimed at the graduate students. It consists of the lectures on the feature points of TR (e.g. ethical considerations of TR, and the role of research nurse), role-plays of 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 type of clinical research including clinical research, basic medical/biological research. We have collaborated with other members in IMSUT and other institutions through the consulting.

## **Publications**

1. Meshitsuka S, Shingaki S, Hotta M, Goto M, Kobayashi M, Ukawa Y, Sagesaka YM, Wada Y, Nojima M, Suzuki K. Phase 2 trial of daily, oral epigallocatechin gallate in patients with light-chain amyloidosis. *Int J Hematol*. 2016. [Epub ahead of print]
2. Adachi Y, Nojima M, Mori M, Matsunaga Y, Akutsu N, Sasaki S, Endo T, Kurozawa Y, Wakai K, Tamakoshi A; for JACC Study. Insulin-like growth factor-related components and the risk of liver cancer in a nested case-control study. *Tumour Biol*. 2016. [Epub ahead of print]
3. Matsumoto T, Motoya S, Watanabe K, Hisamatsu T, Nakase H, Yoshimura N, Ishida T, Kato S, Nakagawa T, Esaki M, Nagahori M, Matsui T, Naito Y, Kanai T, Suzuki Y, Nojima M, Watanabe M, Hibi T; DIAMOND study group. Adalimumab Monotherapy and a Combination with Azathioprine for Crohn's Disease: A Prospective, Randomized Trial. *J Crohns Colitis*. 2016. [Epub ahead of print]
4. Akai H, Kiryu S, Shibata E, Maeda E, Sato J, Tomizawa N, Nojima M, Ohtomo K. Reducing CT radiation exposure with organ effective modulation: A retrospective clinical study. *Eur J Radiol*. 2016; 85: 1569-73.
5. Shimada N, Ishiki H, Iwase S, Chiba T, Fujiwara N, Watanabe A, Kinkawa J, Nojima M, Tojo A, Imai K. Cancer Transitional Care for Terminally Ill Cancer Patients Can Reduce the Number of Emergency Admissions and Emergency Department Visits. *Am J Hosp Palliat Care*. 2016. [Epub ahead of print]
6. Inazawa N, Hori T, Nojima M, Saito M, Igarashi K, Yamamoto M, Shimizu N, Yoto Y, Tsutsumi H. Virus reactivations after autolo-

- gous hematopoietic stem cell transplantation detected by multiplex PCR assay. *J Med Virol*. 2016. [Epub ahead of print]
7. Nitta J, Nojima M, Ohnishi H, Mori M, Wakai K, Suzuki S, Fujino Y, Lin Y, Tamakoshi K, Tamakoshi A. Weight Gain and Alcohol Drinking Associations with Breast Cancer Risk in Japanese Postmenopausal Women - Results from the Japan Collaborative Cohort (JACC) Study. *Asian Pac J Cancer Prev*. 2016; 17: 1437-43.
  8. Matsumoto K, Katanuma A, Maguchi H, Takahashi K, Osanai M, Yane K, Kin T, Takaki R, Matsumori T, Gon K, Tomonari A, Nojima M. Performance of novel tissue harmonic echo imaging using endoscopic ultrasound for pancreatic diseases. *Endosc Int Open*. 2016; 4: E42-50.
  9. Saito M, Yamashita K, Arimura Y, Kaneto H, Okuda H, Nojima M, Hagiwara T, Suzuki K, Adachi T, Goto A, Nakachi K, Yawata A, Yoshimoto M, Tanuma T, Adachi Y, Yamaoka S, Mizukoshi T, Kawayama M, Hamamoto Y, Shinomura Y. Serum HER2 as an adjunct to assess HER2 status for advanced gastric cancer: A prospective multicenter trial (SHERLOCK). *Acta Oncol*. 2016; 55: 309-17.
  10. Yoshikawa N, Shimizu N, Uehara M, Oda A, Matsumiya R, Matsubara E, Kobayashi H, Hosono O, Kuribara-Souta A, Baba H, Nagamura F, Kiryu S, Tanaka H. The effects of bolus supplementation of branched-chain amino acids on skeletal muscle mass, strength, and function in patients with rheumatic disorders during glucocorticoid treatment. *Mod Rheumatol*. in press
  11. Nagamura F. The Importance of Recruiting a Diverse Population for Stem Cell Clinical Trials. *Current Stem Cell Reports*. 2: 321-327, 2016
  12. 長村文孝 ウイルス療法のガイドライン・ガイドランスについて *実験医学* 34(1): 53-54, 2016
  13. 長村文孝 ウイルスを用いたがん治療における治験に向けたガイドライン作成の取り組み 次世代がん治療研究最前線 エヌ・ティー・エス印刷中

## IMSUT Hospital

# Center for Antibody and Vaccine Therapy

## 抗体・ワクチンセンター

Professor	Hirotohi Tanaka, M.D., D.M.Sc.
Project Professor	Yataro Daigo, M.D., D.M.Sc.
Associate Professor	Osamu Hosono, M.D., D.M.Sc.
Project Associate Professor	Hiroaki Taniguchi, M.D., D.M.Sc.
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特任教授	医学博士	醍醐弥太郎
准教授(兼任)	医学博士	細野治
特任准教授	医学博士	谷口博昭
特任講師	医学博士	高野淳
特任講師	工学博士	清水宣明
病院講師(兼任)	医学博士	吉川賢忠

*This center was established in April 1st, 2012, in the memory of Professor Shibasaburo Kitasato, the founder and the first director of our institute. Prof Kitasato was keen to utilize "serum therapy" for patients with infectious diseases and actually developed therapeutic sera from horses. Now, we can use monoclonal antibodies to cytokines and their receptors, growth factor receptors, cellular kinases, for treatment of autoimmune diseases and cancer. The aim of this center is to develop novel state-of-the-art therapy for patients with various diseases. Moreover, attractive clinical trials are also ongoing in collaboration with research groups in IMSUT. Part of the funding for this center was supported by the special grant from the Ministry of Education, Culture, Sports, Science and Technology, Japan from 2013-2017.*

### 1. Clinical activities of Division of Rheumatology in IMSUT Hospital

**Osamu Hosono, Noritada Yoshikawa, Toshiki Eri, Erika Matsubara, Hiroyuki Baba, Aya Oda, Masaaki Uehara, Hirotohi Tanaka**

Rheumatologists at our division provide state-of-the-art diagnosis and treatment for diseases that affect the joints and connective tissues (rheumatic diseases). 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. We, as rheumatologists, treat many types of arthritis and autoimmune diseases, including rheumatoid arthritis, osteoarthritis, and collagen vascular diseases (e.g., systemic lupus erythematosus, polymyositis, and vasculitic syndromes).

Rheumatologic services offered at IMSUT Hospital include:

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

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

### 2. Translational Research of Division of Rheumatology

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

### 3. Clinical Trial of Division of Rheumatology

#### (i) Effect of branched-chain amino acid - enriched beverage "Amino - Value [CONC.]" supplementation in patients with glucocorticoid - induced muscle atrophy (UMIN 000006972)

**Hirotooshi Tanaka, Noritada Yoshikawa, Noriaki Shimizu, Erika Matsubara, Hiroyuki Baba, Akiko Souta-Kuribara, Masaaki Uehara, Aya Oda, Osamu Hosono, Shigeru Kiryu<sup>1</sup>, Fumitaka Nagamura<sup>2</sup>:** <sup>1</sup>Department of Radiology, IMSUT Hospital, <sup>2</sup>Division of Advanced Medicine Promotion, Advanced Clinical Research Center, IMSUT

To test the effects of bolus supplementation of branched-chain amino acids (BCAA) on skeletal muscle mass, strength, and function in patients with rheumatic disorders taking glucocorticoid (GC), we conducted a Phase I-II open label, randomized, and parallel group clinical trial.

Patients with rheumatic disorders treated with prednisolone ( $\geq 10$  mg/day) were randomized to ingest additional daily 12 g of BCAA (n = 9) or not (n = 9) for 12 weeks. BCAA supplementation was achieved by drinking commercially available concentrated BCAA drink Amino-value CONC<sup>®</sup> (Otsuka Pharmaceutical, Co., Ltd., Tokyo, Japan) containing BCAA in 100 ml solution; valine, 500 mg; leucine, 1,000 mg; isoleucine, 500 mg (2g as BCAA). BCAA (+) patients were designed to take 2 bottles of Amino-value CONC<sup>®</sup> three times a day after each meal. At baseline, and 4, 8, and 12 weeks, they underwent bioelectrical impedance analysis (BIA), muscle strength and functional tests, and computed tomography (CT) analysis for cross sectional area (CSA) of mid-thigh muscle.

Disease activities of the patients were well controlled and daily GC dose was similarly reduced in both groups, indicating that bolus oral supplementation of BCAA did not exacerbate disease activity of the patients, and was almost tolerable. Limb muscle mass was recovered in both groups. Whole-body muscle mass and muscle strength and functional mobility were increased only in BCAA (+) group. The effects of BCAA supplementation on recovering skeletal muscle mass were prominent in particular muscles such as trunk muscles and biceps femoris muscle.

This trial is the first-in-man clinical trial to demonstrate that BCAA supplementation might be safe and, at least in part, improve skeletal muscle mass, strength, and function in patients with rheumatic disorders treated with GC.

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

The team of Professor Hiroshi Kiyono (Division of Mucosal Immunology, IMSUT) succeeded in developing a molecularly uniform rice-based oral cholera vaccine (MucoRice-CTB) by using an over-expression 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 IMSUT, which was approved as GMP (Good Manufacturing Practices) factory by the Japanese Ministry of Health, Labour and Welfare in 2014. Osamu Hosono (Department of Rheumatology and Allergy, IMSUT Hospital), PI of this clinical trial, and collaborators prepared a "First-in-man" clinical trial phase I study of MucoRice-CTB in cooperation of many departments of the hospital. After the consultation with PMDA (Pharmaceuticals and Medical Devices Agency) in January 2015, this clinical trial was registered at UMIN Clinical Trial Registry (UMIN000018001) and approved by the Institutional Review Board of IMSUT (26-55) in March 2015. The randomized, double-blind, dose-escalation, placebo-controlled study was launched in June 2015 and the results of this clinical trial will be published in near future.

### 4. Novel therapeutic target discovery for solid cancers

**Yataro Daigo, Atsushi Takano, Koji Teramoto, Hidetoshi Sumimoto, Yoshinori Murakami, Phung Manh Thang, Kayo Daigo, Masako Nakamura, Tomoyuki Igarashi**

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

in normal tissues by northern-blot analyses, iii) validation of the clinicopathological significance of its higher expression with tissue microarray containing thousands of archived solid cancers, iv) verification of a critical role of each target gene in the growth or invasiveness of cancer cells by RNAi and cell growth/invasion assays, v) evaluation of their usefulness as targets for passive immunotherapy using specific antibodies and/or as a serum biomarker for solid cancer by high throughput ELISA and proteomics analysis, if they are tumor-specific transmembrane or secretory proteins, vi) screening of the epitope peptides recognized by human histocompatibility leukocyte (HLA)-A\*0201- or A\*2402-restricted cytotoxic T lymphocyte (CTL) and dendritic cell (DC). This systematic approach identified dozens of molecules that appear to fall into the category of oncoantigens whose overexpression is an important feature of the malignant nature of cancer cells and that have very high immunogenicity to induce antigen-specific CTLs in cancer patients. We further validated these molecules identified as potential targets for the development of antibodies, small-molecular compounds, growth-suppressive cell-permeable peptides, and cancer vaccines that could have a more specific and strong anti-cancer effect with minimal risk of adverse events. During this process, cell division cycle associated 1 (CDCA1) was found to be activated in oral cavity carcinoma (OCC), and was suggested to be a novel prognostic biomarker and therapeutic target for OCC.

#### **5. Identification of variations in HLA class II and other loci associated with susceptibility to *EGFR*-mutated lung adenocarcinoma.**

**Yataro Daigo, Atsushi Takano**

Lung adenocarcinoma driven by somatic *EGFR* mutations is more prevalent in East Asians (30-50 %) than in European/Americans (10-20%). We investigate genetic factors underlying the risk of this disease by conducting a genome-wide association study, followed by two validation studies, in 3,173 Japanese patients with *EGFR* mutation-positive lung adenocarcinoma and 15,158 controls. Four loci, 5p15.33 (*TERT*), 6p21.3 (*BTNL2*), 3q28 (*TP63*) and 17q24.2 (*BPTF*), previously shown to be strongly associated with overall lung adenocarcinoma risk in East Asians, were re-discovered as loci associated with a higher susceptibility to *EGFR* mutation-positive lung adenocarcinoma. In addition, two additional loci, HLA class II at 6p21.32 and 6p21.1 (*FOXP4*) were newly identified as loci associated with *EGFR* mutation-positive lung adenocarcinoma. This study indicates that multiple genetic factors underlie the risk of lung adenocarcinomas with *EGFR* mutations.

#### **6. Identification of association between GWAS-identified lung adenocarcinoma susceptibility loci and *EGFR* mutations in never-smoking Asian women, and comparison with findings from Western populations.**

**Yataro Daigo, Atsushi Takano**

To evaluate associations by *EGFR* mutation status for lung adenocarcinoma risk among never-smoking Asian women, we conducted a meta-analysis of 11 loci previously identified in genome-wide association studies (GWAS). Genotyping in an additional 10,780 never-smoking cases and 10,938 never-smoking controls from Asia confirmed associations with eight known single nucleotide polymorphisms (SNPs). Two new signals were observed at genome-wide significance, namely, rs7216064 (17q24.3, *BPTF*), for overall lung adenocarcinoma risk, and rs3817963 (6p21.3, *BTNL2*) which is specific to cases with *EGFR* mutations. In further sub-analyses by *EGFR* status, rs9387478 (*ROS1-DCBLD1*) and rs2179920 (*HLA-DPB1*) showed stronger estimated associations in *EGFR*-positive compared to *EGFR*-negative cases. Comparison of the overall associations with published results in Western populations revealed that the majority of these findings were distinct, underscoring the importance of distinct contributing factors for smoking and non-smoking lung cancer. The results extend the catalog of regions associated with lung adenocarcinoma in non-smoking Asian women and highlight the importance of how the germline could inform risk for specific tumor mutation patterns.

#### **7. Identification of multiple lung cancer susceptibility loci in never-smoking Asian women by Meta-analysis of genome-wide association studies.**

**Yataro Daigo, Atsushi Takano**

To identify new susceptibility loci associated with lung cancer risk, we imputed data from four genome-wide association studies (GWAS) of Asian non-smoking female lung cancer (6877 cases and 6277 controls) using the 1000 Genomes Project (Phase 1 Release 3) data as the reference and genotyped additional samples (5878 cases and 7046 controls) for possible replication. In our meta-analysis, three new loci achieved genome-wide significance, marked by single nucleotide polymorphism (SNP) rs7741164 at 6p21.1, rs72658409 at 9p21.3 and rs11610143 at 12q13.13. These findings identified new genetic susceptibility alleles for lung cancer in never-smoking women in Asia and merit follow-up to understand their biological underpinnings.

## 8. Characterization of RAS-Mitogen-activated protein kinase signal that is required for enhanced PD-L1 expression in human lung cancers.

**Yataro Daigo, Hidetoshi Sumimoto, Atsushi Takano, Koji Teramoto**

Ectopic programmed cell death ligand 1 (PD-L1) expression in non-small cell lung cancers (NSCLCs) is related to immune evasion by cancer, and it is a molecular target of immune checkpoint therapies. Although some altered signals in NSCLCs are responsible for ectopic PD-L1 expression, the precise mechanisms remain obscure. Because we found a higher frequency of *EGFR/KRAS* mutations in NSCLC cell lines with high PD-L1 expression, we evaluated the relationships between downstream signals and PD-L1 expression, particularly in three *KRAS*-mutant adenocarcinoma cell lines. The MEK inhibitor U0126 significantly decreased the surface PD-L1 levels by 50-60% compared with dimethyl sulfoxide. Phorbol 12-myristate 13-acetate stimulation increased and two ERK2 siRNAs as well as *KRAS* siRNAs decreased PD-L1 expression. The transcriptional activity of the potential AP-1 site in the PD-L1 gene was demonstrated by luciferase assays, which was inhibited by U0126. The chromatin immunoprecipitation assay demonstrated the binding of cJUN to the AP-1 site. Two STAT3 siRNAs decreased PD-L1 expression by 10-32% in two of the three *KRAS*-mutant lung adenocarcinoma cell lines, while the PI3K inhibitor LY294002 did not change the expression level. Supervised cluster analysis and gene set enrichment analysis between the PD-L1-high and -low NSCLCs revealed a correlation between PD-L1 expression and genes/pathways related to cell motility/adhesion. These results suggest that MAPK, along with STAT3, is important for determining PD-L1 expression, which could be useful for targeted therapies against lung cancers.

## 9. Scoring of PD-L1 expression intensity on pulmonary adenocarcinomas and the correlations with clinicopathological factors.

**Yataro Daigo, Tomoyuki Igarashi, Koji Teramoto**

The contribution of programmed cell death ligand-1 (PD-L1) immune checkpoint molecule toward progression of non-small cell lung cancer (NSCLC) has not yet been elucidated, in part, because of lack of a standardised method to evaluate PD-L1 expression. We developed a novel method for the evaluation of PD-L1 expression on NSCLC cells and examined its correlation with clinicopathological characteristics. After immunohistochemical examination of PD-L1 expression for surgically

resected pulmonary adenocarcinomas (n=106), based on the findings that PD-L1 are consistently expressed on alveolar macrophages, PD-L1 staining intensity of tumor cells was classified into four levels relative to PD-L1 staining intensity in alveolar macrophages. PD-L1 expression score was significantly higher in tumors with G2/3 differentiation than in those with G1 and higher in those with lymphatic invasion than in those without invasion. Postoperative relapse-free survival was significantly shorter in patients with a high PD-L1 expression score than in those with low PD-L1 expression score. Smoking habits, histological subtype, and *EGFR* mutation status were not associated with PD-L1 expression score. The scoring of PD-L1 expression on tumor cells relative to that in alveolar macrophages appears to be a valid indicator of PD-L1 status of patients with pulmonary adenocarcinomas, demonstrating a significant correlation with several factors associated with tumour progression.

## 10. Development of therapeutic cancer vaccine

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

Using the systematic screening system shown above, we identified conoantigens 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 IMSUT Hospital and its collaborative hospitals, International Conference on Harmonization (ICH) - Good Clinical Practice (GCP)-based clinical study using the combination of some of these peptides derived from oncoantigens in patients with lung cancer is now being conducted. In addition, new type of peptides-pulsed DC vaccination therapy is under development.

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

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

Immune responses play a critical role in various disease conditions including cancer. Although various immunotherapies are being developed, predictive biomarkers for the choice of effective therapy are urgently required. Using systematic cancer

genomics approach on clinical materials obtained from cancer patients treated with cancer vaccine, peptides-pulsed DC vaccination therapy, or Immune checkpoint inhibitors, we are clarifying how molecular profiles of cancers can be used to identify biomarkers for predicting clinical outcomes. For example, there has not been a rapid, sensitive, comprehensive, and quantitative analysis method to examine T-cell or B-cell immune responses, therefore we developed a new approach to characterize T cell receptor (TCR) repertoire by sequencing millions of cDNA of TCR  $\alpha$  and  $\beta$  chains in combination with a newly-developed algorithm. Using samples from lung cancer patients treated with cancer peptide vaccines as a model, we demonstrated that detailed information of the V-(D)-J combination along with complementary determining region 3 (CDR3) sequences can be determined. This newly developed TCR NGS platform can be applied to better understand immune responses in many disease areas including immune disorders, allergies, and organ transplantations.

## **12. Scientific Platform of Supporting Cohort Study and Biospecimen Analysis**

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

To support life science researchers in the field of basic life science, cancer diagnostics and therapeutics, we are collecting cancer tissue, serum, plasma, and peripheral blood mononuclear cell (PBMC) from about 6500 patients with solid cancers originated from 13 organs. We also constructed tissue microarray system covering about 5000 archived clinical cancers. Using these clinical materials, we are validating the clinicopathological significance of various candidate disease biomarkers as requested by researchers and contributed to their clinical application and publications in international journals.

## **13. Development of artificial intelligence (AI)-based Cancer Precision Medicine System.**

**Yataro Daigo, Atsushi Takano, Koji Teramoto, Yusuke Nakamura**

To establish Cancer Precision Medicine System for personalized treatment by using the masses of scientific and medical data which are constantly updated including genome-based information, we are constructing artificial intelligence (AI)-based system. This system will consist of the following 3 main units: (i) Information support unit from which doctors can access the most up-to-date data for cancer treatments and drugs, (ii) Consent support unit that partly supports the doctors to explain treatment and drugs using AI, (iii) Diagnosis support

unit that recommends the most suitable treatment methods and drugs based on the EBM and reliable scientific reports that are available to the doctors as references.

## **14. Targetting of stemness factor inhibites the growth of tumors and the formation of metastases in solid tumor.**

**Hiroaki Taniguchi**

Tumors contain a small population of putative cancer stem cells (CSC), which possess unique self-renewal properties, and survive in a quiescent state for many years after remission and result in later relapse and metastasis. Therefore, it is conceivable that targeting CSCs will eradicate tumor-initiating cells, whereas conventional chemotherapies will only eradicate the bulk of a tumor. Cancer stem cells and normal tissue stem cells utilize the same self-renewal pathway. However, researchers characterize some of changes, which occur in cancer stem cells, not in normal tissue stem cells. The design of new therapeutic agents should be aimed at targeting these unique molecular changes. We have currently focused on studying these unique molecular changes, which occur in cancer stem cells, not in normal tissue stem cells. This could be a new therapeutic target against solid tumors.

PR domain-containing protein (PRDM) has 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 against PRDM14 and plan clinical trial for pancreatic cancer and triple negative breast cancer.

## Publications

- Ono T, Kamimura N, Matsushashi T, Nagai T, Nishiyama T, Endo J, Hishiki T, Nakanishi T, Shimizu N, Tanaka H, Ohta S, Suematsu M, Ieda M, Sano M, Fukuda K, Kaneda R. The histone 3 lysine 9 methyltransferase inhibitor chaetocin improves prognosis in a rat model of high salt diet-induced heart failure. *Sci Rep* 7, 39752 (2017)
- Matsubara E, Yoshikawa N, Hosono O, Baba H, Eri T, Uehara M, Oda A, Sekita C, Taniguchi A, and Tanaka H. A rheumatoid arthritis patient complicated with adenine phosphoribosyltransferase deficiency and unilateral renal agenesis: a first case report. *Mod Rheumatol Case Rep*. In press.
- Yoshikawa N, Shimizu N, Uehara M, Oda A, Matsumiya R, Matsubara E, Kobayashi H, Hosono O, Kuribara-Souta A, Baba H, Nagamura F, Kiryu S, and Tanaka H. The effects of bolus supplementation of branched-chain amino acids on skeletal muscle mass, strength, and function in patients with rheumatic disorders during glucocorticoid treatment. *Mod Rheumatol*. In press
- Kobayashi H, Uehara M, Oda A, Matsubara E, Baba H, Matsumiya R, Yoshikawa N, Hosono O, Tanaka H. Normal pressure hydrocephalus, a possible complication in IgG4-related disease. *Interdiscip Neurosurg*. 5, 1-2, 2016.
- Ishii H, Konuma T, Ohnuma K, Hosono O, Tanaka H, Kato S, Tojo A, Takahashi S. Remission of remitting seronegative symmetrical synovitis with pitting edema after unrelated cord blood transplantation for myelodysplastic syndrome. *Ann Hematol*. 95(3): 523-4, 2016.
- Shiraishi K, Okada Y, Takahashi A, Kamatani Y, Momozawa Y, Ashikawa K, Kunitoh H, Matsumoto S, Takano A, Shimizu K, Goto A, Tsuta K, Watanabe S, Ohe Y, Watanabe Y, Goto Y, Noki-hara H, Furuta K, Yoshida A, Goto K, Hishida T, Tsuboi M, Tsuchihara K, Miyagi Y, Nakayama H, Yokose T, Tanaka K, Nagashima T, Ohtaki Y, Maeda D, Imai K, Minamiya Y, Sakamoto H, Saito A, Shimada Y, Sunami K, Saito M, Inazawa J, Nakamura Y, Yoshida T, Yokota J, Matsuda F, Matsuo K, Daigo Y, Kubo M, Kohno T. Association of variations in HLA class II and other loci with susceptibility to EGFR-mutated lung adenocarcinoma. *Nat Commun* 7: 12451, 2016.
- Baghdadi M, Wada H, Nakanishi S, Abe H, Han N, Putra WE, Endo D, Watari H, Sakuragi N, Hida Y, Kaga K, Miyagi Y, Yokose T, Takano A, Daigo Y, Seino KI. Chemotherapy-Induced IL34 Enhances Immunosuppression by Tumor-Associated Macrophages and Mediates Survival of Chemoresistant Lung Cancer Cells. *Cancer Res* 76: 6030-6042, 2016.
- Seow WJ, Matsuo K, Hsiung CA, Shiraishi K, Song M, Kim HN, Wong MP, Hong YC, Dean Hosgood H 3rd, Wang Z, Chang IS, Wang JC, Chatterjee N, Tucker M, Wei H, Mitsudomi T, Zheng W, Kim JH, Zhou B, Caporaso NE, Albanes D, Shin MH, Ping Chung L, An SJ, Wang P, Zheng H, Yatabe Y, Zhang XC, Kim YT, Shu XO, Kim YC, Bassig BA, Chang J, Ho JC, Ji BT, Kubo M, Daigo Y, Ito H, Momozawa Y, Ashikawa K, Kamatani Y, Honda T, Sakamoto H, Kunitoh H, Tsuta K, Watanabe SI, Nokihara H, Miyagi Y, Nakayama H, Matsumoto S, Tsuboi M, Goto K, Yin Z, Shi J, Takahashi A, Goto A, Minamiya Y, Shimizu K, Tanaka K, Wu T, Wei F, Wong JY, Matsuda F, Su J, Kim YH, Oh IJ, Song F, Lee VH, Su WC, Chen YM, Chang GC, Chen KY, Huang MS, Yang PC, Lin HC, Xiang YB, Seow A, Yong Park J, Kweon SS, Chen CJ, Li H, Gao YT, Wu C, Qian B, Lu D, Liu J, Jeon HS, Hsiao CF, Sung JS, Tsai YH, Jung YJ, Guo H, Hu Z, Wang WC, Chung CC, Lawrence C, Burdett L, Yeager M, Jacobs KB, Hutchinson A, Berndt SI, He X, Wu W, Wang J, Li Y, Choi JE, Park KH, Sung SW, Liu L, Kang CH, Hu L, Chen CH, Yang TY, Xu J, Guan P, Tan W, Wang CL, Sihoe AD, Chen Y, Choi YY, Hung JY, Kim JS, Yoon HI, Cai Q, Lin CC, Park IK, Xu P, Dong J, Kim C, He Q, Perng RP, Chen CY, Vermeulen R, Wu J, Lim WY, Chen KC, Chan JK, Chu M, Li YJ, Li J, Chen H, Yu CJ, Jin L, Lo YL, Chen YH, Fraumeni JF Jr, Liu J, Yamaji T, Yang Y, Hicks B, Wyatt K, Li SA, Dai J, Ma H, Jin G, Song B, Wang Z, Cheng S, Li X, Ren Y, Cui P, Iwasaki M, Shimazu T, Tsugane S, Zhu J, Jiang G, Fei K, Wu G, Chien LH, Chen HL, Su YC, Tsai FY, Chen YS, Yu J, Stevens VL, Laird-Offringa IA, Marconett CN, Lin D, Chen K, Wu YL, Landi MT, Shen H, Rothman N, Kohno T, Chanock SJ, Lan Q. Association between GWAS-identified lung adenocarcinoma susceptibility loci and EGFR mutations in never-smoking Asian women, and comparison with findings from Western populations. *Hum Mol Genet* 2016 Dec 26. [Epub ahead of print].
- Wang Z, Seow WJ, Shiraishi K, Hsiung CA, Matsuo K, Liu J, Chen K, Yamaji T, Yang Y, Chang IS, Wu C, Hong YC, Burdett L, Wyatt K, Chung CC, Li SA, Yeager M, Hutchinson A, Hu W, Caporaso N, Landi MT, Chatterjee N, Song M, Fraumeni JF Jr, Kohno T, Yokota J, Kunitoh H, Ashikawa K, Momozawa Y, Daigo Y, Mitsudomi T, Yatabe Y, Hida T, Hu Z, Dai J, Ma H, Jin G, Song B, Wang Z, Cheng S, Yin Z, Li X, Ren Y, Guan P, Chang J, Tan W, Chen CJ, Chang GC, Tsai YH, Su WC, Chen KY, Huang MS, Chen YM, Zheng H, Li H, Cui P, Guo H, Xu P, Liu L, Iwasaki M, Shimazu T, Tsugane S, Zhu J, Jiang G, Fei K, Park JY, Kim YH, Sung JS, Park KH, Kim YT, Jung YJ, Kang CH, Park IK, Kim HN, Jeon HS, Choi JE, Choi YY, Kim JH, Oh IJ, Kim YC, Sung SW, Kim JS, Yoon HI, Kweon SS, Shin MH, Seow A, Chen Y,



- Lim WY, Liu J, Wong MP, Lee VH, Bassig BA, Tucker M, Berndt SI, Chow WH, Ji BT, Wang J, Xu J, Sihoe AD, Ho JC, Chan JK, Wang JC, Lu D, Zhao X, Zhao Z, Wu J, Chen H, Jin L, Wei F, Wu G, An SJ, Zhang XC, Su J, Wu YL, Gao YT, Xiang YB, He X, Li J, Zheng W, Shu XO, Cai Q, Klein R, Pao W, Lawrence C, Hosgood HD 3rd, Hsiao CF, Chien LH, Chen YH, Chen CH, Wang WC, Chen CY, Wang CL, Yu CJ, Chen HL, Su YC, Tsai FY, Chen YS, Li YJ, Yang TY, Lin CC, Yang PC, Wu T, Lin D, Zhou B, Yu J, Shen H, Kubo M, Chanock SJ, Rothman N, Lan Q. Meta-analysis of genome-wide association studies identifies multiple lung cancer susceptibility loci in never-smoking Asian women. *Hum Mol Genet* 25: 620-629, 2016.
- Sumimoto H, Takano A, Teramoto K, Daigo Y. RAS-Mitogen-Activated Protein Kinase Signal Is Required for Enhanced PD-L1 Expression in Human Lung Cancers. *PLoS One* 11: e0166626, 2016.
- Igarashi T, Teramoto K, Ishida M, Hanaoka J, Daigo Y. Scoring of PD-L1 expression intensity on pulmonary adenocarcinomas and the correlations with clinicopathological factors. *ESMO Open* 1: e000083, 2016.
- Teramoto K, Ozaki Y, Hanaoka J, Sawai S, Tezuka N, Fujino S, Daigo Y, Kontani K. MUC1-targeted dendritic cell-based vaccine in patients with refractory non-small-cell lung cancer. *Ther Adv Med Oncol*, in press.
- Mai TH, Takano A, Suzuki H, Hirose T, Mori T, Teramoto K, Kiyotani K, Nakamura Y, Daigo Y. Quantitative Analysis and Clonal Characterization of T-cell Receptor Beta Repertoires in Advanced Non-small Cell Lung Cancer Patients Treated with Cancer Vaccine Treatment. *Oncol Lett*, in press.
- Thang PM, Takano A, Yoshitake Y, Shinohara M, Murakami Y, Daigo Y. Cell division cycle associated 1 as a novel prognostic biomarker and therapeutic target for oral cancer. *Int J Oncol* 49: 1385-1393, 2016.
- Nishii T, Yokose T, Miyagi Y, Daigo Y, Isaka T, Furumoto H, Ito H, Murakami S, Kondo T, Saito H, Oshita F, Yamada K, Matsukuma S, Nakayama H, Masuda M. Prognostic value of EGFR mutations in surgically resected pathological stage I lung adenocarcinoma. *Asia Pac J Clin Oncol* 2016 Jun 28. doi: 10.1111/ajco.12512. [Epub ahead of print]
- Koyama N, Matsumura C, Morii H, Hasegawa C, Hira D, Daigo Y, Terada T, Yano Y. Investigation of Optimal Time for Starting Betamethasone Using Fatigue Scores and Prognostic Nutritional Index in Terminally Ill Patients With Cancer-Related Fatigue. *Am J Hosp Palliat Care* 2016 Feb 16. pii: 1049909116632487. [Epub ahead of print]
- Funauchi Y, Tanikawa C, Lo PHY, Mori J, Daigo Y, Takano A, Miyagi Y, Okawa A, Nakamura Y, Matsuda K. Regulation of iron homeostasis by the p53-ISCU pathway. *Sci Rep* 5: 16497, 2015.
- Taniguchi H, Hoshino D, Moriya C, Zembutsu H, Nishiyama N, Yamamoto H, Kataoka K, Imai K. Silencing PRDM14 expression by an innovative RNAi therapy inhibits stemness, tumorigenicity, and metastasis of breast cancer. *Oncotarget*, in press.
- Taniguchi H, Moriya C, Igarashi H, Saitoh A, Yamamoto H, Adachi Y, Imai K. Cancer stem cells in human gastrointestinal cancer. *Cancer Sci*, 107(11): 1556-1562. 2016

IMSUT Hospital

# Therapeutic Vector Development Center

治療ベクター開発センター

Professor Tomoki Todo, M.D., Ph.D.  
Associate Professor Yasushi Ino, M.D., Ph.D.

教授 医学博士 藤 堂 具 紀  
准教授 医学博士 稲 生 靖

*The Therapeutic Vector Development Center (TVDC) has been reorganized from the former Core Facility for Therapeutic Vectors in 2016 due to the increase in its activity and its importance as a foundation facility for translational research. This center was established in 2002 as the first facility in Japanese academia for the clinical-grade production of viral or cellular vectors. The primary function of TVDC is to support clinical trials that require production of recombinant viral vectors, genetic modification and/or ex vivo manipulation of patients' tissue or cells under current Good Manufacturing Practice (cGMP) conditions.*

## Maintenance of the Standard Operating Procedures (SOPs)

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

## Adoption of ISO

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

## Validation of TVDC

The TVDC consists of two distinct units; 1) Vector Unit, the primary viral vector production suite which may also function as ex vivo transduction

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

## Production of clinical grade oncolytic HSV-1

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

## Oncolytic MV project

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

## IMSUT Hospital

# Department of Nursing

## 看護部

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

看護部長	博士(保健学)	小	林	康	司
副看護部長	リウマチケア看護師	久	原	みな	代
看護師長		小	澤	昌	子
看護師長		佐	藤	朋	子
看護師長		成	田	初	子
看護師長	感染制御実践看護師	小	粥	美	香
看護師長		須	山	寿	子
看護師長		谷	井	真	弓
看護師長		桐	山	里	美

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

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

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

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

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

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

In 2015-2016, we accelerate utilizing competency model for developing nurse manager. Nurse Managers cooperate with the competency training courses held at various places in Japan many times as facilitator.

## Publications

- 小林康司, 武村雪絵(2016). コンピテンシーを深く理解し看護管理に活かすための東大病院・医科研病院式グループワーク実践講座① 学習会を理解する. 看護展望 41(1): 44-49.
- 佐藤朋子, 武村雪絵(2016). コンピテンシーを深く理解し看護管理に活かすための東大病院・医科研病院式グループワーク実践講座② 第1ステップの学習会で“信念の維持”を学ぶ. 看護展望 41(3): 56-59.
- 久原みな代, 小澤昌子, 成田初子, 武村雪絵(2016). コンピテンシーを深く理解し看護管理に活かすための東大病院・医科研病院式グループワーク実践講座③ 第1ステップ/“内省力”を考える 第2ステップ/2つの事例でX副看護師長が発揮したコンピテンシーとは?. 看護展望 41(4): 56-64.
- 久原みな代, 小粥美香, 小林康司, 武村雪絵(2016). コンピテンシーを深く理解し看護管理に活かすための東大病院・医科研病院式グループワーク実践講座④ 第1ステップ/異動直後の看護師長に見る“専門性の発揮” 第2ステップ/患者用パンフ作成チームを結成した副看護師長の行動. 看護展望 41(5): 40-45.
- 谷井真弓, 佐藤朋子, 小林康司, 武村雪絵(2016). コンピテンシーを深く理解し看護管理に活かすための東大病院・医科研病院式グループワーク実践講座⑤ 第1ステップ: “新人教育”と“植物への水やり”との共通点から概念化を見いだす/第2ステップ/人材育成で発揮されたコンピテンシー. 看護展望 41(6): 52-57.
- 須山寿子, 成田初子, 小林康司, 武村雪絵(2016). コンピテンシーを深く理解し看護管理に活かすための東大病院・医科研病院式グループワーク実践講座⑪ PART 1: X副看護師長が部下への指導で振るったコンピテンシーとは/PART 2: A副看護師長が病棟改革で発揮したコンピテンシーとは. 看護展望 41(12): 43-49.
- 桐山里美, 谷井真弓, 小林康司, 武村雪絵(2016). コンピテンシーを深く理解し看護管理に活かすための東大病院・医科研病院式グループワーク実践講座⑫【最終回】 PART 1: 不測の事態に対するB副看護師長の思考と行動に含まれていたコンピテンシーとは/PART 2: 新人看護師が危機に陥ったときX副看護師長が発揮したコンピテンシーとは. 看護展望 41(14): 43-49.
- 町田亜子(2016). 【高齢患者の退院を考える一困難事例への対応】 困難事例への取り組み. 看護実践の科学 41(8): 6-12.
- 中野貴美子(2016). ビリーブメント(死別). 監修: 森田達也, 木澤義之(監修), 西智弘, 松本禎久, 森雅紀, 山口崇(編). 緩和ケアレジデントマニュアル 392-399. 東京: 医学書院.

## Conference Presentation

- 亀田史絵, 小粥美香. 看護助手に対する感染対策教育の取り組み. 第31回日本環境感染学会総会・学術集会. 京都. 2016. 2. 19-20.
- 宮野由美, 砂田純子. 重症GVHDに対するスルファジン銀クリームを用いた皮膚処置の効果について. 第38回日本造血細胞移植学会総会. 名古屋. 2016. 3. 3-5.
- 松下はるゑ, 成瀬昂, 山本なつ紀, 松本博成, 永田智子. 介護老人福祉施設の職員と入所者の間の会話時間に関連する要因. 日本地域看護学会第19回学術集会. 下野. 2016. 8. 26-27.

*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 (15 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

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

教授(委嘱) 医学博士 俣野哲朗  
客員准教授 医学博士 立川(川名)愛

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

### 1. Biphasic CD8<sup>+</sup> T-cell responses in simian immunodeficiency virus control by acute-phase passive neutralizing antibody immunization

Sumire Iseda, Naofumi Takahashi<sup>1</sup>, Hugo Popli-mont, Takushi Nomura<sup>1</sup>, Sayuri Seki<sup>1</sup>, Taku Nakane, Midori Nakamura<sup>1</sup>, Shoi Shi, Hiroshi Ishii<sup>1</sup>, Shota Furukawa<sup>1</sup>, Shigeyoshi Harada<sup>1</sup>, Taeko K. Naruse<sup>2</sup>, Akinori Kimura<sup>2</sup>, Tetsuro Matano, and Hiroyuki Yamamoto<sup>1</sup>: <sup>1</sup>AIDS Research Center, National Institute of Infectious Diseases; <sup>2</sup>Medical Research Institute, Tokyo Medical and Dental University

Identification of the mechanism of human immunodeficiency virus (HIV) control by neutralizing antibodies (NAbs) is critical for anti-HIV-1 strategies. Our recent *in vivo* studies on macaque AIDS models have shown the efficacy of post-infection NAb passive immunization against viral replication, suggesting involvement of cellular immune responses in the control. In this study, we described simian immunodeficiency virus (SIV) control with biphasic CD8<sup>+</sup> T-cell responses following acute-phase NAb passive immunization in a macaque AIDS model. Analysis of four SIV-infected rhesus macaque pairs matched with major histocompatibility complex class I (MHC-I) haplotypes, respectively, found that

counterparts receiving passive anti-SIV polyclonal NAb immunization at day 7 post-infection suppressed viremia for up to 2 years without accumulating viral CD8<sup>+</sup> T-cell escape mutations. In the first phase of primary viremia control, CD8<sup>+</sup> cells had high capacities to suppress *in vitro* replication of SIVs carrying CD8<sup>+</sup> T-cell escape mutations. In the second sustained phase of SIV control, a pattern of immunodominant CD8<sup>+</sup> T-cell preservation was observed, and SIV-specific CD8<sup>+</sup> T cells showed retention of phosphorylated extracellular signal-related kinase (ERK)<sup>hi</sup>/phosphorylated AMP-activated protein kinase (AMPK)<sup>lo</sup> subpopulations, implying their correlation with SIV control. This study suggests the potential of virus-specific CD8<sup>+</sup> T cells functionally boosted by acute-phase NAbs to control HIV replication.

### 2. Association of lymph-node antigens with lower Gag-specific central-memory and higher Env-specific effector-memory CD8<sup>+</sup> T-cell frequencies in a macaque AIDS model

Hiroshi Ishii<sup>1</sup>, Saori Matsuoka<sup>1</sup>, Takushi Nomura<sup>1</sup>, Midori Nakamura<sup>1</sup>, Teiichiro Shiino<sup>1</sup>, Yuko Sato<sup>3</sup>, Naoko Iwata-Yoshikawa<sup>3</sup>, Hideki Hasegawa<sup>3</sup>, Kazuta Mizuta<sup>4</sup>, Hiromi Sakawaki<sup>4</sup>, Tomoyuki Miura<sup>4</sup>, Yoshio Koyanagi<sup>4</sup>, Taeko K. Naruse<sup>2</sup>, Akinori

**Kimura<sup>2</sup>, Tetsuro Matano:** <sup>1</sup>Department of Pathology, National Institute of Infectious Diseases; <sup>4</sup>Institute for Virus Research, Kyoto University

Virus-specific CD8<sup>+</sup> T cells exert strong suppressive pressure on HIV and SIV replication. These responses have been intensively examined in peripheral blood mononuclear cells (PBMCs) but not fully analyzed in lymph nodes (LNs), where interaction between CD8<sup>+</sup> T cells and HIV/SIV-infected cells occurs. In this study, we investigated target antigen specificity of CD8<sup>+</sup> T cells in LNs in a macaque AIDS model. Analysis of virus antigen-specific CD8<sup>+</sup> T-cell responses in the inguinal LNs obtained from twenty rhesus macaques in the chronic phase of SIV infection showed an inverse correlation between viral loads and frequencies of CD8<sup>+</sup> T cells with CD28<sup>+</sup>CD95<sup>+</sup> central memory phenotype targeting the N-terminal half of SIV core antigen (Gag-N). In contrast, analysis of LNs but not PBMCs revealed a positive correlation between viral loads and frequencies of CD8<sup>+</sup> T cells with CD28<sup>-</sup>CD95<sup>+</sup> effector memory phenotype targeting the N-terminal half of SIV envelope (Env-N), soluble antigen. Indeed, LNs with detectable SIV capsid p27 antigen in the germinal center exhibited significantly lower Gag-N-specific CD28<sup>+</sup>CD95<sup>+</sup>CD8<sup>+</sup> T-cell and higher Env-N-specific CD28<sup>-</sup>CD95<sup>+</sup>CD8<sup>+</sup> T-cell responses than those without detectable p27. This study suggests that core and envelope antigen-specific CD8<sup>+</sup> T cells show different patterns of interactions with HIV/SIV-infected cells.

### **3. Recursion-based depletion of HIV-specific naive CD4<sup>+</sup> T cells may facilitate persistent viral replication and chronic viremia leading to AIDS**

**Tetsuo Tsukamoto<sup>5</sup>, Hiroyuki Yamamoto<sup>1</sup>, Seiji Okada<sup>5</sup>, and Tetsuro Matano:** <sup>5</sup>Center for AIDS Research, Kumamoto University

Although antiretroviral therapy has made HIV infection a controllable disease, it is still unclear how viral replication persists in untreated patients and causes CD4<sup>+</sup> T-cell depletion leading to AIDS in several years. Theorists tried to explain it with the diversity threshold theory in which accumulated mutations in the HIV genome make the virus so diverse that the immune system will no longer be able to recognize all the variants and fail to control the viremia. Although the theory could apply to a number of cases, macaque AIDS models using SIV have shown that failed viral control at the set point is not always associated with T-cell escape mutations. Moreover, even monkeys without a protective MHC allele can contain replication of a super infected SIV following immunization with a live-attenuated SIV vaccine, while those animals are

not capable of fighting primary SIV infection. In this study, we proposed a recursion-based virus-specific naive CD4<sup>+</sup> T-cell depletion hypothesis through thinking on what may happen in individuals experiencing primary immunodeficiency virus infection. This could explain the mechanism for impairment of virus-specific immune response in the course of HIV infection.

### **4. Increased HIV-1 sensitivity to neutralizing antibodies by mutations in the Env V3-coding region for resistance to CXCR4 antagonists**

**Yuta Hikichi, Masaru Yokoyama<sup>6</sup>, Taichiro Take-mura<sup>7</sup>, Masayuki Fujino<sup>1</sup>, Sei Kumakura<sup>8</sup>, Yosuke Maeda<sup>9</sup>, Naoki Yamamoto<sup>1</sup>, Hironori Sato<sup>6</sup>, Tetsuro Matano, Tsutomu Murakami<sup>1</sup>:** <sup>6</sup>Pathogen Genomics Center, National Institute of Infectious Diseases; <sup>7</sup>Institute of Tropical Medicine, Nagasaki University; <sup>8</sup>Kureha Corporation; <sup>9</sup>Faculty of Life Sciences, Kumamoto University

HIV-1 passage in cell culture in the presence of chemokine receptor antagonists can result in selection of viruses with env mutations that confer resistance to these inhibitors. In this study, we examined the effect of HIV-1 env mutations that confer resistance to CXCR4 antagonists on envelope (Env) sensitivity to NAbs. Serial passage of CXCR4-tropic HIV-1 NL4-3 in PM1/CCR5 cells under CXCR4 antagonists KRH-3955, AMD3100 and AMD070 yielded two KRH-3955-resistant, one AMD3100-resistant and one AMD070-resistant viruses. These viruses had multiple env mutations including the Env gp120 V3 region. The majority of viruses having these CXCR4 antagonist-resistant Envs showed higher sensitivity to NAbs 447-52D, b12 and 2F5 targeting the V3 region, the gp120 CD4-binding site and the gp41 membrane proximal region, respectively, compared to NL4-3 WT virus. Recombinant NL4-3 viruses with the V3-coding region replaced with those derived from the CXCR4 antagonist-resistant viruses showed increased sensitivity to NAbs b12, 2F5 and 447-52D. Molecular dynamics simulations of Env gp120 outer domains predicted that the V3 mutations increased levels of fluctuations at the tip and stem of the V3 loop. This study indicates that mutations in the V3-coding region that result in loss of viral sensitivity to CXCR4 antagonists increase viral sensitivity to NAbs, providing insights into our understanding of the interplay of viral Env accessibility to chemokine receptors and sensitivity to NAbs.

### **5. Short intracellular HIV-1 transcripts as biomarkers of residual immune activation in patients on antiretroviral therapy**

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HIV-1 patients continue to remain at an abnormal immune status despite prolonged combination antiretroviral therapy (cART), which results in an increased risk of non-AIDS-related diseases. Given the growing recognition of the importance of understanding and controlling the residual virus in patients, additional virological markers to monitor infected cells are required. In this study, we identified prematurely terminated short HIV-1 transcripts (STs) in peripheral blood mononuclear cells (PBMCs) as an efficient intracellular biomarker to monitor viral activation and immune status in patients with cART-mediated full viral suppression in plasma. ST levels in untreated patients generally increased with disease progression and decreased after treatment initiation. However, some patients exhibited sustained high levels of ST and low CD4 cell counts despite full viral suppression by treatment. The levels of STs strongly reflected chronic immune activation defined by coexpression of HLA-DR and CD38 on CD8<sup>+</sup> T cells, rather than circulating proviral load. These observations represent evidence for a relationship between viral persistence and host immune activation, which in turn results in the suboptimal increase in CD4<sup>+</sup> T cells despite suppressive antiretroviral therapy.

## **6. Rapid HIV-1 disease progression in individuals infected with a virus adapted to its host population**

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HIV-1 escape from CTL is predictable based on the Human Leukocyte Antigen (HLA) class

I alleles expressed by the host. As such, HIV-1 sequences circulating in a population of hosts will harbor escape mutations specific to the HLA alleles of that population. In theory, this should increase the frequency of escape mutation transmission to persons expressing the restricting HLA allele, thereby compromising host immunity to the incoming HIV-1 strain. However, the clinical impact of infection with HIV-1 containing immune escape mutations has not conclusively been demonstrated. Japan's population features limited HLA diversity which is driving population-level HIV adaptation: for example, >60% of Japanese express HLA-A\*24:02 and its associated Nef-Y135F escape mutation represents the population consensus. As such, Japan is an ideal population in which to examine this phenomenon. In this study, we combined genetic and immunological analyses to identify A\*24:02-positive individuals likely to have been infected with Y135F-containing HIV-1. Over a ~5 year follow-up, these individuals exhibited significantly lower CD4 counts compared to individuals inferred to have been infected with wild-type HIV-1. This study supports a significant negative clinical impact of pathogen adaptation to host pressures at the population level.

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## **Publications**

1. Seki, S., and Matano, T. Development of a Sendai virus vector-based AIDS vaccine inducing T cell responses. *Expert Rev. Vaccines* 15: 119-127, 2016.
2. Iseda, S., Takahashi, N., Poplimont, H., Nomura, T., Seki, S., Nakane, T., Nakamura, M., Shi, S., Ishii, H., Furukawa, S., Harada, S., Naruse, T.K., Kimura, A., Matano, T., and Yamamoto, H. Biphasic CD8<sup>+</sup> T-cell defense in simian immunodeficiency virus control by acute-phase passive neutralizing antibody immunization. *J. Virol.* 90: 6276-6290, 2016.
3. Ishii, H., Matsuoka, S., Nomura, T., Nakamura, M., Shiino, T., Sato, Y., Iwata-Yoshikawa, N., Hasegawa, H., Mizuta, K., Sakawaki, H., Miura, T., Koyanagi, Y., Naruse, T.K., Kimura, A., and Matano, T. Association of lymph-node antigens with lower Gag-specific central-memory and higher Env-specific effector-memory CD8<sup>+</sup> T-cell frequencies in a macaque AIDS model. *Sci. Rep.* 6: 30153, 2016.
4. Tsukamoto, T., Yamamoto, H., Okada, S., and Matano, T. Recursion-based depletion of human immunodeficiency virus-specific naïve CD4<sup>+</sup> T cells may facilitate persistent viral replication and chronic viraemia leading to acquired immunodeficiency syndrome. *Med. Hypotheses* 94: 81-85, 2016.



5. Hikichi, Y., Yokoyama, M., Takemura, T., Fujino, M., Kumakura, S., Maeda, Y., Yamamoto, N., Sato, H., Matano, T., and Murakami, T. Increased HIV-1 sensitivity to neutralizing antibodies by mutations in the Env V3-coding region for resistance to CXCR4 antagonists. *J. Gen. Virol.* 97: 2427-2440, 2016.
6. Yamamoto, H., Iseda, S., Nakane, T., Nomura, T., Takahashi, N., Seki, S., Nakamura, M., Ishii, H., and Matano, T. Augmentation of anti-SIV activity in CD8<sup>+</sup> cells by neutralizing but not non-neutralizing antibodies in the acute phase. *AIDS* 30: 2391-2394, 2016.
7. Yamamoto, H., and Matano, T. Patterns of HIV/SIV prevention and control by passive antibody immunization. *Front. Microbiol.* 7: 1739, 2016.
8. Nyombayire, J., Anzala, O., Gazzard, B., Karita, E., Bergin, P., Hayes, P., Kopycinski, J., Omosa-Manyonyi, G., Jackson, A., Bizimana, J., Farah, B., Sayeed, E., Parks, C.L., Inoue, M., Hironaka, T., Hara, H., Shu, T., Matano, T., Dally, L., Barin, B., Park, H., Gilmour, J., Lombardo, A., Excler, J.-L., Fast, P., Laufer, D.S., Cox, J.H., and the S001 Study Team. First-in-human evaluation of the safety and immunogenicity of a replicating intranasally administered Sendai HIV-1 Gag vaccine: induction of potent T-cell or antibody responses in prime-boost regimens. *J. Infect. Dis.*, in press.
9. Ishizaka, A., Sato, H., Nakamura, H., Koga, M., Kikuchi, T., Hosoya, N., Koibuchi, T., Nomoto, A., Kawana-Tachikawa, A., and Mizutani, T. Short intracellular HIV-1 transcripts as biomarkers of residual immune activation in patients on antiretroviral therapy. *J. Virol.* 90: 5665-5676, 2016.
10. Katoh, J., Kawana-Tachikawa, A., Shimizu, A., Zhu, D., Han, C., Nakamura, H., Koga, M., Kikuchi, T., Adachi, E., Koibuchi, T., Gao, G.F., Brumme, Z.L., and Iwamoto, A. Rapid HIV-1 disease progression in individuals infected with a virus adapted to its host population. *PLoS One* 11: e0150397, 2016.