IMSUT Hospital

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

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

We are challenging to cure intractable hematological disorders such as leukemia and lymphoma with the aid of hematopoietic stem cell transplantation (HSCT). Our major stem cell source for recipients without suitable family donors is unrelated cord blood, with which no less than 20 adult patients receive cord blood transplantation (CBT) annually. Since 1998, we have performed around 350 cases of CBT, which appears a distinguished experience in the world.

Recent advances in identification of tumor-specific therapeutic targets resulted in a series of rationally designed therapeutic agents. In the field of hematological malignancies, we have already experienced remarkable clinical efficacies of molecular targeted drugs including tyrosine kinase inhibitors for Philadelphia-chromosome positive leukemia, monoclonal antibodies (MAb) for CD20$^+$ B cell lymphoma and CCR4$^+$ adult T cell leukemia/lymphoma (ATL), and proteasome inhibitors, immunomodulatory drugs for multiple myeloma (MM), respectively. Additionally, novel therapeutic modalities including anti-CD319 and anti-CD38 MAb are available for MM. We extensively apply these molecular targeted therapies for in- and out-patients. Furthermore, our department is one of the hub facilities in Japan for clinical practice and clinical research in ATL and Langerhans cell histiocytosis (LCH), both of which are rare and intractable tumors.

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

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

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

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

2. Autologous peripheral blood stem cell transplantation for double-refractory myeloma with K-RAS an N-RAS mutations.

Jimbo K[1,3], Yokoyama K[3,7], Ogawa M[1], Hirano M[1], Ochi K[1], Kobayashi M[1], Yusa N[2], Shimizu E[4], Kawamata T[3], Ohno N[3], Yamaguchi R[4], Imoto S[5], Furukawa Y[2,6], Miyano S[4], Imai Y[3], Tojo A[1,3]: [1]Division of Molecular Therapy, [2]Department of Applied Genomics, IMSUT Hospital, [3]Department of Hematology/Oncology, IMSUT Hospital, [4]Laboratory of Genome Database, [5]Division of Health Medical Data Science, [6]Division of Clinical Genome Research, [7]Center for Gene and Cell Therapy

The prognosis of multiple myeloma (MM) has been improved due to the introduction of novel agents like proteasome inhibitors and immunomodulatory drugs (IMiDs). However, some cases are refractory to the use of novel agents, and the prognosis of such cases is poor. A 53-year-old male was diagnosed with MM and categorized as follows: Bence-Jones protein lambda type MM, Durie-Salmon IIIA, international staging system (ISS) stage II, and revised ISS stage II. Mutations in K-RAS and IGH/FGFR3 translocation were detected at diagnosis. His tumor was refractory to seven therapeutic regimens including bortezomib, IMiDs (lenalidomide, thalidomide, pomalidomide), conventional chemotherapy, and radiation therapy. N-RAS mutations, CKS1B gains, and C-MYC split signals were detected after treatment. We performed high-dose melphalan/autologous stem cell transplantation (HD-MEL/ASCT) as a salvage therapy and achieved very good partial response. The correlation between K-RAS mutations and poor prognosis or between N-RAS mutations and reduced sensitivity to bortezomib is reported. However, RAS mutations are reported as a favorable factor for HD-MEL/ASCT. In general, mutations of both the K-RAS and N-RAS are known to be mutually exclusive. This rare MM case has mutations in both K-RAS and N-RAS, and the possible relevance of these mutations to both the refractoriness to novel therapies and sensitivity to HD-MEL/ASCT is suggested.

3. Therapy-related acute myeloid leukemia after the long-term administration of low-dose etoposide for chronic-type adult T-cell leukemia-lymphoma.

Shimada N, Ohno N, Yuji K, Uchimaru K, Tojo A.

A 61-year-old woman with chronic-type adult T-cell leukemia-lymphoma (ATL) had been taking low-dose oral etoposide for progressive lymphocytosis. After taking this for 3.5 years, she was diagnosed with therapy-related acute myeloid leukemia (t-AML), with a chromosomal translocation of t (6: 11) (q27; q23). She thus received remission induction therapy, consolidation therapy, and allogeneic hematopoietic stem cell transplantation. Although both t-AML and ATL were in remissive states, she died of a therapy-related infection within 1 year. We reviewed 12 reported cases of AML complicating ATL to better characterize this unusual disease. We should therefore include t-AML in the differential diagnosis when administering low-dose etoposide for ATL over a long period of time.

4. Ponatinib in Japanese patients with Philadelphia chromosome-positive leukemia, a phase 1/2 study.

Tojo A, Kawamata T, Yokoyama K, Yuji K, Ohno N, on behalf of AP24534-11-106 clinical trial group.

In this Phase 1/2 study (NCT01667133), we evaluated ponatinib (the third generation BCR-ABL tyrosine kinase inhibitor; 3G-TKI) and assessed its recommended dose in Japanese patients with chronic myeloid leukemia (CML) resistant/intolerant to dasatinib or nilotinib, or with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) resistant/intolerant to ≥1 TKI. The primary endpoints were safety of the recommended dose (Phase 1) and major cytogenetic response (MCyR) by 12 months in chronic-phase CML (CP-CML) patients or major hematologic response (MaHR) by 6 months in patients with advanced phase disease (Phase 2). MCyR was achieved/maintained by 12 months in 65% of CP-CML patients; MaHR was achieved by 6 months in 61% of patients with advanced phase disease. The most common nonhematologic grade 3/4 treatment-emergent adverse event (AE) was hypertension (37%); common hematologic grade 3/4 AEs were thrombocytopenia (57%), neutropenia (34%), and leukopenia (26%). Overall, five (14%) patients experienced arterial occlusive events (AOEs); no grade 5 AOEs were reported. The steady-state accumulation ratio of ponatinib (based on area under the curve) ranged from 2.6 (15 mg/day) to 1.3 (45 mg/day). In summary, ponatinib demonstrated efficacy in Japanese patients with CML and Ph+ ALL resistant/intolerant to prior TKI treatment; safety data support a recommended starting dose of 45 mg/day in these patients.

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

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

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

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IMSUT Hospital

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

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

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

Founded in 1981, Department of Infectious Diseases and Applied Immunology (DIDAI) started HIV clinic in 1986. In 2017, 30 new patients with HIV infection have visited to our hospital and 546 patients in total are currently under our clinical management. The total number of in-patients with HIV-infection during 2017 was 34, 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[1], Hidenori Sato, Lay Ahyoung Lim, Eisuke Adachi, Tadashi Kikuchi[1], Hitomi Nakamura, Takashi Odawara, Hiroshi Yotsuyanagi[1]: [1]Division of Infectious Diseases, The Advanced Clinical Research Center

30 new patients with HIV-1 infection visited to our hospital this year (from January 1 to December 31, 2017), and 546 patients in total are under medical management in our outpatient clinic. The total number of HIV-infected in-patients during 2017 was 34. 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 538 HIV-infected patients in our hospital, and most of their HIV viral loads have been well controlled. After one year of ART, the viral loads become less than 100 copies/ml in 97.5% of HIV-infected patients in our outpatient clinic,

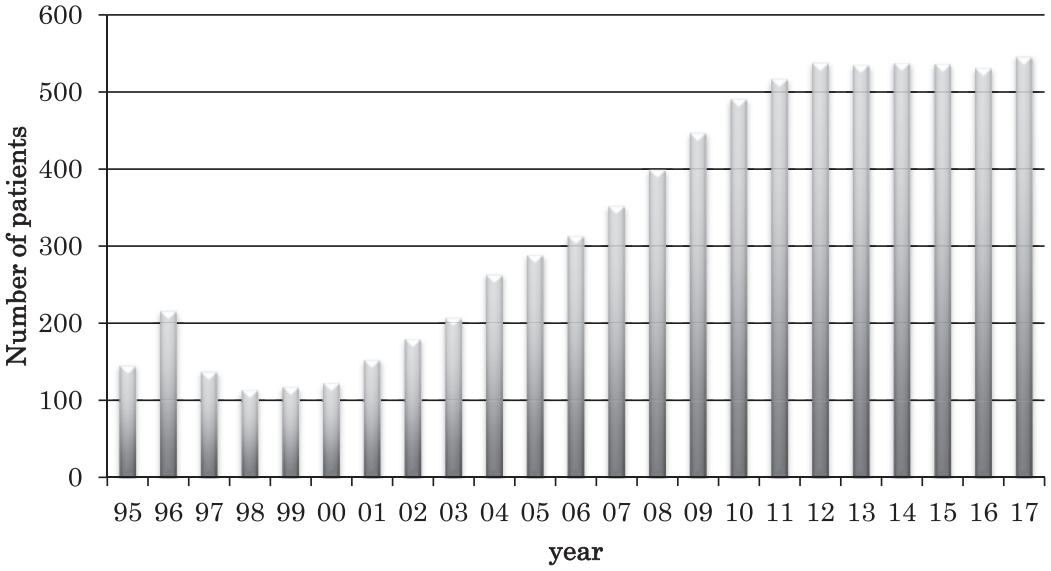

Figure 1. Number of HIV-infected outpatients in IMSUT Hospital

presumably underscored by the change in the method of quantitative HIV-RNA assay. Consequently, the patients are able to maintain good condition as long as they keep excellent drug adherence rates. The clinical management of HIV-infected patients have been changing from how to treat opportunistic infections into how to control patients with ART.

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

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

The Japanese guidelines for treatment of HIV-infected patients have been established since 1998 with support from Ministry of Health, Labor and Welfare. The representatives from our department have played critical roles in development of the current practice guidelines in Japan. It is vital to create practice guidelines that are specific for the unique genetic and social backgrounds of the HIV-infected population in Japan. In collaboration with other Japanese HIV-experts, the physicians from our department update the practice guidelines annually, as we deem necessary. The guidelines are available at http://www.haart-support.jp/guideline.htm and used widely by Japanese clinicians. It has been downloaded 16,786 times in 2017. In Japan, where the number of HIV-experts are limited compared to other countries, the practice guidelines have substantially improved the standard of care for the HIV-infected patients in our country.

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

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

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

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IMSUT Hospital

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

Professor	Hirotoshi Tanaka, M.D., D.M.Sc.		教　授	医学博士	田　中　廣　壽
Senior Assistant Professor	Noritada Yoshikawa, M.D., D.M.Sc.		講　師	博士(医学)	吉　川　賢　忠
Project Senior Assistant Professor	Noriaki Shimizu, Ph.D.		特任講師(兼務)	博士(工学)	清　水　宣　明
Assistant Professor	Toshiki Eri, M.D., D.M.Sc.		助　教	博士(医学)	江　里　俊　樹
Assistant Professor	Hiroki Yamazaki, M.D., D.M.Sc.		助　教	博士(医学)	山　崎　広　貴

Our department is founded in 2001 to tackle systemic autoimmune inflammatory diseases including rheumatoid arthritis, systemic lupus erythematosus and vasculitic syndromes. We provide patients personalized and evidence-based medical service. Moreover, we challenge cutting edge science of autoimmune, rheumatic and allergic diseases and novel treatments for patients with these disorders. As part of an elite teaching hospital, we also contribute to preparing the next generation of leading academic physicians, scientists and clinician-educators.

1. Clinical activities in IMSUT Hospital

Hirotoshi Tanaka, Noritada Yoshikawa, Toshiki Eri, Hiroki Yamazaki, Erika Matsubara, Hiroyuki Baba, Aya Oda, Masaaki Uehara

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. Our 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

2. Development of novel approaches to overcome undesired side effects of glucocorticoid therapy

Hirotoshi Tanaka, Noritada Yoshikawa, Noriaki Shimizu, Toshiki Eri, Hiroki Yamazaki, Takako Maruyama, Akiko Souta-Kuribara, Erika Matsubara, Yuki Tasaka, Aya Oda, Masaaki Uehara, Yuji Nakamura, Akane Fukuda, Naoki Ito

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

(i) Development of novel GR regulators

Despite the established role of 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 GC 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. Although nowadays it is realized the transrepression vs transactivation concept is a too simplistic and far from watertight approach, currently developed these novel GR modulators have nevertheless been helpful in elucidating various molecular actions of the GR. We further try to achieve a selective GR-mediated activation of particular anti-inflammatory profiles may offer the potential for the development of safer and disease-tailored GR-targeting medicines.

(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. Recently, it has been shown that excessive loss of muscle mass is associated with poor prognosis in several diseases and the maintenance of healthy muscles is crucial for preventing metabolic disorders. Thus, elucidating the mechanisms of GC action in skeletal muscle contribute to overcoming not only GC-induced myopathy but also wide spectrum of medical disorders. 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 demonstrated that KLF15 participates in muscle catabolism via the transcriptional regulation of atrogin-1 and MuRF1. Moreover, KLF15 affects mTOR through BCAA degradation and negatively modulates myofiber size. mTOR activation inhibits GR-mediated transcription by suppressing GR recruitment onto target genes, strongly suggesting a mutually exclusive crosstalk between mTOR and GR. Pharmacological activation of mTOR with BCAA attenuated GR-mediated gene expression, leading to the substantial restoration of muscle in glucocorticoid-treated rats. We, therefore, indicate the critical importance of the interaction of GR and mTOR in the regulation of metabolism-volume coupling in skeletal muscle. Recently, we have created skeletal muscle-specific GR knockout mice (mGRKO) and revealed that mGRKO show significant increase of their myofiber size and muscle mass. Given this, we have been working with the clinical trial in IMSUT hospital to verify our scenario in glucocorticoid-treated patients.

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

Hirotoshi Tanaka, Noritada Yoshikawa, Noriaki Shimizu, Toshiki Eri, Hiroki Yamazaki, Takako Maruyama, Akiko Souta-Kuribara, Erika Matsubara, Yuki Tasaka, Aya Oda, Masaaki Uehara, Yuji Nakamura, Akane Fukuda, Naoki Ito, Shin'ichi Takeda[1]: [1]Department of Molecular Therapy, National Institute of Neuroscience, National Center of Neurology and Psychiatry

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

Obesity and its associated ills, such as diabetes and metabolic syndrome, are increasing at an alarming rate worldwide. The quest for antiobesity therapies has been bolstered by recent work suggesting that nuclear receptors and their coactivators may represent tractable targets. We created mGRKO and these mice show skeletal muscle hypertrophy and loss of adipose tissues, suggesting that mGRKO mimic the opposite phenotype against metabolic syndrome. Metabolically, mGRKO mice show a drastic shift of energy utilization and storage in muscle, liver and adipose tissues. We investigated that the resulting depletion of plasma alanine serves as a cue to increase plasma levels of fibroblast growth factor 21 (FGF21) and activates liver-fat communication, leading to the activation of lipolytic genes in adipose tissues. Prolonged treatment in wild-type mice with excess GC exhibited metabolic syndrome involving central obesity, fatty liver, and impaired glucose tolerance, as expected, mGRKO mitigated such metabolic unhealthy phenotype. Targeting the skeletal muscle-liver-fat sig-

nalling axis involving glucose-alanine cycle, therefore, would be a novel approach for treatment of patients with obesity, diabetes and metabolic syndrome.

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

The metabolic syndrome is basically a maturity-onset disease. Typically, its manifestations begin to flourish years after the initial dietary or environmental aggression began. In addition, the metabolic syndrome tends to appear more often and/or earlier in adult males than in females, the differences in incidence decreasing sharply after menopause, suggesting that sex hormones and their receptors play a certain role in metabolic pathways. Globally, in the metabolic syndrome, there is a decrease in all functions related to the androgen-estrogen system. This decrease in systemic sex hormones may have tissue-specific effects on androgen and/or estrogen-responsive tissues such as adipose tissue and skeletal muscle. Recently, impaired estrogen receptor α (ERα) and androgen receptor (AR) action has shown to promote obesity and metabolic dysfunction in humans and mice. On the other hand, we revealed that mGRKO shows the opposite phenotype against metabolic syndrome. Therefore, we hypothesized that clarification of functional crosstalk between GR and ERα/AR in adipose tissue and skeletal muscle contributes to developing a novel therapeutic modality for metabolic syndrome. Now, we are challenging to unveil the crosstalk between GR and ERα/AR in skeletal muscle by using mGRKO, mERαKO, mGR/ERα double KO, mARKO, mGR/AR double KO, ovariectomized, and orchiectomized mice, and a mice model of Cushing's disease.

(iii) Development of novel therapeutic approach for regeneration of skeletal muscle

Satellite cells comprise a functionally heterogeneous population of stem cells in skeletal muscle. Separation of an undifferentiated subpopulation and elucidation of its molecular background are necessary to identify the reprogramming factors to induce skeletal muscle progenitor cells. We found that intracellular esterase activity distinguishes a subpopulation of cultured satellite cells with high stemness using esterase-sensitive cell staining reagent, calcein-AM. Gene expression analysis of this subpopulation revealed that defined combinations of transcription factors reprogrammed fibroblasts into skeletal muscle progenitor cells. These reprogrammed cells formed Dystrophin-positive mature muscle fibers when transplanted into a mouse model of Duchenne muscular dystrophy. These results highlight the new marker for heterogeneous population of cultured satellite cells, potential therapeutic approaches and cell sources for degenerative muscle diseases.

4. Analysis of direct and sex hormone-independent action of sex hormone-binding globulin (SHBG) for preventing chronic inflammation and metabolic syndrome

Hiroki Yamazaki, Noriaki Shimizu, Noritada Yoshikawa, Toshiki Eri, Masaaki Uehara, Aya Oda, Yuki Tasaka, Takako Maruyama, Akiko-Souta Kuribara, Naoki Ito, Yuji Nakamura, Akane Fukuda, Hirotoshi Tanaka

Sex hormone-binding globulin (SHBG) regulates the levels of free sex hormones. However, biological functions through itself have been largely unknown. In human studies, serum SHBG was negatively correlated with obesity, dyslipidemia, metabolic syndrome, insulin resistance, and type 2 diabetes. Moreover, the lower concentrations of SHBG are correlated with higher level of serum inflammatory markers. Recently, the chronic low-grade inflammatory condition that often accompanies the metabolic syndrome has been implicated as a major factor both in the installation of the metabolic syndrome and its associated pathophysiological consequences. Thus, we hypothesized that SHBG may exert anti-inflammatory effects and contribute to preventing metabolic syndrome. We revealed that SHBG treatment suppressed lipopolysaccharide-induced inflammatory cytokine expressions in differentiated 3T3-L1 adipocytes and murine peritoneal macrophages independent of sex steroid hormones. In co-culture system using mature 3T3-L1 cells and murine peritoneal macrophages, we revealed that inflammatory cytokine expressions were downregulated by treatment with SHBG via suppressing phosphorylations of JNK and ERK. We investigated a novel function of SHBG and further studies are warranted to develop a novel strategy against metabolic syndrome.

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

Toshiki Eri, Kimito Kawahata[1], Takeyuki Kanzaki[2], Mitsuru Imamura[2], Kazuya Michishita[2], Lisa Aakahira[2], Ei Bannai[2], Takeshi Satoh[3], Kimura Yasumasa[3], Satoshi Uematsu[3], Hirotoshi Tanaka, Kazuhiko Yamamoto[2]: [1]Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine, [2]The Department of Allergy and Rheumatology, The University of Tokyo Hospital, [3]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 immune 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 $CD4^+CD25^-$ 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 $PD\text{-}1^+CXCR5^-$ 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 was essential for their generation, since depletion of intestinal microbiota in recipient mice by antibiotics resulted in a reduction of LIP-induced $PD\text{-}1^+CXCR5^-$ 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.

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

Hirotoshi Tanaka, Noritada Yoshikawa, Masaaki Uehara, Aya Oda, Erika Matsubara, Hiroyuki Baba, Naoki Ito, Yuki Tasaka, Takako Maruyama, Akiko Souta-Kuribara, Yuji Nakamura, Akane Fukuda, Toshiki Eri, Hiroki Yamazaki, Noriaki Shimizu, Shigeru Kiryu[1], Fumitaka Nagamura[2]: [1]Department of Radiology, IMSUT Hospital, [2]Division of Advanced Medicine Promotion, Advanced Clinical Research Center, IMSUT Hospital, Institute of Medical Science, The University of Tokyo

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, "Effect of branched-chain amino acid - enriched beverage "Amino - Value [CONC.]" supplementation in patients with glucocorticoid - induced muscle atrophy (UMIN000006972)". We revealed that BCAA supplementation in patients with rheumatic disorders taking GC might be safe and, at least in part, improve their skeletal muscle mass, strength, and function. 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.

7. 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 overexpression system for modified cholera toxin B subunit, and confirmed that orally administered rice-based vaccine effectively inhibited cholera toxin-induced diarrhea in mice. To establish MucoRice-CTB for human use, hygromycin phosphotransferase selection marker-free MucoRice-CTB line 51A was developed. MucoRice-CTB was new generation of mucosal vaccine, "Cold-chain- and Needle-free Rice-based Vaccines", which is promising especially in

developing countries.

For clinical trials, they established a prototype of a closed MucoRice hydroponic factory at IMSUT, which was approved as GMP (Good Manufacturing Practices) factory by the Japanese Ministry of Health, Labour and Welfare in 2014. We 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.

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IMSUT Hospital

Department of General Medicine
総合診療科

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

【兼務】
*1Division of Infectious Diseases, The Advanced Clinical Research Center
（先端医療研究センター感染症分野）
*2Division of Advanced Genome Medicine, The Advanced Clinical Research Center
（先端医療研究センター先端ゲノム医学分野）
*3Corporate Sponsored Research Programs, Social Cooperation Research Programs, Project Division of ALA Advanced Medical Research（寄付研究部門・社会連携研究部門　ALA先端医療学社会連携研究部門）

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

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

Matsubara Y., Hirata Y.

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

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

Matsubara Y., Hirata Y.

548 cases of upper gastrointestinal endoscopy and 208 cases of colonic endoscopy were performed from April 1 to December 31, 2017. We have diagnosed relatively rare disease (eg. infectious disease, malignancy, other disease) in patients with immune dysfunction. We also participated in endoscopic health check up in Minato Ward.

3. Treatment of patients with advanced cancer.

Hijikata Y.

Eighteen patients with advanced cancer received medical management in our department between April 1 and December 31, 2017. As shown in Table 1, patients with various types of cancer were

Table 1. Types of malignant disease in 2017

Type of disease	Number
Gastric cancer	5
Lung cancer	3
Breast cancer	3
Head and neck cancer	2
Gall bladder cancer	1
Cutaneous T cell Lymphoma	1
Diffuse large B cell lymphoma	1
Neuroendcrine carcinoma	1
Pancreatic cancer	1

treated by standard therapy including chemotherapy, molecular target drugs, immune checkpoint blockade, surgery and radiation therapy. By the help of special patient support team undergirded by conference twice a week, overall survival of our patients was longer than respectively reported overall survival. Importantly, it looked like they enjoyed their stay in our hospital. We actively make use the patient's cancer genome data to introduce the best treatment for patient refractory to standard treatment after the approval of our ethical committee. We also are trying to start clinical trials of new immune therapy targeting standard chemotherapy refractory cases.

Our team has recently published following manuscript in the international journal.

A phase I clinical trial of RNF43 peptide-related immune cell therapy combined with low-dose cyclophosphamide in patients with advanced solid tumors (PLoS One. 2018 Jan 2: 13(1): e0187878)

The objective of this study was to investigate the safety and the tolerability of combined cellular immunotherapy with low-dose cyclophosphamide (CPA) 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^2 CPA followed by autologous lymphocytes, preliminarily cultured with autologous RNF43 peptide-pulsed dendritic cells (DCs), RNF43 peptide-pulsed DCs and systemic low dose interleukin-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 CPA administration. The ratio of interferon-γ-producing, tumor-reactive CD8+ T cells increased with time in patients with SD. We successfully showed that the combination of immune cell therapy and CPA was safe, might induce tumor-specific immune responses and clinical efficacy, and was accompanied by a decreased ratio of Tregs in patients with RNF43-positive advanced solid tumors.

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IMSUT Hospital

Department of Applied Genomics
ゲノム診療科

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

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

1. Genetic testing 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 2017, a total of 539 genetic analyses were performed in our department. The results were utilized for the precise classification of neoplasms, evaluation of disease status, selection of therapeutic drugs, and evaluation of the response to treatment.

2. Genetic counseling and related activities

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

We provided genetic counseling and genetic tests to clients who visited our counseling clinic. In 2017, we had a total of 40 counseling cases including familial breast cancer, Lynch syndrome, familial adenomatous polyposis, Peutz-Jeghers syndrome, multiple endocrine neoplasia, Von Hippel-Lindau syndrome, Charcot-Marie-Tooth disease, 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[1], Tsuneo Ikenoue, Yoichi Furukawa: [1]Division of Clinical Genome Research, Advanced Clinical Research Center

We analyzed genetic alterations in Japanese pseudomyxoma peritonei of the colon (PMP) using multiplex PCR-based targeted enrichment and next generation sequencing (NGS).

We previously analyzed 18 PMPs containing 10 low-grade tumors (DPAMs) and 8 high-grade tumors (PMCAs). As a result, a total of 35 somatic mutations were identified. Frequent mutations were identified in *KRAS* (14/18) and *GNAS* (8/18), but their frequencies were not significantly different between DPAMs and PMCAs. On the other hand, *TP53* mutations were found in PMCAs (3/8), but not in the DPAMs. *PIK3CA* and *AKT1* mutations were also identified in two PMCAs, but not in the DPAMs. These results suggest that *KRAS* and/or *GNAS* mutations are common genetic features of PMP, and that mutations in *TP53* and/or genes related to the PI3K-AKT pathway may render malignant properties to PMP. To comprehensively understand genetic alterations in PMP, we extensively analyzed PMP tumors and matched normal colonic mucosa by the whole-genome sequencing and RNA sequencing. Ongoing analysis of genetic and transcriptome data will provide the better understanding of tumor characteristics, and facilitate the development of personalized medicine for PMP.

4. Clinical sequence for the implementation of genomic medicine

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

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

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

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

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IMSUT Hospital

Department of Radiology
放射線科

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

Department of Radiological Technology
放射線部

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

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

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

1. Deep learning for liver radiological imaging

Yasaka K, Akai H, Kunimatsu A, Abe O[1], Kiryu S[2]: [1]Department of Radiology, Graduate School of Medicine, The University of Tokyo, [2]Department of Radiology, Graduate School of Medical Sci-

ences, International University of Health and Welfare

First, we investigated diagnostic performance of a deep learning method with a convolutional neural network (CNN) for the differentiation of liver masses at dynamic contrast agent-enhanced computed tomography (CT). This clinical retrospective study used CT image sets of liver masses over three phases (unenhanced, arterial, and delayed). Masses were diagnosed according to five categories (category A, classic hepatocellular carcinomas [HCCs]; category B, malignant liver tumors other than classic and early HCCs; category C, indeterminate masses or mass-like lesions [including early HCCs and dysplastic nodules] and rare benign liver masses other than hemangiomas and cysts; category D, hemangiomas; and category E, cysts). Supervised training was performed by using 55,536 image sets obtained in 2013 (from 460 patients, 1068 sets were obtained and they were augmented by a factor of 52 [rotated, parallel-shifted, strongly enlarged, and noise-added images were generated from the original images]). The CNN was composed of six convolutional, three maximum pooling, and three fully connected layers. The CNN was tested with 100 liver mass image sets obtained in 2016 (74 men and 26 women; mean age, 66.4 years ± 10.6 [standard deviation]; mean mass size, 26.9 mm ± 25.9; 21, nine, 35, 20, and 15 liver masses for categories A, B, C, D, and E, respectively). Training and testing were performed five times. Accuracy for categorizing liver masses with CNN model and the area under receiver operating characteristic curve for differentiating categories A-B versus categories C-E were calculated. Median accuracy of differential diagnosis of liver masses for test data were 0.84. Median area under the receiver operating characteristic curve for differentiating categories A-B from C-E was 0.92. In conclusion, deep learning with CNN showed high diagnostic performance in differentiation of liver masses at dynamic CT.

Second, we investigated the performance of a deep convolutional neural network (DCNN) model in the staging of liver fibrosis using gadoxetic acid-enhanced hepatobiliary phase magnetic resonance (MR) imaging. This retrospective study included patients for whom input data (hepatobiliary phase MR images, static magnetic field of the imaging unit, and hepatitis B and C virus testing results available, either positive or negative) and reference standard data (liver fibrosis stage evaluated from biopsy or surgical specimens obtained within 6 months of the MR examinations) were available were assigned to the training (534 patients) or the test (100 patients) group. For the training group (54, 53, 81, 113, and 233 patients with fibrosis stages F0, F1, F2, F3, and F4, respectively; mean patient age, 67.4 ± 9.7 years; 388 males and 146 females), MR images with three different section levels were augmented 90-fold (rotated, parallel-shifted, brightness-changed and contrast-changed images were generated; a total of 144 180 images). Supervised training was performed by using the DCNN model to minimize the difference between the output data (fibrosis score obtained through deep learning [FDL score]) and liver fibrosis stage. The performance of the DCNN model was evaluated in the test group (10, 10, 15, 20, and 45 patients with fibrosis stages F 0, F1, F2, F3, and F4, respectively; mean patient age, 66.8 years ± 10.7; 71 male patients and 29 female patients) with receiver operating characteristic (ROC) analyses. The FDL score was correlated significantly with fibrosis stage (Spearman rank correlation coefficient: 0.63; $P < .001$). Fibrosis stages F4, F3, and F2 were diagnosed with areas under the ROC curve of 0.84, 0.84, and 0.85, respectively. In conclusion, the DCNN model exhibited a high diagnostic performance in the staging of liver fibrosis.

2. Role of delayed-time-point imaging during abdominal and pelvic cancer screening using FDG-PET/CT in the general population

Naganawa S[1], Yoshikawa T[3], Yasaka K, Maeda E[3], Hayashi N[3], Abe O: [1]Department of Radiology, Graduate School of Medicine, The University of Tokyo, [3]Department of Computational Diagnostic Radiology and Preventive Medicine, The University of Tokyo Hospital

Although delayed-time-point imaging is expected to improve the results of [F]-fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT), how examinees will benefit from dual-time-point imaging versus initial-time-point imaging alone, remains unclear. This study investigated the role of delayed-time-point imaging in improving the results of abdominal and pelvic cancer screening using FDG-PET/CT. This retrospective review included 3131 screening results (average subject age: 55.5 years, range: 40-88 years). First, 2 nuclear medicine physicians tentatively evaluated whole-body initial-time-point PET/CT scans. Subsequently, delayed-time-point imaging of the abdomen and pelvis was performed approximately 150 min after FDG injection, followed by re-evaluation for necessary changes. All changed records were retrospectively reviewed and classified as either lesions that were found in initial-time-point images but were changed into negative by adding delayed scan or newly detected findings of suspected malignancy on delayed-time-point images; lesions suspected to be malignant were subjected to further pathologic review. Diagnostic performance according to sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated and com-

pared between initial-time-point and dual-time-point imaging. Fifty-four records were changed after addition of the delayed-time-point imaging. Of the 105 suspected malignancies on initial-time-point images, 10 were changed into negative following the delayed scan. In addition, 44 lesions were newly detected as suspected malignancies on delayed-time-point images. Thirty-six lesions were proven to be pathologically malignant. Of these, 26 were detected on initial-time-point images, and 8 lesions (gastrointestinal adenocarcinoma, 6; prostate adenocarcinoma, 2) were observed on delayed-time-point images. The sensitivity of dual-time-point imaging (58.6% [34/58]) was significantly higher than that of initial-time-point imaging only (44.8% [26/58]) (P = .005); however, specificity and accuracy of dual-time-point imaging (96.6% [2968/3073] and 95.9% [3002/3131], respectively) were significantly lower than those of initial-time-point imaging only (97.4% [2994/3073] and 96.5% [3020/3131], respectively) (P<.0001 and P=.013, respectively). There were no significant differences in PPV (initial-time-point imaging: 24.8% [26/105], dual-time-point imaging: 24.5% [34/139]) and NPV (98.9% [2994/3026] and 99.2% [2968/3073], respectively). The inclusion of delayed PET/CT in screening examinations facilitated the detection of pathologically malignant lesions, particularly in the gastrointestinal tract, while also detecting benign and false-negative lesions.

3. Gadoxetate disodium-induced tachypnoea and the effect of dilution method: A proof-of-concept study in mice

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

We performed this experiment to directly investigate the rapid respiratory effect of gadoxetate disodium in an experimental study using mice. After confirming the steady respiratory state under general anaesthesia, eight mice were injected with all test agents in the following order: phosphate-buffered saline (A,control group), 1.25 mmol/kg of gadoteridol (B) or gadopentetate dimeglumine (C), or 0.31 mmol/kg of gadoxetate disodium (D, E). The experimenter was not blinded to the agents. The injection dose was fixed as 100 μL for Groups A-D and 50 μL for Group E. We continuously monitored and recorded respiratory rate (RR), peripheral oxygen saturation (SpO2), and heart rate. The time-series changes from 0 to 30 s were compared by the linear mixed method. As a result, Groups D and E showed the largest RR increase (20.6 and 20.3 breaths/min, respectively) and were significantly larger compared to Group A (3.36 breaths/min, both P<0.001). RR change of Groups D and E did not differ. RR change of Groups B and C was smaller (0.72 and 12.4 breaths/min, respectively) and did not differ statistically with Group A. Significant bradycardia was observed only in Group C (P<0.001). SpO2 was constant in all groups. In conclusion, gadoxetate disodium causes a rapid tachypnoea without significant change of SpO2 and heart rate regardless of the dilution method.

4. New prognostic feature for resected hepatocellular carcinoma; Radiomics analysis via dynamic-enhanced computed tomography with a machine learning classifier

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

We investigated the impact of random survival forest (RSF) classifier trained by radiomics features over the prediction of the overall survival of patients with resectable hepatocellular carcinoma (HCC). The dynamic computed tomography data of 127 patients newly diagnosed with resectable HCC were retrospectively analyzed. After manually setting the region of interest to include the tumor within the slice at its maximum diameter, texture analyses were performed with or without a Laplacian of Gaussian filter. Using the extracted 96 quantitative texture features, RSFs were trained using 10-fold cross-validation to predict the individual risk for each patient on disease free survival (DFS) and overall survival (OS). The associations between individual risk and DFS or OS were evaluated using Kaplan-Meier analysis. The effects of the predicted individual risk and clinical variables upon OS were analyzed using a multivariate Cox proportional hazards model. As a result, among the 96 quantitative texture features, RSF extracted 8 of high importance for DFS and 15 for OS. The RSF trained by these features distinguished two patient groups with high and low predicted individual risk ($p = 3.7 \times 10\text{-}3$ for DFS, $2.4 \times 10\text{-}6$ for OS). Based on the multivariate Cox proportional hazards model, high predicted individual risk (hazard ratio = 1.058 per 1% increase, $p = 3.3 \times 10\text{-}8$) and vascular invasion (hazard ratio = 1.720, p = 0.043) were the only unfavorable prognostic factors. In conclusion, the combination of radiomics analysis and RSF showed high prognostic performance over the prediction of the prognosis of patients with resectable HCC.

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IMSUT Hospital

Department of Palliative Medicine
緩和医療科

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

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

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IMSUT Hospital

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

Project Associate Professor Yasunori Ota, M.D., Ph.D. 特任准教授 博士(医学) 大 田 泰 徳

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

Overview

We study about the hematological malignancy and transplantation pathology. We emphasize many clinical cases and write case reports about human diseases.
Acinic cell carcinoma in parotid gland is a rare tumor. Lymphoblasts proliferate around tumor cells mimicking lymphoblastic lymphoma. We reported this rare phenomenon and served as a warn of the overdiagnosis and over chemotherapy.
We also reported a rare gastric tumor, plexiform angiomyxoid myofibroblastic tumor.

We analyze tissue specimens of laboratory animals and try to help research by grasping pathophysiology. We clarified the immune reactions occurring in all organs of the body in chimeric mice, and made recommendations for efficient generation of chimeric mice.

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IMSUT Hospital

Department of Surgery
外科

Professor	Keiya Ozawa, M.D., Ph.D.	教　授(兼務)	医学博士	小　澤　敬　也
Associate Professor	Masaru Shinozaki, M.D., Ph.D.	准教授	博士(医学)	篠　崎　　大
Senior Assistant Professor	Giichiro Tsurita, M.D., Ph.D.	講　師	博士(医学)	釣　田　義一郎
Assistant Professor	Kentaro Yazawa, M.D., Ph.D.	助　教	博士(医学)	谷　澤　健太郎

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

1. Treatment for gastrointestinal malignancy

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

2. Treatment for benign colon anal disease

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

3. Endoscopic examination or treatment

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

4. Hospital collaboration, personnel exchange

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

5. International research activities

Dr. Tomohiro Kurokawa, a senior fellow belonging to our department, has studied at Massachusetts General Hospital in Boston. We also performed many research presentations at international

conferences and published many papers to international journals

Publications

1. Yazawa K, Azuma Y, Kurokawa T, Yoshioka Y, Tsurita G, Shinozaki M. Abdominal CT-aided diagnosis of acute appendicitis in the presence of mobile cecum: A case report. Int J Surg Case Rep. in press
2. Kanemoto Y, Tanimoto T, Maeda Y, Kurokawa T, Tsurita G. Timing of surgical antimicrobial prophylaxis. Lancet Infect Dis. 17(10): 1019-20, 2017
3. Yoshioka Y, Suzuki T, Matsuo Y, Tsurita G, Watanabe T, Dohmae N, Nakamura Y, Hamamoto R. Protein lysine methyltransferase SMYD3 is involved in tumorigenesis through regulation of HER2 homodimerization. Cancer Med. 6(7): 1665-72, 2017
4. Kurokawa T, Tsurita G, Tanimoto T, Kanzaki N, Ejiri T. Short-course radiotherapy with delayed surgery for rectal cancer. Lancet Oncol. 18(6): e293, 2017.
5. Kurokawa T, Tsurita G, Yazawa K, Shinozaki M. Ileal strangulation by a secondary perineal hernia after laparoscopic abdominoperineal rectal resection: A case report. Int J Surg Case Rep. 33: 107-11, 2017
6. Inoue E, Hata K, Kimura H, Yamaguchi K, Nojima M, Endo I, Shinozaki M. Altered expression of microRNAs in patients with pouchitis after restorative proctocolectomy. Surg Today. 47(12): 1484-91, 2017

IMSUT Hospital

Department of Anesthesia
麻酔科

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

准教授 博士(医学) 折井 亮
助 教 医学士 柴田玲子

Our clinical practice and clinical studies have been focused on (1) anesthetic management in patients undergoing major surgery including joint arthroplastic surgery for hemophilia patients, variable surgical procedures for translational researches (2) assessment of 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 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. Anesthetic management for carrier hemophilia.

Anesthesia cases of hemophilia patients require special hemostatic management.

Among them, female hemophilia patients are often not informed as carriers themselves, and there is a possibility that medical practice may be performed without recognizing them as hemophilia patients.

We experienced anesthesia of female hemophilia patients and safety managed anesthesia with appropriate hemostatic management. Female hemophilia anesthesia experience in Japan is mostly reported as acquired hemophilia, and case reports on definite and estimated carriers are few in overseas. We report that knowledge of female hemophilia should be obtained as an anesthesiologist.

3. Assessment of reliability of cardiac output measurements.

Knowing a patient's cardiac output (CO) could contribute to a safe, optimized hemodynamic control during surgery. Precise CO measurements can serve as a guide for resuscitation therapy, catecholamine use, differential diagnosis, and intervention during a hemodynamic crisis. Despite its invasiveness and intermittent nature, the thermodilution technique via a pulmonary artery catheter (PAC) remains the clinical gold standard for CO measurements. LiDCO rapid™(LiDCO, London, UK) and FloTrac/Vigileo™ (Edwards Lifesciences, Irvine, CA) are less invasive continuous CO monitors that use arterial waveform analysis. We found both devices tended to underestimate the caluculated CIs when

the CIs were relatively high. These proportional bias produced large parcentage errors in the present study.

4. Risk management of medical electronic devices.

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

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. 31(4):709-716, 2017.
2. 柴田玲子，竹谷英之，土田陸平，西田恭二，大野久美子，折井　亮．女性血友病患者の麻酔経験．日本麻酔科学会第57回支部学術集会，プログラム：P17，2017

IMSUT Hospital

Department of Joint Surgery
関節外科

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

講 師 博士(医学) 竹 谷 英 之
助 教 博士(医学) 大 野 久美子

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

Surgical treatment for haemophilia

From 2006 to 2016, more than 200 surgical treatments for hemophilia included other coagulation diseases such as deficiency factor VII or Von Willebrand disease. Some of them have the deficiency factor antibody as well.

In 2017, we were performed 9 surgical treatments (5 total joint arthroplasties and 4 other surgical treatments).

Publications

1. Hampton K, Chowdary P, Dunkley S, Ehrenforth S, Jacobsen L, Neff A, et al. First report on the safety and efficacy of an extended half-life glycoPEGylated recombinant FVIII for major surgery in severe haemophilia A. Haemophilia. Sep; 23(5):689-96, 2017.
2. 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. Mar;23(2):e116-e23, 2017.
3. Ono K, Hirose J, Chang SH, Kubota M, Kinkawa J, Noguchi M, et al. Orthotropic live transplantation for cirrhosis from hepatitis C virus leads to correction of factor IX deficiency allowing for ankle arthroplasty without factor replacement in a patient with moderate haemophilia B. Blood Coagul Fibrinolysis. Jan;29(1):131-4, 2018.
4. 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. Jan;23(1):59-66, 2017.
5. Takedani H, Solimeno L, Saxena K, Kalweit L, Mathew P. The Haemophilia Joint Visualizer: development of a personalized, interactive, web-based tool to help improve adherence to prophylaxis. Haemophilia. Haemophilia. Mar;23(2):e155-e8, 2017.
6. Yasui T, Hirose J, Ono K, Takedani H. Arthroscopic debridement for advanced haemophilic ankle arthropathy. Haemophilia. Sep;23(5):e479-e 81, 2017.

IMSUT Hospital

Department of Surgical Neuro-Oncology
脳腫瘍外科

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

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 (G 47Δ) in patients with glioblastoma

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

A clinical study of G47Δ in patients with progressive olfactory neuroblastoma

A phase I clinical trial of G47Δin 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.

Treatment of malignant glioma patients

Our department started treating in-patients in April 2012. Standard craniotomies and image guided stereotactic biopsies of deep seated lesions, as well as high-tech brain tumor resections have been performed. The high-tech equipment regularly used in brain tumor resection surgeries includes an operative microscope, a 3-D neuro-navigation system, intraoperative motor evoked potential monitoring, intraoperative ultrasonography and an ultrasonic surgical aspirator. A total of 36 operations were carried out in 2017 including 35 glioma and one brain metastases.

Patients with newly diagnosed malignant glioma have been treated with high dose or standard dose

radiation therapy and concomitant chemotherapy. Temozolomide was administered to glioma patients during radiation therapy followed by a maintenance therapy every 28 days for as long as possible. The overall survival of patients with glioblastoma was 30.3 months (95% confidence interval, 23.4-37.2 months). The five-year overall survival rate was 31.1%.

Recurrent malignant glioma patients are treated with innovative non-standard therapies whenever possible. Small recurrent glioma lesions are treated with extended field stereotactic radiosurgery. To enhance the efficacy of stereotactic radiosurgery (SRS), the irradiation field is enlarged to include as many tumor cells as possible that are invasive to the surrounding tissue. This approach demonstrated 93% local control in patients who received 20 Gy to a 0.5-1.0 cm extended field SRS, whereas 47% of patients who received 20 Gy to the gadolinium-enhancing margin only.

Treatment of primary central nervous system lymphoma

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

IMSUT Hospital

Department of Medical Informatics
医療情報部

Associate Professor	Akira Kunimatsu, M.D., D.M.Sc.	准教授	博士(医学)	國松　聡
Senior Assistant Professor	Hiroyuki Akai, M.D., D.M.Sc.	講　師	博士(医学)	赤井宏行
Assistant Professor	Koichiro Yasaka, M.D., D.M.Sc.	助　教	博士(医学)	八坂耕一郎

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

1. Management and operation of hospital information system and network

Akira Kunimatsu, Hiroyuki Akai, Koichiro Yasaka

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

Our missions are as follows:

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

2. IT support to community-based healthcare provider network

Akira Kunimatsu, Hiroyuki Akai, Koichiro Yasaka

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

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

IMSUT Hospital

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

Associate Professor Tokiko Nagamura-Inoue, M.D., Ph.D.
Assistant Professor Toyotaka Kawamata, M.D., Ph.D.

准教授 博士(医学) 長 村 登紀子
助 教 博士(医学) 川 俣 豊 隆

Our department was established in 1990, in order to manage the transfusion medicine and the cell processing for hematopoietic stem cell transplantation. In addition to the transfusion medicine and testing in the hospital, our department has been supporting translational research and managing IMSUT-Cell Resource Center (IMSUT-CRC), which has been established in 1997. Recent our projects include Research Cord Blood Bank (RCBB), as National BioResource Project (NBRP) supported by AMED (MEXT) and CB and umbilical cord (UC)-derived mesenchymal stromal cell (MSC) banking for clinical use supported by AMED (MHLW). Now we developed immunosuppressive cell therapy for severe acute GVHD after hematopoietic stem cell transplantation, using UC-MSCs. We also explore the clinical application of UC-MSC for newborn encephalopathy, some of which develop to cerebral palsy.

1. Transfusion medicine and related tests

Abe Y, Ogami K, Hiratak K, Kawamata T, Tsuda M., Nagamura-Inoue T

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

2. Peripheral Blood Stem Cell mobilization and collection:

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

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

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

Nagamura-Inoue T, Takahashi A, Shimazu T, Hori A, Okada M, Mori Y, Ichimura S, Mukai T, Nagayama, Nagamura F, Konuma T, Saito Y, Tojo A

Umbilical cord (UC) is a rich source of mesenchy-

mal stromal cells (MSCs). MSCs have self-renewal capacity, multi-lineage differentiation potential and the ability to migrate toward sites of inflammation or injury, where MSCs control the inflammation and repair the damaged tissues. UC-MSCs harbored the immunosuppressive effects. Even 3rd party donor-derived UC-MSCs suppress the activated T cells stimulated by allogeneic dendritic cells, through IDO, PGE2, and HGF etc. We succeeded the serum free processing, expansion, and cryopreservation of UC-MSCs. Now we are going to apply the UC-MSCs for the treatment of severe acute graft-versus-host disease (GVHD), as the investigator initiated clinical trial.

4. 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.

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

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

Izawa M, Horie I, Natori M, Ichimura S, Takahashi A, Hori A, Shimazu T, Nagamura-Inoue T,

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

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

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

To promote the cell therapy in translational researches, IMSUT-Cell Resource Center (IMSUT-CRC) has been established in 1997 (originally called as Room for Clinical Cellular Technology (RCCT)). Until now, the following projects had 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).

Visit our website: http://www.ims.u-tokyo.ac.jp/dcpt/english/

Publications

1) Nagamura-Inoue T, Atsuta Y, Kodera Y, and Okamoto S, Chapter 13 "Transfusion", Editor(s) name(s): Éliane Gluckman, Dietger Niederwieser and Mahmoud Aljurf., Establishing a Hematopoietic Stem Cell Transplantation Unit: A Practical Guide,183-195, 2017
2) Toyotaka Kawamata, Kyoko Hirata, Yuka Abe, Kazuo Ogami, Arinobu Tojo and Tokiko Nagamura-Inoue., A single institutional retrospective analysis of underlying diseases in patients with abo blood grouping discrepancy Japanese Journal of Transfusion and Cell Therapy, Vol. 63. No. 5 63(5):683-690, 2017 (Japanese)
3) Isobe M, Konuma T, Abe-Wada Y, Hirata K, Ogami K, Kato S, Oiwa-Monna M, Tanoue S, Nagamura-Inoue T, Takahashi S, Tojo A. Alloimmune hemolysis due to major RhE incompatibility after unrelated cord blood transplantation.

Leuk Lymphoma. 2017, doi: 10.1080/10428194. 2017.1352095. in press
4) Kondo T, Nagamura-Inoue T, Tojo A, Nagamura F, Uchida N, Nakamae H, Fukuda T, Mori T, Yano S, Kurokawa M, Ueno H, Kanamori H, Hashimoto H, Onizuka M, Takanashi M, Ichinohe T, Atsuta Y, Ohashi K. Clinical impact of pretransplant use of multiple tyrosine kinase inhibitors on the outcome of allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia. Am J Hematol. 92, 902-908, 2017
5) Mukai T., Mori Y., Shimazu T., Takahashi A., Tsunoda H., Yamaguchi S., Kiryu S, Tojo A., and Nagamura-Inoue T. Intravenous injection of umbilical cord derived mesenchymal stromal cells attenuates reactive gliosis and hypomyelination in a neonatal intraventricular hemorrhage model, Neuroscience, 355,175-187, 2017 doi: 10.1016/j.neuroscience.2017.05.006
6) Shigematsu A, Kako S, Mitsuhashi K, Iwato K, Uchida N, Kanda Y, Fukuda T, Sawa M, Senoo Y, Ogawa H, Miyamura K, Takada S, Nagamura-Inoue T, Morishima Y, Ichinohe T, Atsuta Y, Mizuta S, Tanaka J. Allogeneic stem cell transplantation for adult patients with acute lymphoblastic leukemia who had central nervous system involvement: a study from the Adult ALL Working Group of the Japan Society for Hematopoietic Cell Transplantation. Int J Hematol. 2017 Feb 14. doi: 10.1007/s12185-017-2197-1.

IMSUT Hospital

Surgical Center
手術部

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

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

Equipment in the surgical center

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

TV monitoring system

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

Induction of electronic ordering system

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

Facts in the fiscal year 2016

Total number of operations	205
Planned operations	196
Emergency operations	11
General anesthesia	142
Spinal	5
Epidural	0
Local	56
Others	2

IMSUT Hospital

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

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

All members of staff.

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

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

2. Statistics and Quality control in Clinical Trials

Masanori Nojima, Motoki Amai, Mitsumi Tokunaga, Fumitaka Nagamura

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

All members of staff

Our mission is to develop efficient approaches for conducting investigator-initiated clinical trials under Investigational New Drug application (IND) to promote translational research. In 2017, we supported three investigator-sponsored clinical trials under IND by site management as well as project management. These three clinical trials were: oncolytic virus for glioma, peptide therapy for after rejection of non-small cell lung cancer, and novel gene-induced adjuvant cells for acute myelogenous leukemia.

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

Minako Kouno, Riyo owada, Fumitaka Nagamura

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

5. Statistical consulting

Masanori Nojima

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

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IMSUT Hospital

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

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

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

Hirotoshi Tanaka, Noritada Yoshikawa, Toshiki Eri, Hiroki Yamazaki, Erika Matsubara, Hiroyuki Baba, Aya Oda, Masaaki Uehara

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. Our 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

2. Translational Research and Clinical Trial of Division of Rheumatology

See the section of Department of Rheumatology

and Allergy, IMSUT Hospital.

3. 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, Kinesin family member 11 (KIF11) was found to be activated in oral cavity carcinoma (OCC), and was suggested to be a novel prognostic biomarker and therapeutic target for OCC.

4. The mechanism of *de novo* expression of programmed cell death-ligand 1 in squamous cell carcinoma of the lung

Yataro Daigo, Tomoyuki Igarashi, Koji Teramoto

Immune checkpoint mechanisms such as the programmed cell death-ligand 1-programmed cell death 1 (PD-L1-PD-1) axis are utilized by tumor cells to evade the cytotoxicity of effector immune cells. However, environmental factors responsible for the expression of PDL1 on tumor cells remain to be fully elucidated. We hypothesized that an immunological interaction with tumor-infiltrating CD8+ lymphocytes (CD8+ TILs) would contribute to PD-L1 expression in tumor cells. To verify this hypothesis, we examined the effect of interferon-γ (IFN-γ), a cytokine secreted by CD8+ TILs, on PD-L1 expression in pulmonary squamous cell carcinomas in vitro. We also evaluated the expression of PD-L1 and major histocompatibility complex (MHC) class I molecules on tumor cells and CD8+ TILs in squamous cell carcinomas of the lung (n=77) by immunohistochemistry. IFN-γ upregulated PD-L1 expression on pulmonary squamous carcinoma cells, and the reaction was reversible. In cases where which MHC class I molecule-positive tumor cells were dominant (n=72, 93.5%), cases in which PD-L1-positive tumor cells were dominant (PD-L1+ tumor cell-dominant cases; n=45) were more frequently observed than PD-L1-negative tumor cell-dominant cases (n=27). The number of CD8+ TILs was significantly higher in PD-L1+ tumor cell-dominant cases compared with PD-L1- tumor cell-dominant cases. These data suggest that the de novo expression of PD-L1 on tumor cells is upregulated by IFN-γ secreted from CD8+ TILs upon recognition of the tumor cells with an MHC class I molecule.

5. Predictive biomarkers and effectiveness of MUC1-targeted dendritic-cell-based vaccine in patients with refractory non-small cell lung cancer

Yataro Daigo, Koji Teramoto

The dendritic cell (DC)-based vaccine targeting the highly immunogenic tumor antigen, MUC1, has been promising for a cancer immunotherapy; however, predictive biomarkers for beneficial clinical responses of the vaccine remain to be determined. DCs loaded with MUC1-derived peptide were subcutaneously administered to patients with MUC1-positive non-small cell lung cancer (NSCLC) that was refractory to standard anticancer therapies, every 2 weeks. The effectiveness and tolerability of the vaccine were evaluated, and predictive biomarkers of clinical responses were explored. Between August 2005 and May 2015, 40 patients received the vaccines. The median survival time (MST) after the initial vaccination was 7.4 months, and the 1-year survival rate was 25.0%. The MST for patients who received more than six vaccinations was 9.5 months, and the 1-year survival rate

was 39.3%. In this cohort, patients who experienced immune-related adverse events, including skin reactions at the vaccination site and fever, had significantly longer survival times compared with patients without those immune-related adverse events (12.6 *versus* 6.7 months, $p = 0.042$). Longer survival times were also observed in patients whose peripheral white blood cells contained >20.0% lymphocytes (12.6 *versus* 4.5 months; $p = 0.014$). MUC1-specific cytotoxic immune responses were achieved in all of seven patients analyzed who received six vaccinations. The MUC1-targeted DC-based vaccine induced an antitumor immune response that promoted prolonged survival of patients with refractory NSCLC. The occurrence of immune-related adverse events and having a higher percentage of peripheral lymphocytes were predictive biomarkers of a beneficial clinical response during cancer immunotherapy for NSCLC.

6. 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 oncoantigens 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.

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

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

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

8. 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 6800 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.

9. 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.

10. Targeting of PRDM14 via siRNA combined with an innovative nanoparticle or small molecule drug inhibits the growth of tumors and the formation of metastases in breast and pancreatic tumor.

Hiroaki Taniguchi

Triple negative breast cancer (hereafter TNBC) and pancreatic cancer exhibits resistant to chemotherapy and radiotherapy, and develops distant metastases. Conventional treatments have had little impacts on them. PRDI-BF1 and RIZ (PR) domain zinc finger protein 14 (PRDM14) is specifically expressed in embryonic stem cells (ESC) and primordial germ cells (PgC), and is required for the maintenance of ESC pluripotency and early differentiation in PgC. There is no expression of PRDM14 in the non-cancerous tissues, however PRDM14 is expressed in ～50% of TNBC and ～30% of pancreatic cancer, approximately. PRDM14 conferred the ability of resistance to chemotherapy, tumorigenicity and metastasis, in other words 'cancer stemness', on cancer cells (Oncotarget 2017, and Carcinogenesis 2017).

i) PRDM14 silencing by siRNA combined with an innovative nanoparticle reduced breast and pancreatic tumor formation and metastasis in vivo.

PRDM14 was localized in nucleus, then we planned to develop an oligonucleotide therapeutics against PRDM14.

Our therapeutic methods are built on clinical application of basic science and technologies. #1. Methods of design the siRNA sequences with higher selectivity to its target and elimination off-target effects. #2. RNA-DNA chimera modification of small interfering RNA (chimera siRNA) exhibited stability in the bloodstream and low immunogenicity. #3. Innovative nanoparticle as a drug delivery system for siRNA exhibited high retention in blood, and accumulated siRNA in targeted cancer tissues, not in liver and spleen, due to the enhanced permeability and retention effect compared with typical nanocarriers, such as Lipid Nanoparticle.

Mice were grafted with PRDM14＋ TNBC or pancreatic cancer cells. We also injected PRDM14＋ TNBC cells into mice via the tail vein for lung metastasis, or PRDM14＋ pancreatic cancer cells into mice via the splenic vein. PRDM14-specific chimera siRNA (1mg/kg) mixed with a nanocarrier was injected into mice tail vain 3 times a week for a month, after the grafted tumor reached over 100 mm3. This treatment caused reduction of tumor volume, reduction by synergistic effect with chemo Tx, and almost no metastatic lesions of cancer cells without any adverse effects.

ii) Development of small molecule drugs as PRDM14 inhibitor in cancer via analysis for protein-protein interactions (PPIs).

We search for the proteins interacting with PRDM14 in cancer cells. We obtained several candidates interacting to PRDM14 via pulldown assay followed by mass spectrometry, and surface plasmon resonance (SPR) analysis, etc. We have already reported HSP90α and GRP78 as the binding partners of PRDM14 in TNBC cells (Cancer Sci 2017).

The interactions between HSP90α or GRP78 and PRDM14 are promising targets for breast cancer treatment.

11. Biophysical analyses of various antibody to propose new strategy for development of the next generation antibody

Satoru Nagatoishi

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

i) Thermodynamic analyses of amino acid residues at the interface of an antibody B2212A and its antigen roundabout homolog 1

A. Yui, H. Akiba, S. Kudo, M. Nakakido, S. Nagatoishi and K. Tsumoto

Artificial affinity maturation of antibodies is promising but often shows difficulties because the roles of each amino acid residue are not well known. To elucidate their roles in affinity against the antigen and thermal stability, interface residues

in single-chain Fv of an antibody B2212A with its antigen roundabout homolog 1 were mutated and analyzed. Some amino acids played important roles in the affinity while others contributed to thermal stability.

ii) Structure of the triose-phosphate/phosphate translocator reveals the basis of substrate specificity

Y. Lee, T. Nishizawa, M. Takemoto, K. Kumazaki, K. Yamashita, K. Hirata, A. Minoda, S. Nagatoishi, K. Tsumoto, R. Ishitani and O. Nureki

The triose-phosphate/phosphate translocator (TPT) catalyses the strict 1:1 exchange of triose-phosphate, 3-phosphoglycerate and inorganic phosphate across the chloroplast envelope, and plays crucial roles in photosynthesis. Despite rigorous study for more than 40 years, the molecular mechanism of TPT is poorly understood because of the lack of structural information. Here we report crystal structures of TPT bound to two different substrates, 3-phosphoglycerate and inorganic phosphate, in occluded conformations. The structures reveal that TPT adopts a 10-transmembrane drug/metabolite transporter fold. Both substrates are bound within the same central pocket, where conserved lysine, arginine and tyrosine residues recognize the shared phosphate group. A structural comparison with the outward-open conformation of the bacterial drug/metabolite transporter suggests a rocker-switch motion of helix bundles, and molecular dynamics simulations support a model in which this rocker-switch motion is tightly coupled to the substrate binding, to ensure strict 1:1 exchange. These results reveal the unique mechanism of sugar phosphate/phosphate exchange by TPT.

iii) Biophysical characterization of the interaction between heme and proteins responsible for heme transfer in S. pyogenes

M. Hoshino, M. Nakakido, S. Nagatoishi, J. M. M. Caaveiro, C. Aikawa, I. Nakagawa and K. Tsumoto

Streptococcus pyogenes, an important pathogen that causes a wide range of diseases, possesses the sia gene cluster, which encodes proteins involved in the heme acquisition system. Although this system was previously described, the molecular mechanism of effective heme transfer remains to be elucidated. Here, we have characterized the interactions between heme and each domain of Streptococcal hemoprotein receptor (Shr) and Streptococcal heme-binding protein (Shp). Our kinetic and thermodynamic analyses suggested that effective heme transfer within this system is achieved not only by affinity-based transfer but also by the difference of the binding driving force. The biophysical characterization of the above-mentioned interaction will lead to an indication for the selection of the target for a chemical screening of inhibitors as novel antibacterial agents based on biophysical approaches.

iv) Structural Basis for Binding and Transfer of Heme in Bacterial Heme-Acquisition Systems

Y. Naoe, N. Nakamura, MM. Rahman, T. Tosha, S. Nagatoishi, K. Tsumoto, Y. Shiro, H. Sugimoto

Periplasmic heme-binding proteins (PBPs) in Gram-negative bacteria are components of the heme acquisition system. These proteins shuttle heme across the periplasmic space from outer membrane receptors to ATP-binding cassette (ABC) heme importers located in the inner-membrane. In the present study, we characterized the structures of PBPs found in the pathogen Burkholderia cenocepacia (BhuT) and in the thermophile Roseiflexus sp. RS-1 (RhuT) in the heme-free and heme-bound forms. The conserved motif, in which a well-conserved Tyr interacts with the nearby Arg coordinates on heme iron, was observed in both PBPs. The heme was recognized by its surroundings in a variety of manners including hydrophobic interactions and hydrogen bonds, which was confirmed by isothermal titration calorimetry. Furthermore, this study of 3 forms of BhuT allowed the first structural comparison and showed that the heme-binding cleft of BhuT adopts an "open" state in the heme-free and 2-heme-bound forms, and a "closed" state in the one-heme-bound form with unique conformational changes. Such a conformational change might adjust the interaction of the heme(s) with the residues in PBP and facilitate the transfer of the heme into the translocation channel of the importer.

v) Use of SpyTag/SpyCatcher to construct bispecific antibodies that target two epitopes of a single antigen

K. Yumura, H. Akiba, S. Nagatoishi, O. Kusano-Arai, H. Iwanari, T. Hamakubo and K. Tsumoto

Bispecific antibody targeting of two different antigens is promising, but when fragment-based antibodies are used, homogeneous production is difficult. To overcome this difficulty, we developed a method using the SpyTag/SpyCatcher system in which a covalent bond is formed between the two polypeptides. Using this method, we constructed a bispecific antibody that simultaneously interacted with two different epitopes of roundabout homologue 1 (ROBO1), a membrane protein associated with cancer progression. A bispecific tetravalent antibody with an additional functional moiety was

also constructed by using a dimeric biotin-binding protein. An interaction analysis of ROBO1-expressing cells and the recombinant antigen demonstrated the improved binding ability of the bispecific antibodies through spontaneous binding of the two antibody fragments to their respective epitopes. In addition, multivalency delayed dissociation, which is advantageous in therapy and diagnosis.

vi) The carboxyl-terminal region of Dok-7 plays a key, but not essential, role in activation of muscle-specific receptor kinase MuSK and neuromuscular synapse formation

R. Ueta, T. Tezuka, Y. Izawa, S. Miyoshi, S. Nagatoishi, K. Tsumoto and Y. Yamanashi

As the synapse between a motor neuron and skeletal muscle, the neuromuscular junction (NMJ) is required for muscle contraction. The formation and maintenance of NMJs are controlled by the muscle-specific receptor kinase MuSK. Dok-7 is the essential cytoplasmic activator of MuSK, and indeed mice lacking Dok-7 form no NMJs. Moreover, DOK7 gene mutations underlie DOK7 myasthenia, an NMJ synaptopathy. Previously, we failed to detect MuSK activation in myotubes by Dok-7 mutated in the N-terminal pleckstrin homology (PH) or phosphotyrosine binding (PTB) domain or that lacked the C-terminal region (Dok-7-ΔC). Here, we found by quantitative analysis that Dok-7-ΔC marginally, but significantly, activated MuSK in myotubes, unlike the PH- or PTB-mutant. Purified, recombinant Dok-7-ΔC, but not other mutants, also showed marginal ability to activate MuSK's cytoplasmic portion, carrying the kinase domain. Consistently, forced expression of Dok-7-ΔC rescued Dok-7-deficient mice from neonatal lethality caused by the lack of NMJs, indicating restored MuSK activation and NMJ formation. However, these mice showed only marginal activation of MuSK and died by 3 weeks of age apparently due to an abnormally small number and size of NMJs. Thus, Dok-7's C-terminal region plays a key, but not fully essential, role in MuSK activation and NMJ formation.

vii) Disruption of cell adhesion by an antibody targeting the cell-adhesive intermediate (X-dimer) of human P-cadherin

S. Kudo, J. M. M. Caaveiro, S. Nagatoishi, T. Miyafusa, T. Matsuura, Y. Sudou and K. Tsumoto

Human P-cadherin is a cell adhesion protein of the family of classical cadherins, the overexpression of which is correlated with poor prognosis in various types of cancer. Antibodies inhibiting cell-cell adhesion mediated by P-cadherin show clear therapeutic effect, although the mechanistic basis explaining their effectiveness is still unclear. Based on structural, physicochemical, and functional analyses, we have elucidated the molecular mechanism of disruption of cell adhesion by antibodies targeting human P-cadherin. Herein we have studied three different antibodies, TSP5, TSP7, and TSP11, each recognizing a different epitope on the surface of the cell-adhesive domain (EC1). Although all these three antibodies recognized human P-cadherin with high affinity, only TSP7 disrupted cell adhesion. Notably, we demonstrated that TSP7 abolishes cell adhesion by disabling the so-called X-dimer (a kinetic adhesive intermediate), in addition to disrupting the strand-swap dimer (the final thermodynamic state). The inhibition of the X-dimer was crucial for the overall inhibitory effect, raising the therapeutic value of a kinetic intermediary not only for preventing, but also for reversing, cell adhesion mediated by a member of the classical cadherin family. These findings should help to design more innovative and effective therapeutic solutions targeting human P-cadherin.

viii) Through-bond effects in the ternary complexes of thrombin sandwiched by two DNA aptamer

A. Pica, I. Russo Krauss, V. Parente, H. Tateishi-Karimata, S. Nagatoishi, K. Tsumoto, N. Sugimoto and F. Sica

Aptamers directed against human thrombin can selectively bind to two different exosites on the protein surface. The simultaneous use of two DNA aptamers, HD1 and HD22, directed to exosite I and exosite II respectively, is a very powerful approach to exploit their combined affinity. Indeed, strategies to link HD1 and HD22 together have been proposed in order to create a single bivalent molecule with an enhanced ability to control thrombin activity. In this work, the crystal structures of two ternary complexes, in which thrombin is sandwiched between two DNA aptamers, are presented and discussed. The structures shed light on the cross talk between the two exosites. The through-bond effects are particularly evident at exosite II, with net consequences on the HD22 structure. Moreover, thermodynamic data on the binding of the two aptamers are also reported and analyzed.

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IMSUT Hospital

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

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

教　授　博士(医学)　藤　堂　具　紀
准教授　博士(医学)　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 is 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

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

Oncolytic MV project

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

IMSUT Hospital

IMSUT Cord
臍帯血・臍帯バンク

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

IMSUT CORD is the umbilical cord blood (CB) and cord (UC) derived cell bank. It has been established in IMSUT hospital, since 2016. The aim of IMSUT CORD is to collect, processing, culture, cryopreservation, stock, and release of the CB and UC/UC-derived cells including mesenchymal stromal cells (MSCs) for clinical and research use. We have released CB and UC-MSCs for research use to the collaborators to accelerate the translational researches in the fields of immunotherapy, regenerative medicine, disease specific drug discovery. We have succeeded the serum-free processing, expansion, and cryopreservation of UC-MSCs and are producing the UC-MSCs product (IMSUT-CORD) for the treatment of severe acute graft-versus-host disease (GVHD) as the investigator initiated clinical trial.

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

Nagamura-Inoue T, Takahashi A, Shimazu T, Hori A, Okada M, Mori Y, Ichimura S, Mukai T, Nagayama, Nagamura F, Konuma T, Saito Y, Tojo A

Umbilical cord (UC) is a rich source of mesenchymal stromal cells (MSCs). The UC is normally disused after birth and its collection does not require an invasive procedure for donors with ethical concerns. Moreover, UC-derived MSCs (UC-MSCs) possess many advantageous features, (1) ease of collection, storage, and transport; (2) abundant sources and high proliferation capacity, (3) multipotency to differentiate into various cell types; (4) low immunogenicity with immunosuppressive ability, (5) migration toward the inflammatory or injured site to subside the inflammationandn repair the damaged tisseus, and (6) no donor age-dependent variations. We have studied these characteristics and succeeded an efficient expansion system of UC-MSCs, in order to apply the regenerative medicine and immunotherapy, supported by AMED.

Collected, CB and UC/UC-MSCs were cryopreserved in liquid nitrogen tank and controlled by IMSUT CORD bank staff. We have released some of them to the collaborator for research use to accelerate the translational researches in the fields of immunotherapy, regenerative medicine, disease specific drug discovery.

We succeeded the serum-free processing, expansion, and cryopreservation of UC-MSCs and are producing the UC-MSCs product (IMSUT-CORD) for the treatment of severe acute graft-versus-host disease (GVHD) as the investigator initiated clinical trial. We also preparing next UC-MSCs product for the treatment of neonatal encephalopathy as the next clinical trial.

Visit our website: http://www.ims.u-tokyo.ac.jp/dcpt/english/

IMSUT Hospital

Department of Nursing
看護部

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

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

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

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

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

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

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

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

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

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IMSUT Hospital

Department of Pharmacy
薬剤部

Director　Seiichiro Kuroda

薬剤部長　　黒　田　誠一郎

The Department of Pharmacy seeks to provide high-quality pharmaceutical care services.We contribute to the team approach to patient-oriented medical care and provides a drug distribution services.
We are also trying to contribute to propel the right use of medicines for patients.

Our mission is "Taking of the effective pharmacotherapy for the individual patient". We provide to contribute the risk management from the pharmacist's point of view.

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Conference Presentation

安武夫，小沼貴晶，黒田誠一郎，高橋聡，東條有伸：造血器腫瘍症例におけるボリコナゾール静注製剤による腎機能への影響，ポスター発表，第27回日本医療薬学会年会，2017年
小林俊介，安武夫，黒田誠一郎：成人造血器悪性腫瘍患者の高リスク腫瘍崩壊症候群に対するラスブリカーゼ投与期間の検討，ポスター発表，第27回日本医療薬学会年会　2017年
小林秋景，佐藤圭，小林俊介，安武夫，黒田誠一：非ホジキンリンパ腫患者の造血間採用採取を目的にPlerixaforを投与したが効果が不十分であった1症例，ポスター発表，日本病院薬剤師会関東ブロック第47回学術大会，2017年

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.	教授(委嘱) 博士(医学)	俣 野 哲 朗
Visiting Associate Professor	Ai Kawana-Tachikawa, D.M.Sc.	客員准教授 博士(医学)	立川(川名) 愛

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

1. Increased *in vivo* virulence of MHC adapted AIDS virus serially passaged through MHC-mismatched hosts

Sayuri Seki[1], Takushi Nomura[2], Masako Nishizawa[1], Hiroyuki Yamamoto[1], Hiroshi Ishii[1], Saori Matsuoka[1], Teiichiro Shiino[1], Hironori Sato[3], Kazuta Mizuta[4], Hiromi Sakawaki[4], Tomoyuki Miura[4], Taeko K. Naruse[5], Akinori Kimura[5], Tetsuro Matano: [1]AIDS Research Center, National Institute of Infectious Diseases; [2]Center for AIDS Research, Kumamoto University; [3]Pathogen Genomics Center, National Institute of Infectious Diseases; [4]Institute for Virus Research, Kyoto University; [5]Medical Research Institute, Tokyo Medical and Dental University

CD8$^+$ T-cell responses exert strong suppressive pressure on HIV replication and select for viral escape mutations. Some of these major histocompatibility complex class I (MHC-I)-associated mutations result in reduction of *in vitro* viral replicative capacity. While these mutations can revert after viral transmission to MHC-I-disparate hosts, recent studies have suggested that these MHC-I-associated mutations accumulate in populations and make viruses less pathogenic *in vitro*. In this study, we directly showed an increase in the *in vivo* virulence of an MHC-I-adapted virus serially-passaged through MHC-I-mismatched hosts in a macaque AIDS model despite a reduction in *in vitro* viral fitness. The first passage simian immunodeficiency virus (1pSIV) obtained 1 year after SIVmac239 infection in a macaque possessing a protective MHC-I haplotype *90-120-Ia* was transmitted into *90-120-Ia*$^-$ macaques, whose plasma 1 year post-infection was transmitted into other *90-120-Ia*$^-$ macaques to obtain the third passage SIV (3pSIV). Most of the *90-120-Ia*-associated mutations selected in 1pSIV did not revert even in 3pSIV. 3pSIV showed lower *in vitro* viral fitness but induced persistent viremia in *90-120-Ia*$^-$ macaques. Remarkably, 3pSIV infection in *90-120-Ia*$^+$ macaques resulted in significantly higher viral loads and reduced survival compared to wild-type SIVmac239. These results indicate that MHC-I-adapted SIVs serially-transmitted through MHC-I-mismatched hosts can have higher virulence in MHC-I-matched hosts despite their lower *in vitro* viral fitness. This study suggests that multiply-passaged HIVs could result in loss of HIV-specific CD8$^+$ T cell responses in human populations and the *in vivo* pathogenic potential of these escaped viruses may be enhanced.

2. Characterization of in vitro expanded virus-specific T cells toward adoptive immunotherapy against virus infection

Toshiaki Ono[6], Yuriko Fujita Y[7], Tetsuro Matano, Satoshi Takahashi[7], Tomohiro Morio T[1], Ai Kawana-Tachikawa: [6]Department of Pediatrics and Developmental Biology, Tokyo Medical and Dental University; [7]Division of Molecular Therapy, Advanced Clinical Research Center

Adoptive transfer of virus-specific T cells has emerged as a promising therapeutic approach for treatment of virus infections in immunocompromised hosts. Characterization of virus-specific T cells provides essential information for the curative mechanism of the treatment. In this study, we developed a T cell epitope mapping system for 718 overlapping peptides spanning 6 viral proteins from three viruses (pp65 and IE1 from CMV; LMP 1, EBNA1 and BZLF1 from EBV; Penton from AdV). PBMCs from 33 healthy Japanese donors were stimulated with these peptides and virus-specific $CD4^+$ and $CD8^+$ T cell were expanded *in vitro* in the presence of IL4 and IL7. A median of 13 (min-max, 2-46) peptides was recognized in the cohort. Both fresh and cryopreserved PBMCs were used for *in vitro* expansion, and the expansion and the breadth of T cell responses were not significantly different between them. We assessed viral regions frequently recognized by T cells in a Japanese cohort that could become pivotal T cell targets for immunotherapy in Japan. We tested epitope prediction for $CD8^+$ T cell responses against common target region using freely available online tool, and some epitopes were considered to be predictive.

3. Conserved Vδ1 binding geometry in a setting of locus-disparate pHLA recognition by δ/αβTCRs: insight into recognition of HIV peptides by TCR

Shi Y[8], Kawana-Tachikawa A, Gao F[8], Qi J[8], Liu C[8], Gao J[8], Cheng H[8], Ueno T[2], Iwamoto A, Gao GF[8]: [8]CAS Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, Beijing, China

Given a limited set of TCR V genes which are used to create TCRs that are reactive to different ligands, such as MHC class I, MHC class II and MHC-like proteins (for example, MIC molecules and CD1 molecules), the Vδ1 segment can be rearranged with Dδ-Jδ-Cδ or Jα-Cα segments, to form classical γδTCR or uncommon αβTCR using a Vδ1 segment (δ/αβTCR). Here we have determined two complex structures of the δ/αβTCRs (S19-2 and TU 55) bound to different locus-disparate MHCIs with HIV peptides (HLA-A*2402-Nef138-10 and HLA-B*3501-Pol448-9). The overall binding modes resemble classical αβTCRs, but display a strong tilt binding geometry of Vδ1 domain towards the HLA α1 helix, due to a conserved extensive interaction between the CDR1δ loop and N-terminal region of α1 helix (mainly in position 62). The aromatic amino acids of the CDR1δ loop exploit different conformations ("aromatic-ladder" or "aromatic-hairpin") to accommodate distinct MHC helical scaffolds. This tolerance helps to explain how a particular TCR V region can similarly dock onto multiple MHC molecules, and thus, may potentially explain the nature of TCR cross-reactivity. In addition, the length of CDR3δ loop could affect the extent of tilt binding of Vδ1 domain, and adaptively, the pairing Vβ domains adjust their mass centers to generate differential MHC contacts, hence probably ensuring the TCR specificity to a certain peptide-MHC. Our data have provided further structural insights into the TCR recognition of classical pMHCI molecules, unifying the cross-reactivity and specificity together.

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