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Department of Advanced Medical Science was established in September 1997. Our aim is to contribute to the performance and the development of advanced therapeutic approach to the diseases. We have been participating in the potentially important clinical trials and the several projects in line with our principles. Our research projects are (1) Antigen-specific induction of allogeneic umbilical cord or peripheral blood-derived cytotoxic T lymphocytes, (2) Analysis of the effect of Helicobacter pylori eradication on non-ulcer patients, (3) Treatment of drug-resistant H. pylori infection, (4) Effect of H. pylori eradication on the expression of microRNAs in gastric mucosa, (5) Analysis of the role of leptin in hematological malignancies and parallel study on using umbilical cord blood-derived cytotoxic T lymphocytes as therapeutic strategy for hematological disorders, (6) Early diagnosis of cardiotoxicity in chemotherapy-treated patients, (7) Analysis of the potential therapeutic advantages of cell lysate from human placenta in promoting impaired cutaneous wound healing, and (8) application of 5-aminolevulinic acid for cancer therapy

1. Induction of tumor antigen-specific cytotoxic T lymphocytes from allogeneic umbilical cord blood or peripheral blood

Fujita S. et al.

We are pursuing the possibility of using adoptive transfer of cytotoxic T lymphocytes (CTLs) as a treatment for solid tumors. Using cryopreserved umbilical cord blood or peripheral blood as the source of lymphocytes, we were able to induce the expansion of CTLs using combination of certain T cell growth factors and tumor antigen-specific stimulation. Currently we are developing a more efficient protocol to induce HLA-restricted tumor antigen-specific CTL using modified bead-based artificial antigen presenting cell (aAPC) system.

2. Analysis of the effect of *Helicobacter pylori* eradication on non-ulcer patients

Ohno H. et al.

Recent reports showed that eradication of *H. pylori* has prophylactic effect on the development of gastric cancer. The guideline of the Japanese Society for Helicobacter Research strongly recommended the eradication therapy for all *H. pylori*-positive patients including non-ulcer patients. Therefore, we set up outpatient clinic for the eradication therapy to prevent *H. pylori* associated disease such as gastric cancer. But it is unclear that *H. pylori* eradication therapy can improve gastrointestinal symptoms of non-ulcer patients. We are investigating the long-term effects of *H. pylori* eradication on non-ul-

cer patients.

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

Matsubara Y., Ohno H. et al.

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

4. Effect of *H. pylori* eradication on the expression of microRNAs in gastric mucosa

Ohno H. et al.

H. pylori infection is a significant risk factor for gastric cancer. Recent study reported the prophylactic effect of *H. pylori* eradication on the development of metachronous gastric cancer after endoscopic resection. However, the development of gastric cancer after successful eradication of *H. pylori* has been reported in some cases and the mechanism of it remains unclear. To elucidate the mechanism, we are investigating changes of expression level of genes such as microRNAs in gastric mucosa after *H. pylori* eradication therapy.

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

Lam Q.L.K. et al.

The objective of our research is to study the role of leptin in the survival and activity of multiple myeloma with consideration of the bone marrow microenvironment. We will analyze how leptin acts directly on myeloma cell growth, and explore alternative mechanisms of its potential action through acting on the bone marrow stroma. In parallel studies, we actively explored therapeutic alternatives for hematological malignancies using available resources in our laboratory including cryopreserved umbilical cord blood. We have successfully developed methods to isolate and expand cytotoxic T lymphocytes from either cryopreserved or fresh umbilical cord blood, and we have been testing the feasibility of different strategies to derive tumor-specific cytotoxic T lymphocytes. Future success of our study will potentially be novel addition to the existing cancer therapies.

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

Watanabe A. et al.

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

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

Zhang X. et al

One of the major factors responsible for the appearance of chronic wounds is the impairment of cytokine released by local fibroblasts and inflammatory cells, which can result in reduced angiogenesis. A high level amount of VEGF secreted by human placenta-derived cell was discovered in our previous study. Currently, we are examining therapeutic effects of the cell lysate from placenta on excisional skin wound healing. The objective of this study is to determine whether we can use the cell lysate for treatment of non-healing chronic wounds in clinic. We are trying to determine cytokines included in the cell lysate. By applying the cell lysate in vitro and in vivo, we examined its effects on the proliferation and migration of various type cells; and its effects on enhancing of cutaneous wound healing in mice skin excisional wound model.

8. An application of 5-aminolevulinic acid for cancer therapy

Kimura Y. et al.

5-aminolevulinic acid (ALA) is a heme precursor and common in the human body. Once absorbed and converted by the heme biosynthetic pathway, 5-ALA becomes photoactive PpIX (protoporphyrin IX), which accumulates preferentially in tumors cells and can be detected by light exposure. Thus, we hypothesize that PpIX accumulation could be

enhanced by adding exogenous 5-ALA so that tumors or circulating tumor cells (CTCs) are detected among normal cells by a photodetector such as fluorescence activated cell sorting (FACS). In addition, the detected and recovered tumor cells could be used as tumor associated antigen for cancer vaccine, including peptide and dendritic cell (DC) cancer vaccines. For the former purpose, we have established the experimental conditions where CTCs are detected within human peripheral blood mononuclear cells (PBMCs) in the presence of PpIX. Currently, we are planning a clinical study to detect CTCs in the PBMCs of patients with cancer. For the latter propose, we have established the *ex vivo* DC culture and have confirmed that the resulting DCs are functional in terms of inducing antigen specific cytotoxic T cells (CTLs). Nest, we will test whether DCs are able to induce CTC-specific immune reactions in humans using CTC-derived tumor antigens.

Publications

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We have been challenging to cure intractable hematological disorders such as leukemia and lymphoma mainly with the aid of hematopoietic stem cell transplantation (HSCT). No less than 30 patients per year receive allogeneic HSCT in our facilities. In recent years, unrelated cord blood has been our major stem cell source for recipients who have no suitable family donors in HSCT. Since 1998 we have performed over 370 cases of cord blood transplantation (CBT) for adult patients, which appears a distinguished experience in the world. Recent advance in identification of signaling molecules activated in a tumor-specific manner or associated with tumor-specific genomic recombination have disclosed many candidate therapeutic targets in tumors. In the field of hematological malignancies, we have already experienced remarkable clinical efficacies of novel therapeutic agents including tyrosine kinase inhibitors for Philadelphia-chromosome positive leukemias, RI-conjugated or non-conjugated anti-CD20 monoclonal antibodies for B cell lymphoma, and proteasome inhibitors as well as immunomodulatory drugs for multiple myeloma. We extensively apply these molecular targeted therapies for in- and outpatients. Furthermore, in recent years, our department has been a hub facility in the greater Tokyo area for treating patients with intractable adult T-cell leukemia/lymphoma, for which a novel anti-CCR4 monoclonal antibody was just introduced into clinical practice.

1. CADM1 expression and stepwise down regulation of CD7 are closely associated with clonal expansion of HTLV-1-infected cells in adult T-cell leukemia/lymphoma

Kobayashi S, Nakano K[1], Watanabe E[2], Ishigaki T[2], Ohno N, Yuji K, Oyaizu N[3], Asanuma S[1], Yamagishi M[1], Yamochi T[1], Watanabe N[2], Tojo A, Watanabe T[1], Uchimaru K: [1]Graduate School of Frontier Sciences, UTokyo, [2]FACS Core Laboratory for Human Specimens, IMSUT, [3]Department of Laboratory Medicine, IMSUT Hospital

Cell adhesion molecule 1 (CADM1), initially identified as a tumor suppressor gene, has recently been reported to be ectopically expressed in primary adult T-cell leukemia-lymphoma (ATL) cells. We incorporated CADM1 into flow cytometric analysis to reveal oncogenic mechanisms in human T-cell leukemia virus type I (HTLV-1) infection by purifying cells from the intermediate stages of ATL development. We isolated CADM1- and CD7-expressing peripheral blood mononuclear cells of asymptomatic carriers (ACs) and ATLs using multicolor flow cytometry. FACS-sorted subpopulations were subjected to clonal expansion and gene expression analysis. HTLV-1-infected cells were efficiently enriched in $CADM1^{+}$ subpopulations (D, $CADM1^{pos}CD7^{dim}$; and N, $CADM1^{pos}CD7^{neg}$). Clonally expanding cells were detected exclusively in these subpopulations in ACs with high proviral load, suggesting that the appearance of D and N could be a surrogate marker of progression from AC to early ATL. Further disease progression was accompanied by an increase in N with a reciprocal decrease in D, indicating clonal evolution from D to N. The gene expression profiles of D and N in ACs showed similarities to those of indolent ATLs, suggesting that these subpopulations represent premalignant cells. This is further supported by the molecular hallmarks of ATL; i.e., drastic downregulation of miR-31 and upregulation of abnormal *Helios* transcripts. The CADM1 vs. CD7 plot accurately reflects disease progression in HTLV-1 infection, and $CADM1^{+}$ cells with downregulated CD7 in ACs have common properties with those in indolent ATLs.

2. Adult T-cell leukemia cells are characterized by abnormalities of Helios expression that promote T cell growth.

Asanuma S, Yamagishi M, Nakano K, Yamochi T, Kobayashi S, Utsunomiya A[1], Iwanaga M[2], Yamaguchi K[3], Uchimaru K, Ogawa S[4], Watanabe T.: [1]Department. of Hematology, Imamura Branch Hospital, [2]Department of Public Health, Jikei University School of Medicine, [3]Department of Safety Research on Blood and Biologics, NIID, [4]Cancer Genomics Project, Graduate School of Medicine, UTokyo

Molecular abnormalities involved in the multistep leukemogenesis of adult T-cell leukemia (ATL) remain to be clarified. Based on our integrated database, we focused on the expression patterns and levels of Ikaros family genes, *Ikaros*, *Helios*, and *Aiolos*, in ATL patients and HTLV-1 carriers. The results revealed profound deregulation of Helios expression, a pivotal regulator in the control of T-cell differentiation and activation. The majority of ATL samples (32/37 cases) showed abnormal splicing of Helios expression, and four cases did not express Helios. In addition, novel genomic loss in *Helios* locus was observed in 17/168 cases. We identified four ATL-specific short Helios isoforms and revealed their dominant-negative function. Ectopic expression of ATL-type Helios isoform as well as knockdown of normal Helios or Ikaros promoted T-cell growth. Global mRNA profiling and pathway analysis showed activation of several signaling pathways important for lymphocyte proliferation and survival. These data provide new insights into the molecular involvement of Helios function in the leukemogenesis and phenotype of ATL cells, indicating that Helios deregulation is one of the novel molecular hallmarks of ATL.

3. Loss of CCR4 antigen expression after mogamulizumab therapy in a case of adult T-cell leukaemia-lymphoma.

Ohno N, Kobayashi S, Ishigaki T, Yuji K, Kobayashi M, Sato K, Watanabe N, Tojo A, Uchimaru K

Mogamulizumab, a novel molecular targeting agent, is humanized anti-CCR4 immunoglobulin G1 (IgG1) monoclonal antibody with a defucosylated Fc region, and 50% of efficacy was shown as a single agent in a phase II study for relapsed and refractory ATL. We report an acute ATL case whose tumor cells lost CCR4 expression after administration of mogamulizumab. Sixty three-year-old female ATL received a dose intensified chemotherapy, VCAP-AMP-VECP (vincristine, cyclophosphamide, doxorubicin, and prednisone; doxorubicin, ranimustine, and prednisone; and vindesine, etoposide, carboplatin, and prednisone) in our hospital, but ATL cells remained in peripheral blood and skin lesion. We started administration of mogamulizumab as a single agent and complete remission was obtained with disappearence of ATL cells in the peripheral blood, skin lesion and normalization of the LDH by the end of the treatment. Approximately three months later similar eruption aggravated and ATL relapsed and she received mogamulizumab therapy once again. However, the second administration did not have any effect at all, and the patients died by the progression of the disease. We analyzed the CCR4 expression on her ATL cells using multi-color flow cytometric analysis and revealed loss of CCR4 expression on ATL tumor cells after mogamulizumab therapy. Clonal analysis by the inverse long PCR revealed that the major clone is equal before and after mogamulizumab therapy, which suggested relapsed $CCR4^{-}$ ATL cells belonged to the same clone as $CCR4^{+}$ original ATL cells.

To our knowledge, this is the first report of loss of CCR4 antigen with the clonal analysis after

mogamulizumab therapy. Our results indicated that CCR4 expression on ATL cells should be re-evaluated when we treat relapsed ATL patients after mogamulizumab therapy eve if their tumor cells expressed CCR4 on initial evaluation.

4. Development of peripheral T-cell lymphoma not otherwise specified in a HTLV-1 carrier.

Ishigaki T, Isobe M, Kobayashi S, Yuji K, Ohno N, Watanabe K, Tojo A, Uchimaru K

Human T-cell leukemia virus type1 (HTLV-1) causes adult T-cell leukemia (ATL) after a long latency period of about 60 years. Since mature T-cell neoplasms which emerge in HTLV-1 infected patients are often ATL, T-cell neoplasms developing in HTLV-1 infected patients tend to be simply diagnosed as ATL without further investigations. However T-cell neoplasms developing in HTLV-1 infected cases are not always ATL. Mature T-cell malignancies other than ATL should be carefully excluded in HTLV-1 infected patients because of differences in standard first-line chemotherapy. Confirmation of monoclonal integration of the virus with southern blotting makes definite diagnosis of ATL, but it is sometimes difficult to differentiate between ATL and other T-cell malignancies with typical clinical features of ATL when monoclonal bands can't be detected by southern blotting of HTLV-1 genome.

Here we present a case of peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) in a HTLV-1 carrier. Although high HTLV-1 proviral load made it difficult to give a diagnosis, multicolor flow cytometric analysis was helpful to discriminate PTCL-NOS from ATL.

5. Clinical profile of adult Langerhans cell histiocytosis (LCH) experienced in IMSUT Hospital

Kobayashi M, Ohno N, Yuji K, Kawamata T, Sato K, Uchimaru K, Tojo A

Langerhans cell histiocytosis (LCH) is a rare disease characterized by clonal proliferation of Langerhans cells (epidermal antigen-presenting cells) and variable inflammatory infiltrates. It often affects a single organ and is self-limited in some cases, but it can also involve multiple organs with unfavorable clinical outcome. Since more than two-thirds of patients are children, only a few studies have focused on clinical features and treatment outcome of adult LCH. Here, we report a single-institute analysis of the clinical features of 11 adult patients with LCH. In the past 8 years, 11 adult patients were diagnosed as LCH and referred to our hospital for evaluation and treatment. Median age of those at diagnosis was 43 years old (range 29-66), and 82% was female. Seven cases (64%) had a limited LCH lesion (single-system) and others (36%) had multi-organ disease (multi-system). In patients with single-system disease, bone (57%), skin (29%) and pituitary stalk (14%) were involved, respectively. These patients were younger (median age 39) than those with multi-system (median age 52). In two patients with multi-system disease, a high risk organ such as lung, liver, spleen and bone marrow was involved. Eight of 11 patients received chemotherapy including vinblastine, a key drug for LCH, and 2 of them were followed by 2′-chlorodeoxyadenosine (2-CdA) as a salvage therapy. The remaining 3 patients have been under observation without therapy. All the patients are alive at date. Since adult LCH is quite rare and most likely ignored by physicians, the diagnosis is usually delayed and the standard therapy is not yet determined, encouraging that multi-center study of a larger cohort of those patients should be conducted. In addition, recent finding of BRAF mutation in LCH will facilitate the understanding of its pathogenesis and the future therapy.

6. Sustained Molecular Response with IFN after Imatinib Discontinuation in Patients with CML

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Imatinib mesylate (IM) induces sustained molecular remissions in patients with CML but a life-long therapy is required for most of these patients. We have been performing a phase 2 study of treatment discontinuation after the drug change from IM to IFN (Japanese Imatinib Stop And Interferon Study; JISAS). We present here the result of the interim analysis. Patients with CML in 1st chronic phase as well as in CMR following over 2 years of MMR on IM were enrolled in this study. Administration of IFN is started at a dose of 3 million units 2-5 times per week after IM discontinuation. In case of molecular relapse, IM was resumed. Fifteen patients were enrolled. The clinical stage of one patient was amended to be accelerated phase at the time of diagnosis. Two other patients withdrew the consent. Excluding these 3 patients, the remaining 12 patients with Sokal low risk were analyzed. The median follow-up period is 23 months (range: 6-27 months). Three patients lost MMR (1, 3, and 6 months, respectively) and other 9 maintained CMR. Molecular relapse-free survival is 77%. The sustained CMR patients had the significantly longer

CMR period on IM (median 31 months, range 26-79 months) compared with relapsed patients (0, 9, and 14 months, respectively; p=0.01). There was no difference between the relapsed and the sustained CMR patients in the duration of IM treatment. All the relapsed patients achieved MMR within 5 months of IM resumption, respectively. In conclusion, IFN monotherapy is a promising option for sustained molecular response after IM discontinuation in CML patients with CMR.

7. Association between acute myelogenous leukemia and thrombopoietin receptor agonists in patients with immune thrombocytopenia.

Oshima Y, Yuji K, Tanimoto T[1], Hinomura Y[2], Tojo A: [1]Cancer Institute, Japanese Foundation for Cancer Research, [2]Japan Pharmaceutical Information Cente

The development of myeloid malignancies is a concern when administering thrombopoietin receptor (or the myeloproliferative leukemia virus proto-oncogene product, MPL) agonists. Progression from myelodysplastic syndrome (MDS) to acute myelogenous leukemia [AML, 9 (6.12%) AML patients among 147 MDS subjects] was reported in a clinical trial. However, only one (0.15%) case of AML among 653 immune thrombocytopenic purpura (ITP) subjects was reported. Our objective was to determine whether there is currently a safety signal in the FDA files termed Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) for AML in ITP patients who receive MPL agonists. We conducted a case-controlled study using the FAERS as a source of case and control data. We compared demographic characteristics, such as gender, age and exposure to MPL agonists between AML patients and others among ITP subjects registered between 2002 and 2011. Total of 4,821 ITP subjects were identified, including 62 AML patients. The number of patients treated with romiplostim and eltrombopag was 54 (1.74%) AML patients among 3,102 ITP subjects and nine (1.52%) AML patients among 594 ITP subjects, respectively. It should be noted that all AML patients were exposed to one or more MPL agonists. Another factor associated with AML was male gender. We herein report an association between AML and MPL agonist use in ITP subjects. Due to various biases and the incompleteness of the FAERS data, further studies are warranted to determine whether the detected signal is a real risk. Physicians should not alter their prescribing behaviors based on this single preliminary analysis.

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Founded in 1981, Department of Infectious Diseases and Applied Immunology (DIDAI) started HIV clinic in 1986. In 2013, 24 new patients with HIV infection have visited to our hospital and 535 patients in total are currently under our clinical management. The total number of in-patients with HIV-infection during 2013 was 65, and about 6 beds in our ward have been constantly occupied by patients with not only HIV-infection but also other infectious diseases. Since the number of the staff members of DIDAI is too small to care both outpatients and in-patients, members of the Division of Infectious Diseases and the Department of Infectious Disease Control join the clinic. IMSUT hospital provides the most up-to-date medical treatment to HIV-infected patients in Japan. DIDAI is also a treatment center in Japan for international infectious diseases such as malaria and dengue fever.

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

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

24 new patients with HIV-1 infection visited to our hospital this year (from January 1 to December 31, 2013), and 535 patients in total are under medical management in our outpatient clinic. The total number of HIV-infected in-patients during 2013 was 65. The number of total patients declined in 1997, as shown in Fig. 1, because a part of patients as well as medical stuffs moved to newly established AIDS Clinical Center in International Medical Center of Japan. However, the number of patients started to increase again after 1998 in accordance with Japanese statistics of HIV-infected patients (Fig. 1). Anti-retroviral therapy (ART) has been introduced to around 485 HIV-infected patients in our hospital, and most of their HIV viral loads have been well controlled. After one year of ART, the viral loads become less than 50 copies/ml

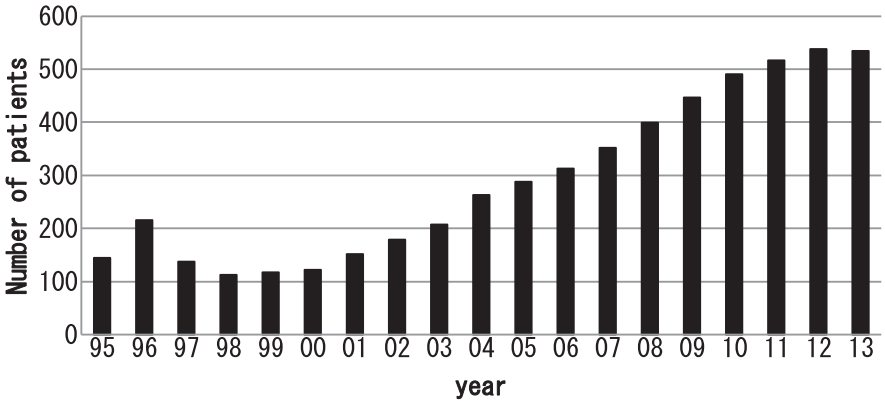

Figure 1. Number of HIV-infected outpatients in IMSUT Hospital

in 95.9% of HIV-infected patients in our outpatient clinic. Consequently, the patients are able to maintain good condition as long as they keep excellent drug adherence rates. The clinical management of HIV-infected patients have been changing from how to treat opportunistic infections into how to provide comprehensive care for patients with ART.

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

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

The Japanese guidelines for treatment of HIV-infected patients have been established since 1998 with support from Ministry of Health, Labor and Welfare. The representatives from our department have played critical roles in development of the current practice guidelines in Japan. It is vital to create practice guidelines that are specific for the unique genetic and social backgrounds of the HIV-infected population in Japan. In collaboration with other Japanese HIV-experts, the physicians from our department update the practice guidelines annually, as we deem necessary. The guidelines are available at http://www.haart-support.jp/guideline.htm and used widely by Japanese clinicians. It has been downloaded more than 10,000 times in 2013. In Japan, where the number of HIV-experts are limited compared to other countries, the practice guidelines have substantially improved the standard of care for the HIV-infected patients in our country.

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

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

Dozens of important medicines essential for treatment of tropical or parasitic diseases are not licensed in Japan. For instance, artesunate and injectable quinine for falciparum malaria, injectable metronidazole for amebiasis, 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 seventy 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 dengue fever (7 patients), typhoid fever (1 patient), post-exposure prophylaxis of rabies (23 patients) and so on.

4. Hemophagocytic syndrome in an acute human immunodeficiency virus infection.

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

In acute stage of HIV infection, hemophagocytic syndrome (HPS) is an unrecognized complication and seldom reported in the literature. We experienced a rare case of HPS during the seroconversion stage of HIV infection and published it as a case report. The patient's pancytopenia and liver dysfunction related to HPS recovered after the initiation of antiretroviral therapy. This case suggests the impor-

tance of early recognition of HPS and that prompt initiation of ART have potential benefit to control HPS in acute stage of HIV infection. Therefore, we would like to propose that the initiation of ART might be one of the treatment options for HPS in acute HIV infection.

5. Tuberculosis examination using whole blood interferon-gamma release assay among health care workers in a Japanese hospital without tuberculosis-specific wards.

Eisuke Adachi and Tomohiko Koibuchi.

Occupational latent tuberculosis infection (LTBI) among health care workers (HCWs) is an important public health issue. To assess prevalence and risk factors of LTBI among Japanese HCWs, we conducted a cross-sectional study in the IMSUT hospital by Quantiferon-TB Gold in Tube (QFT-GIT) and the structured questionnaire. We reviewed medical records of HCWs and questioned HCWs about exposure to M. tuberculosis and employment length in health care industries. 165 HCWs, approximately 80% of the total hospital staff, were enrolled in this study. 18 out of 165 subjects had positive results, suggesting LTBI prevalence rate of 11%. This study is first to offer QFT-GIT positivity rate among Japanese HCWs in a hospital without tuberculosis-specific wards. Multiple regression analysis revealed a significant association between the positive or intermediate QFT-GIT results and history of contact investigation for tuberculosis. QFT-GIT positivity rate among HCWs is higher than among general population in Japan.

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Associate Professor Makoto Otsu
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助 教 医学博士 海老原 康博

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

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

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

2. Novel approach to therapy in juvenile myelomonocytic leukemia

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JMML is a clonal myeloproliferative/myelodysplastic disorder of early childhood with poor prog-

nosis. JMML cells are characterized by hypersensitivity to GM-CSF caused by continuously activated GM-CSF receptor-RAS signal transduction pathway through various molecular mechanisms, resulting in spontaneous colony formation *in vitro*. Bisphosphonate zoledronic acid (ZOL), a RAS-blocking compound, suppressed colony formation from bone marrow (BM) cells of JMML patients and normal volunteers without and with GM-CSF, respectively, in a dose-dependent manner in clonal culture. At 10 μM of ZOL, however, spontaneous colony formation decreased, but formation of granulocyte (G) colonies containing only granulocytes, but no macrophages was enhanced in culture of JMML BM cells, while granulocyte-macrophage (GM) colonies containing both granulocytes and macrophages were retained and G colony formation was not affected in culture of normal BM cells with GM-CSF. In suspension culture, 10 μM of ZOL also inhibited spontaneous proliferation and differentiation along monocyte/macrophage lineage of JMML BM cells, but not development of normal BM cells by GM-CSF assessed in cytochemical and flow cytometric analyses. The inhibitory effect of ZOL on JMML cells was confirmed at a single-clone level, and observed even at 3 μM. The current result offers a novel approach to therapy in JMML.

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

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

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

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

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

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Hemophilia is a congenital disease with a lack of coagulation factors. Arthropathy is a major cause of morbidity in the patients with hemophilia. Approximately one third of the patients need the mobility assistance. Although the pathogenesis of hemophilic arthropathy (HA) still has not been precisely clarified, the destruction of articular cartilage is the most prominent event in HA. Most surgical treatments for HA, such as synovectomy or total

joint arthroplasty, are performed by Department of Joint Surgery in our hospital. So far, however, the efficacy of the treatment has been insufficient. Recently it has been shown that BM contains MSC, which can differentiate into various mesenchymal tissue cells, osteocytes, adipocytes and chondrocytes. Although the mechanism by which MSC are committed to differentiate into each mesenchymal tissue, the environment surrounding MSC plays an important role in the commitment. We are then preparing for the clinical trial of the transplantation of autologous culture-expanded BM-derived MSC into the articular cartilage defect in the HA patients.

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Our department is founded in 2001 to tackle systemic autoimmune inflammatory diseases including rheumatoid arthritis, systemic lupus erythematosus and vasculitic syndoromes, and manages increasing number of those in- and out-patients. We provide patients personalized and evidence-based medical service. We participate in cutting edge science of autoimmune, rheumatic and allergic diseases and novel treatments for patients with these disorders. In addition to conventional drug studies aimed to improve the efficacy and safety of current therapies, we are going to carry out experimental protocols of particular interest for patients not responding to conventional therapy and to perform the translational research

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

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

(i) Development of novel GR regulators

Despite the established role of glucocorticoids (GC) in controlling short-term inflammation, and despite emerging evidence supporting a disease-modifying role in various autoimmune disorders, concern for adverse events associated with GCs often limits their use. Activation of the GR by GC regulates hundreds of genes expression both positively and negatively. It has become quite widely accepted that transrepression accounts for the majority of therapeutic, anti-inflammatory effects of GC, whereas transactivation is responsible for most side effects. This "transrepression hypothesis" has arisen a set of ideas about how to discover novel anti-inflammatory drugs that do not carry the same burden of side effects as GC. We have explored unique GR regulators that have a different mode of action from classical GC. We have recently shown that not only synthetic GC but also certain bile acids could differentially modulate GR function in such a way that preserves transrepression but not transactivation function. Moreover, the effects of those compounds are ascribed to the ligand binding

domain of the receptor. 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. On the other hand, receptor specificity is another important aspect of novel GR regulators. In this line, we have shown that cortivazol is extremely specific for GR and does not bind to mineralocorticoid receptor.

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

We have studied the molecular basis for the receptor specificity of the ligand using cortivazol as a model and develop 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 cardiac muscles and skeletal muscles. We discovered a novel desirable effect of GC and are now tackling their undesirable side effects.

1. Cardiac muscles. We found that the expression of genes that encode 2 key enzymes in a common pathway of prostaglandin biosynthesis were upregulated by GCs via the GR in cardiomyocytes: phospholipase A2 group IVA (*Pla2g4a*; encoding cytosolic calcium-dependent phospholipase A2 [cPLA2]) and prostaglandin-endoperoxide synthase 2 (*Ptgs2*; encoding COX2). Importantly, aldosterone did not have similar stimulatory effects on these genes. The induction of *Pla2g4a* and *Ptgs2* by GR is specific for cardiomyocytes, since GR has been shown to transrepress the activation of these proinflammatory genes in most cells. Therefore, we sought to investigate the major types of prostanoids produced in cardiomyocytes after exposure to glucocorticoids and to clarify the roles of these products in cardiac physiology. Among the genes for PGH2 isomerases, expression of *Ptgds*, which encodes lipocalin-type prostaglandin D synthase (L-PGDS), was selectively upregulated by a GR-specific ligand. Consistent with this result, PGD2 was the most prominently induced prostaglandin by GR-specific ligand stimulation of cultured cardiomyocytes and in vivo hearts. Using isolated Langendorff-perfused hearts and cultured cardiomyocytes, we demonstrated that the activation of L-PGDS-mediated production of PGD2 was crucial for the cardioprotection against ischemia/reperfusion conferred by GC-GR signaling. Our results suggest a novel interaction between GC-GR signaling and the arachidonic acid cascade-mediated cardiomyocyte survival pathway. Recently, we have characterized the cardiac receptor for PGD2 and more precisely analyzed the role of GR in cardiac muscles by developing cardiomyocyte-specific GR knockout mice in collaboration with the Department of Cardiology, Keio University School of Medicine.
2. Skeletal muscle. Muscle comprises ~40% of body mass and contributes not only to the structure and movement of the body but also to nutrient storage and supply. Excessive loss of muscle mass is associated with poor prognosis in several diseases, including myopathies and muscular dystrophies, as well as in systemic disorders such as cancer, diabetes, sepsis, heart failure, and glucocorticoid excess. Muscle atrophy also occurs in aging that is called sarcopenia and recently thought to be one of core features of "Locomotive Syndrome". The maintenance of healthy muscles is crucial for preventing metabolic disorders, maintaining healthy aging and providing energy to vital organs during stress conditions. Recent analyses revealed that the resulting loss of muscle mass in the catabolic states involves a common transcriptional program, resulting in a general acceleration of proteolysis and a decrease in protein synthesis. Atrophy-related genes (atrogenes) induced most dramatically during atrophy are two muscle-specific ubiquitin ligases, atrogin-1 and MuRF-1, which are regulated by the FoxO transcription factors. On the other hands, in growing muscles, FoxOs are maintained in an inactive state by the IGF-1/phosphoinositide 3-kinase (PI3K)/Akt/mTOR signaling cascade. This pathway plays a key role in the regulation of muscle mass and promotes fiber hypertrophy by stimulating overall protein synthesis and suppressing proteolysis.

   The involvement of FoxO transcription factors is reported in the gene regulation of atrogin-1 and MuRF1 under the presence of excess of GC, the biochemical role of GR in the transcriptional regulation of muscle tissue has not yet been determined. Therefore, 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. REDD1 is known to be induced by various stressors, including glucocorticoid, and to inhibit mTOR activity via the sequestration of 14-3-3 and the increase of TSC1/2 activity. We clearly identified the functional GRE via the promoter analysis of REDD1 gene. On the other hand, KLF 15 is a recently discovered transcription factor that is involved in several metabolic processes in skeletal muscle; e.g., KLF15 transcriptionally upregulates the gene expression of branched-chain aminotransferase 2 (BCAT2), a mitochondrial enzyme catalyzing the first reaction in the catabolism of branched-chain amino acids

(BCAA) to accelerate BCAA degradation and alanine production in skeletal muscle. Moreover, phenotypic analysis of cardiac-specific KLF15 knockout mice revealed marked left ventricular hypertrophy, indicating the negative regulatory role of KLF15 on muscle mass. We here demonstrated that KLF15 participates in muscle catabolism via the transcriptional regulation of atrogin-1 and MuRF1. Moreover, KLF15 affects mTOR through BCAA degradation and negatively modulates myofiber size. mTOR activation inhibits GR-mediated transcription by suppressing GR recruitment onto target genes, strongly suggesting a mutually exclusive crosstalk between mTOR and GR. Pharmacological activation of mTOR with BCAA attenuated GR-mediated gene expression, leading to the substantial restoration of muscle in glucocorticoid-treated rats. We, therefore, indicate the critical importance of the interaction of GR and mTOR in the regulation of metabolism-volume coupling in skeletal muscle. Recently, we have created skeletal muscle-specific GR knockout mice (mGRKO) and revealed that mGRKO show significant increase of their myofiber size and muscle mass. Given this, we have just started the clinical trial in IMSUT hospital to verify our scenario in glucocorticoid-treated patients.

(iii) Development of a novel therapy for pulmonary hypertension associated with collagen vascular disease

Pulmonary hypertension (PH) associated with collagen vascular disease causes fatal right ventricular hypertrophy (RVH). To further improve the outcome of those patients, it may be effective to directly interrupt hypertrophy and irreversible remodeling of RV. Hexamethylene bisacetamide inducible protein 1 (HEXIM1) is a negative regulator of positive transcription elongation factor b (P-TEFb), which activates RNA polymerase II (RNAPII)-dependent transcription and whose activation is strongly associated with left ventricular hypertrophy. We revealed that, in the mouse heart, HEXIM1 is highly expressed in the early postnatal period and its expression is gradually decreased, and that prostaglandin I2, a major therapeutic drug for PH, increases HEXIM1 levels in cardiomyocytes, suggesting that HEXIM1 might possess negative effect on cardiomyocyte growth and take part in cardiomyocyte regulation in RV. Using adenovirus-mediated gene delivery to cultured rat cardiomyocytes, we revealed that overexpression of HEXIM1 prevents endothelin-1-induced phosphorylation of RNAPII, cardiomyocyte hypertrophy, and mRNA expression of hypertrophic genes, whereas a HEXIM1 mutant lacking central basic region, which diminishes P-TEFb-suppressing activity, could not. Moreover, we created cardiomyocyte-specific HEXIM1 transgenic mice and revealed that HEXIM 1 ameliorates RVH and prevents RV dilatation in hypoxia-induced PH model. Taken together, these findings indicate that cardiomyocyte-specific overexpression of HEXIM1 inhibits progression to RVH under chronic hypoxia, most possibly via inhibition of P-TEFb-mediated enlargement of cardiomyocytes. We conclude that P-TEFb/HEXIM1-dependent transcriptional regulation may play a pathophysiological role in RVH and be a novel therapeutic target for mitigating RVH in PH.

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

Hirotoshi Tanaka[1,2], Noritada Yoshikawa[1], Ryo Matsumiya[1], Akiko Souta-Kuribara[1], Masaaki Uehara[1], Hiroshi Kobayashi[1], Osamu Hosono[1], Shigeru Kiryu[3], Fumitaka Nagamura[4]: [1]Department of Rheumatology and Allergy, [2]Division of Rheumatology, Center for Antibody and Vaccine Therapy, [3]Department of Radiology, [4]Department of Clinical Trial Safety Management, IMSUT Hospital, University of Tokyo.

Skeletal muscle atrophy is induced by muscle denervation and disuse, and it is also the key component of cachexia, a catabolic, debilitating response to several diseases and one of the undesirable effects of glucocorticoid treatment. Patients in such medical conditions not only sustain a decreased quality of life, but also face a worse prognosis of the underlying pathology, making it an important treatment target, however, skeletal muscle atrophy pose unmet needs for specific and effective treatments. To overcome this issue, we have studied precise mechanisms of glucocorticoid-induced skeletal muscle atrophy, and based on our investigation described above section, we have just started a clinical trial in IMSUT hospital. The objective of this 3-month, open label, randomized, parallel-group, Phase I, II clinical trial is to test the effect of commercially available BCAA-enriched beverage "Amino-Value [CONC.]" in patients with rheumatic diseases taking glucocorticoids and to explore the diagnostic and evaluation procedures for skeletal muscle atrophy in those patients. Primary outcomes of this trial are evaluation of muscle volume and strength using manual muscle test, bioimpedance, CT and MRI imaging. Key secondary outcomes are Performance Status, evaluation of daily living activity, squatting, blood and urine biochemistry. From May/2012 to Dec/2012, 7 patients have been registered in this trial and this trial is currently in progress.

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IMSUT Hospital

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

1. Genetic analyss for hereditary diseases and human neoplasms

As a part of clinical service, we perform genetic analysis of human neoplasms such as leukemia and colorectal cancer. In 2013, more than four hundreds of genetic tests were performed. The results were utilized for the precise classification of neoplasms, selection of therapeutic drugs, and evaluation of the response to treatment.

2. Analysis of variants in patients with hereditary tumors using next generation sequencer

Yoichi Furukawa, Seiya Imoto[1], Mitsuhiro Komura[1], Yuichi Shiraishi[1], Teppei Shimamura[1], Rui Yamaguchi[2], Tetsuo Shibuya[2], Satoru Miyano[1,2]: [1]Laboratory of DNA Information Analysis, [2]Laboratory of Sequence Analysis, Human Genome Center

In collaboration with Human Genome Center, we have two ongoing projects; 1) the determination of germ line mutations in patients suspected for hereditary colon tumor, and 2) identification of somatic mutations in hematopoietic malignancies and solid tumors. Using next generation sequencer (NGS) and a highly secure supercomputer system, we analyzed whole genome sequencing data of two patients with colonic polyposis without family history. As a result, we identified more than 4.6 million germ line variants in one of the two patients. Among them, approximately thirty thousands were located in exons or splicing sites. Interpretation of the variants is now ongoing. We have been analyzing somatic mutations in their polyps.

3. Genetic counseling and related activities.

Yoichi Furukawa, Yoshinori Murakami, Yataro Daigo, Tsuneo Ikenoue, Koichiro Yuji, Sachiyo Kawaichi, Nozomi Yusa, Shifumi Watase, Momoyo Ohki[1], Yoshinari Miyamoto[2], Masae Ono[3], Masahiko Suzuki[4], Toshihiro Tanaka[5], Shiro Ikegawa[6], Mayumi Tamari[6]: [1]Bunkyo University, [2]Tokyo Metropolitan Geriatric Hospital, [3]Tokyo Teishin Hospital, [4]Jikei Medical University, [5]Tokyo Medical and Dental University, [6]Center for Integrative Medical Sciences, RIKEN

We provided genetic counseling and genetic tests to clients who visited our counseling clinic. In 2013, we had a total of 35 counseling cases including familial breast cancer, Lynch syndrome, familial poly-

posis of the colon, spinocerebellar ataxia, and myotonic dystrophy. In the counseling, we provided appropriate information about hereditary diseases and took psychological care of the clients in collaboration with a clinical psychologist. Genetic testing was performed in four cases with informed consent after thoughtful discussion about its merit and demerit.

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

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IMSUT Hospital

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This Department was established in July 1st, 2012 in conjunction with Department of Palliative Medicinal 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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Assistant Professor	Toshihiro Furuta, M.D., D.M.Sc.	助 教	医学博士	古 田 寿	宏

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

Detection of lung tumors in mice using a 1-Tesla compact magnetic resonance imaging system

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Due to their small size, lung tumors in rodents are typically investigated using high field magnetic resonance (MR) systems (4.7 T or higher) to achieve higher signal-to-noise ratios, although low-field MR systems are less sensitive to susceptibility artifacts caused by air in the lung. We investigated the feasibility of detecting lung tumors in living, freely breathing mice with a 1-T compact permanent magnet MR system. In total, 4 mice were used, and MR images of mouse lungs were acquired using a T1-weighted three-dimensional fast low-angle shot sequence without cardiac or respiratory gating. The delineation and size of lung tumors were assessed and compared with histopathological findings. Submillimeter lesions were demonstrated as hyperintense, relative to the surrounding lung parenchyma, and were delineated clearly. Among the 13 lesions validated in histopathological sections, 11 were detected in MR images; the MR detection rate was thus 84.6%. A strong correlation was obtained in size measurements between MR images and histological sections. Thus, a dedicated low-field MR system can be used to detect lung tumors in living mice noninvasively without gating.

Erdheim-Chester disease with an 18F-fluorodeoxyglucose-avid breast mass and BRAF V600E mutation.

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Erdheim-Chester disease (ECD) is a non-Langerhans cell histiocytosis. Herein we report a case of a 49-year-old woman who developed bilateral knee pain. Imaging procedures revealed multiple long bone lesions and a well-defined 18F-fluorodeoxyglucose-avid mass in the left breast. The breast mass was resected, and an open biopsy was performed on the right femoral lesion. Both specimens revealed involvement by histiocytic infiltrates with features suggestive of ECD. The BRAF V600E mutation was detected by DNA sequencing and immunohistochemistry.

Delayed hepatic signal recovery on ferucarbotran-enhanced magnetic resonance images in a rat model with regional liver irradiation.

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We performed this experiment to determine whether superparamagnetic iron oxide (SPIO)-enhanced magnetic resonance (MR) imaging could demonstrate signal recovery delay in irradiated areas of rat livers. We also investigated the relationship between MR imaging and histological findings. Twelve rats received 20 μmol iron/kg of SPIO followed by X-irradiation to the right upper abdomen four hours later. Radiation doses were 0, 50, and 70 Gy. Hepatic signals were assessed on unenhanced T_2^*-weighted images for up to seven days using a 9.4-Tesla scanner. The livers were excised on day 7 and examined histologically. Normalized relative signal intensity of 70 Gy-irradiated right liver (2.36 ± 0.22) and 50 Gy-irradiated right liver (2.37 ± 0.46) was significantly lower than that of the non-irradiated right liver (4.04 ± 0.28) on day 7, respectively ($p < 0.05$). Pearson product-moment correlation coefficient between relative intensity of the liver and the number of hepatic iron deposits was -0.588 ($p < 0.01$). In conclusion, SPIO-enhanced MR imaging could demonstrate signal recovery delay in irradiated areas of rat livers. It seems that the signal recovery delay in irradiated areas was due to SPIO-derived iron deposition. Hepatic signal recovery could be a novel diagnostic marker for delineation of irradiated areas.

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

1. Surgical treatment in 2013

Masaru Shinozaki, Giichiro Tsurita, Kentaro Yazawa, Yoko Tateno, Yuichi Tachikawa, Yuichiro Yoshioka, Keisuke Hata

In April, 2013, three clinical staffmembers joined us: Drs. Tateno, Tachikawa, and Yoshioka. We are consolidated, and performed more operations. Dr. Sameshima and Dr. Kawamura had been unstinting in their support for our operations, especially in the technical field of laparoscopic colorectal surgery. Our target organs are stomach, intestine, anus, gallbladder, liver, biliary tract, pancreas, and spleen, as well as abdominal wall.

Recently, breast cancer has become a particular field only for highly specialized physicians bearing knowledge in this field. Dr. Sanuki, Dr. Tsuji and Dr. Fukatsu continued the out-patient clinic and assisted our breast cancer operations.

2. Endoscopic examination in 2013

Giichiro Tsurita, Kentaro Yazawa, Masaru Shinozaki, Keisuke Hata, Yoko Tateno, Yuichi Tachikawa, Yuichiro Yoshioka

Under cooperation with Department of Advanced Medical Science, we performed 743 (5% increase compared with the number in the previous year) upper gastrointestinal endoscopies and 819 (15% increase) colonoscopies without major complications. Dr. Tsurita has been the chief of Division of Endoscopy and played a crucial role in examinations. For the patients' satisfaction, we aggressively perform endoscopic resection of colorectal neoplasms and avoid operation as much as possible. Our fellows (Y.T., Y.T. and Y.Y.) have learned gastrointestinal endoscopic technique and have made great progress.

3. Clinical Research.

A. The role of micro RNA and its relation to carcinogenesis in inflammatory bowel disease

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

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

B. Whole genome sequencing of inflammatory bowel disease

Masaru Shinozaki, Yoichi Furukawa, Keisuke Hata, Giichiro Tsurita, Kentaro Yazawa

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

C. Whole genome sequencing of colorectal neoplasm

Keisuke Hata, Yoichi Furukawa, Masaru Shinozaki, Giichiro Tsurita, Kentaro Yazawa

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

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

Masaru Shinozaki, Keisuke Hata, Giichiro Tsurita, Kentaro Yazawa, Yoko Tateno

In Japan, cancer in small bowel and/or large bowel associated with Crohn's disease is rapidly increasing in number. In Western countries, the distribution of cancer is similar to that of ulcerative colitis, and surveillance colonoscopy is performed just like ulcerative colitis. However, in Japan, quite a little proportion of such cancer is located at perianal region, and the similar methodology of surveillance does not seem to be sufficient for early detection of cancer. We believe that the first step to solve this problem is accumulation and analysis of such tumors. Therefore, we started to make questionnaire and send to hospitals to clarify the clinicopathlogical characteristics.

E. Evaluation of Clinical Guidelines

Emi Inoue, Yoko Tateno, Masaru Shinozaki, Keisuke Hata, Hajime Sato (National Institute of Public Health)

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

4. Clinical research under development

Emi Inoue, Yoko Tateno, Masaru Shinozaki, Giichiro Tsurita, Kentaro Yazawa, Yuichiro Yoshioka, and investigators in the other departments

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

5. Ongoing Clinical trials

A. BK-UM for ovarian cancer

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

BK-UM has been developed at Professor Mekada's laboratory, Osaka University. It was derived from diphtheria toxin, and it exerts anti-cancer effect through heparin binding epithelial growth factor receptors. This phase II trial has been conducted in cooperation with Osaka University and Fukuoka University.

B. Survivin peptide vaccine for pancreatic cancer

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

Survivin is an inhibitor of apoptosis protein, and is highly expressed in most cancers and associated with chemotherapy resistance, increased tumor recurrence, and shorter patient survival. Survivin is expressed at most of malignancy cells, while it is rarely expressed at most of the mature non-cancer cells. Therefore, anti-survivin treatment is expected to have not only tumor apoptosis but also resump-

tion of chemotherapy sensitivity without major side effects. We have been executing a phase II clinical trial using a novel anti-survivin peptide therapy for pancreatic cancer in cooperation with Sapporo Medical College.

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IMSUT Hospital

Department of Joint Surgery
関節外科

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

講　師　医学博士　竹　谷　英　之
特任助教　医学博士　廣　瀬　　旬

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

Surgical treatment for haemophilia

From 2006 to 2012, there are 152 surgical treatments for hemophilia (89 for hemophilia A, 17 for hemophilia B, 1 for deficiency factor VII patient, and 1 for Von Willebrand disease). 18 of them have the deficiency factor antibody.

In 2013, we were performed 24 surgical treatments (20 for hemophilia A, 3 for hemophilia B) and 1 for plasminogen activater inhibitor deficiency. One of them has the deficiency factor antibody. Six were performed total joint arthroplasties, ten was arthroscopic synovectomy and seven were other surgical treatments.

Publications

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IMSUT Hospital

Department of Surgical Neuro-Oncology
脳腫瘍外科

Professor	Tomoki Todo, M.D., Ph.D.	教　授	医学博士	藤　堂　具　紀
Associate Professor	Yasushi Ino, M.D., Ph.D.	准教授	医学博士	稲　生　　靖
Project Lecturer	Minoru Tanaka, M.D., Ph.D.	特任講師	医学博士	田　中　　実
Assistant Professor	Motokazu Ito, M.D., Ph.D.	助　教	医学博士	伊　藤　元　一

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

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

Genetically engineered, conditionally replicating herpes simplex viruses type 1 (HSV-1) are promising therapeutic agents for cancer. We have developed a triple-mutated oncolytic HSV-1, G47Δ, by introducing an additional genetic mutation to the viral genome of G207, an oncolytic HSV-1 used in clinical trials for glioblastoma in the United States. We have been conducting a phase I-IIa clinical trial of G47Δ in patients with progressive glioblastoma at the University of Tokyo Hospital. Patients with a single lesion of recurrent glioblastoma, age 18 or older, and with a good performance status are enrolled. The primary end point is to access the safety of G47Δ, and the secondary end point is to access the efficacy by tumor size and progression free survival. The final approval to perform this study simultaneously at the IMSUT Hospital was obtained from the government in May 2013, and the patients are currently being accrued.

A clinical study of G47Δ in patients with progressive olfactory neuroblastoma

A new phase I clinical trial of G47Δ in patients with progressive olfactory neuroblastoma was approved by the government in August 2013. Olfactory neuroblastoma is a rare cancer that arises at the base of the skull, deep in the nasal cavity, and there is no effective treatment once it recurs. In this clinical protocol, G47Δ is injected into the recurred tumor via nasal cavity repeatedly every 4 weeks. Patient accrual has started at the IMSUT Hospital in September 2013.

Surgical treatment of brain tumor patients

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

ultrasonic surgical aspirator.

Outpatient clinic

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

Publications

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IMSUT Hospital

Surgical Center
手術部

Associate Professor	Mieko Chinzei, M.D., M.D.Sc.	准教授	医学博士	鎮　西　美栄子
Assistant Professor	Reiko Shibata, M.D.	助　教		柴　田　玲　子
Intern Doctor	Akihiro Katsura	医　員		桂　　彰　宏
Clinical Engineer	Emiko Ohba	臨床工学技士		大　場　恵美子

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, (2) management of chronic intractable pain or improving the quality of life of patients with life-threatening illness (3) assessment of the impact of anesthesia and surgery on autonomic nervous activity, and (4) risk management of medical electronic devices in Research Hospital.

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

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

2. Management of chronic intractable pain.

Since 2008, we've provided a palliative care support service in Research Hospital for the patients suffering with intractable physical and mental pain caused by life-threatening illness and/or complications of the treatments. In patients with long treatment history, many of their psychological status have been diagnosed as reaction to severe stress and adjustment disorder, or as depressive disorder.

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

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

4. Risk management of medical electronic devices.

We ourselves engage in preventive maintenance and care of the life support machines including instruments for mechanical ventilation or blood purification and defibrillator. We also supervise physicians during clinical usage of these instruments. We

have promoted dual-directional information system on malfunctions or incidents of the rest of medical electronic devices in this hospital in collaboration with the Division of Clinical Trial Safety Management.

Publications

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3. 大島紀人，高野明，石丸正吾，鎭西美栄子，渡辺慶一郎．精神疾患に罹患した大学生に対する学内支援体制と学外医療機関との協働．第67回国立病院総合医学会．2013. 11. 8　金澤

IMSUT Hospital

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

Professor	Fumitaka Nagamura, M.D., D.M.Sc.		教授(兼)	医学博士	長村文孝
Senior Assistant Professor (Project)	Hiroshi Yasui, M.D., Ph.D.		特任講師(兼)	医学博士	安井寛
Assistant Professor (Project)	Makiko Karasawa, M.D., Ph.D.		特任助教	医学博士	柄澤麻紀子

There are two major missions for Division of Clinical Trial Safety Management (DCTSM). One is the risk management of the Research Hospital (RH), and the other is the support for the conduct of clinical trials, especially for Translational Research (TR).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. Patient Safety Management of Research Hospital

Fumitaka Nagamura, Aki Muraoka, Makiko Karasawa

We engage in the medical safety measures of the hospital and cope with prevention of the medical accident. We have established the report system of the incident and accident report and gave quick responses to medical accidents. We hold "the medical safe executive committee" by the director of each department to make decisions and "the medical safety promoter meeting" by the practitioner to publicize every month. We performe the round of ward, outpatient department, and central medical facilities every month in cooperation with infection control team and report on them at "the medical safe executive committee". We make the manual about the medical safety and revise then as quickly as possible, and this work contributes to improve the quality of medical care and the prevention of medical accident.

2. Promotion of Translational Research at IMSUT Research Hospital

Makiko Karasawa, Hiroshi Nojima, Hiroshi Yasui, Noriko Fujiwara, Fumitaka Nagamura.

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

1) planning research and development (R & D) strategies, including selecting target diseases, planning product designs, and clarifying development pathways;
2) offering opportunities to consult an appointed patent attorney about acquisition and maintenance of intellectual property rights as well as

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

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

Hiroshi Yasui, Noriko Fujiwara, Makiko Karasawa, Fumitaka Nagamura

We started to support two investigator-initiated clinical trials under an Investigational New Drug Application for the development of the academia-oriented innovative drug. The first trial is "the second phase trial of BK-UM against HB-EGF in combination with gemcitabine in patients with advanced or recurrent ovarian cancer". We play the role of clinical trial coordination as the site management by secretariat, clinical research associate, and translational research coordinator.

The second trial is "the multi-center double-blind parallel-group placebo-control Phase II study on the efficacy of survivin-2B peptide vaccine therapy for patients with advanced or recurrent pancreatic cancer, and for which there is no effective treatment". We play the role of clinical trial coordination as the site management by secretariat, project manager, and translational research coordinator. We study approaches to support clinical trials more efficiently by extracting problems through the investigations.

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

Noriko Fujiwara, Makiko Karasawa, Fumitaka Nagamura

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

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IMSUT Hospital

Department of Medical Informatics
医療情報部

Associate Professor	Shigeru Kiryu, M.D., D.M.Sc.	准教授	医学博士	桐　生　　茂(併任)
Senior Assistant Professor	HaruyasuYamada, M.D., D.M.Sc.	講　師	医学博士	山　田　晴　耕(併任)
Assistant Professor	Toshihiro Furuta, M.D., D.M.Sc.	助　教	医学博士	古　田　寿　宏(併任)

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

Management and operation of hospital information system and network

Shigeru Kiryu, Haruyasu Yamada, Toshihiro Furuta, Aki Yamauchi, Kanako Arakawa

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

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

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

Shigeru Kiryu, Haruyasu Yamada, Toshihiro Furuta

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

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

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

Shigeru Kiryu, Haruyasu Yamada, Toshihiro Fu-

ruta

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

An examination of color indication differences of medical color monitors.

Shigeru Kiryu, Jun Sugawara, Mikio Hasegawa, Mamiko Katagiri, Haruyasu Yamada, Toshihiro Furuta, Kuni Ohtomo

Recently, the radiographic diagnosis in medical imaging is performed on a monitor screen in many hospitals. Guidelines for gray scale images have been developed, however the guidelines for color images don't exist so far. In current research, the performance of medical color monitors operated in the hospital were tested using a chromaticity meter and the unevenness of the color indication was assessed. A total of 17 medical color monitors was assessed. The color condition indicator was set at the time of factory shipment except the brightness level which was set at maximum. A total of 32 colors of basics based on IEC 61966-4 was displayed on each color monitor, and measurement was performed using a chromaticity meter and a monitor management tool (Medvisor Color, Totoku, Japan). A standard medical color monitor was used and the difference between the standard monitor and those studied was assessed. On u'v' chromaticity diagram, the color exibiting higher brightness tended to offer small delta, whereas the delta of lower brightness colors was larger. The variance of delta tended to be larger in some color groups of grey, blue, magenta and cyan. The brightness did not affect the variance of the delta. The delta on u'v' chromaticity diagram tended to be bigger in the lower brightness colors and the variance of the delta larger in the specific colors. This information is useful to adjust the color medical monitors for accurate diagnosis in color imaging.

Conference Presentation

桐生茂，菅原淳，長谷川幹夫，片桐磨美子，山田晴耕，古田寿宏，大友邦．医用画像表示用モニターのカラー表示差の検討　第33回医療情報学連合大会(第14回日本医療情報学会学術大会)，兵庫 2013．11．21-23

IMSUT Hospital

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

Professor	Arinobu Tojo, M.D., D.M.Sc.	教　授　医学博士	東　條　有　伸
Senior Assistant Professor	Tokiko Nagamura-Inoue, M.D., D.M.Sc.	講　師　医学博士	長　村　登紀子

Our department was established in 1990, in order to manage the transfusion medicine and the cell processing for hematopoietic stem cell transplantation. Beside the transfusion medicine and testing in the hospital, our department has been supported translational research and managed IMSUT-Cell Resource Center (IMSUT-CRC), where Tokyo Cord Blood Bank has been established in 1997. Our recent projects include Research CB Stem Cells Bank as National Bioresource Project (NBRP) supported by MEXT and CB and umbilical cord (UC)-derived mesenchymal stem cell banking for clinical use in the future supported by Ministry of Health and Welfare. And we developed immunosuppressive therapy for severe GVHD after hematopoietic stem cell transplantation using expanded regulatory T cells from CB and adult blood, or UC-MSCs.

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

Nagamura-Inoue T, Yamamoto Y, Ogami K, Tojo A.

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

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

Nagamura-Inoue T, Nakai M., Yamamoto Y, Takahashi A., Tojo A.

"Research Cord Blood Stem Cell Bank" (former named 'Research Stem Cell Resource Bank') was established supported by MEXT (Ministry of Education, Culture, Sports, Science and Technology) for the development of the medicine including Regenerative Medicine and drug discovery in Japan since 2004. Since 2012, July, this project has been incorporated in National BioResouce Project (NBRP), although the delivery system and service has not been altered. The research CB bank provides processed and cryopreserved CB units which are nonconforming for clinical use, to world-wide researchers via RIKEN Bioresource Center. Visit our home page http://www.nbrp.jp/.

3. Umbilical Cord-derived mesenchymal stem cells research:

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

Umbilical cord (UC) is a rich source of mesenchymal stem cells (MSCs). The UC is normally discarded after birth and its collection does not require

an invasive procedure. Moreover, UC-derived MSCs (UC-MSCs) possess many advantages; high frequency, pluripotency, high proliferation capacity, immunomodulatory properties and no age donor-dependent variations. We have studied these characteristics and efficient expansion system of UC-MSCs, in order to apply the regenerative medicine and immunotherapy. UC-MSCs have the potential to inhibit the activated T cell proliferation upon the allogeneic stimulations, suggesting the clinical possibility to apply those for the GVHD treatment. Our final goal is to establish the CB and UC-MSCs banking for clinical use.

4. Data management of cord blood transplantations via JCBBN:

Ishibashi S, Nagamura-Inoue T

Now, over 1,000 cases of cord blood transplantations (CBT) in Japan have been done every year. To clarify the advantage and evaluate the outcome of CBT, clinical data should be qualified by data cleaning. We support the collection of CBT data and the cleaning of the CB-related data for researchers in Japan.

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

Nagamura-Inoue T, Yamamoto Y, Takahashi A., Shimazu T., Nakai M., Ogami K, Tojo A

To promote the cell therapy in translational researches, IMSUT-Cell Resource Center (IMSUT-CRC, Room for Clinical Cellular Technology (RCCT) as a prior name) has been established in 1997. Until now, the following projects had implemented; 1) CB cell processing for banking (for Tokyo Cord Blood Bank, Research cord blood stem cell bank, and related sibling donors), 2) Dendritic cell therapies, 3) Regenerative therapy of alveolar bone derived from bone marrow mesenchymal cells, 4) Gene therapy for renal cancer.

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IMSUT Hospital

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

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

The primary function of the Core Facility for Therapeutic Vectors (CFTV) is to support clinical trials that require production of recombinant viral vectors, genetic modification and/or ex vivo manipulation of patients' tissue or cells under current Good Manufacturing Practice (cGMP) conditions defined by FDA of USA. In 2002, CFTV was established as the first facility in Japanese academia for the production of viral or cellular vectors of a clinical grade.

Maintenance of the Standard Operating Procedures (SOPs)

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

Adoption of ISO

In order to continuously improve the activities of CFTV, quality management system has been assessed by a third party. It was qualified to be in accordance with the requirements of the quality standards detailed ISO9001: 2008; in the scope of development and manufacture of cell and gene therapy products.

Validation of CFTV

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

Production of clinical grade oncolytic HSV-1

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

IMSUT Hospital

Department of Laboratory Medicine
検査部

Senior Assistant Professor Naouki Isoo, M.D., Ph.D.
Lecturer Yasunori Ota, M.D., Ph.D.

病院講師 医学博士 磯 尾 直 之
講 師 医学博士 大 田 泰 徳

The Department of Laboratory Medicine consists of eight divisions - clinical physiology, hematology, flow cytometrical analysis, biochemistry, serology, bacteriology, molecular diagnosis and pathology. This department engages in the laboratory analysis and pathological examination under stringent quality control. While facilitating the ongoing translational research projects in the research hospital, we have established the pathology core facilities and the TR verification laboratory to undertake state-of the-arts pathological analysis as well as comprehensive infectious agents screening so that the Department can functions as an integrated diagnosis & monitoring laboratory that evaluates that the safety and efficacy of experimental therapeutic approaches.

Overview

Our basic research strategies include the following approaches: characterizing molecular mechanisms underlying the pathology, developing a novel method to measure the disease-defining mechanism in the clinical materials and evaluating the effectiveness of molecular-targeted therapies thereby contributing to the translational research conducted in the institute. Integrating molecular-/biochemical-based laboratory assays on the solid background of pathological examinations enables us to evaluate the effectiveness of experimental clinical trials and leads to appropriate experimental therapies that further promote translational research. Our department also functions as an integrated diagnosis & safety-monitoring laboratory as well as the division of quality control by examining/evaluating the safety of investigational new drugs under GMP conditions.

1. GMP-based biosafety examination laboratory (TR verification laboratory)

Funded by the Ministry of Education, Culture, Sports, and Technology (MEXT), we have established a laboratory, in which we examine safeties of bio-cellular materials for Translational Research (TR) clinical applications, such as the gene therapies, viral therapies and cell therapies, under GMP-based standards. For the present time, we are routinely examining bacteria, fungi, mycoplasma, and endotoxin contaminations by using molecular and biochemical techniques.

2. Development of comprehensive diagnosis system for infectious disease

Since the introduction of new therapeutic maneuver, host-pathogen interactions have drastically altered drawing attention. This has resulted in altered recognition and molecular interaction of infected cells with immune cells, leading to atypical pathological as well as clinical manifestations. While distinguishing infectious disease and immunological disorder calls for urgent attention, it may be difficult to achieve these tasks in some cases due to modified manifestations. To avoid such cases, it is imperative to establish a comprehensive diagnosis system of infectious disease to the earliest possible

opportunity.

The Department of Laboratory Medicine consists of eight divisions - clinical physiology, hematology, flow cytometrical analysis, biochemistry, serology, bacteriology, molecular diagnosis and pathology. This Department engages in the laboratory analysis and pathological examination under stringent quality control. While facilitating the ongoing translational research projects in the research hospital, we have established the pathology core facilities and the TR verification laboratory to undertake state-of the-arts pathological analysis as well as comprehensive infectious agents screening so that the Department can functions as an integrated diagnosis & monitoring laboratory that evaluates that the safety and efficacy of experimental therapeutic approaches.

3. Quantitative Evaluation of a fraction of leukemic cells by flow cytometry

By collaboration with Dept. Hematology (Division of molecular therapy), we are conducting quantitative evaluation of a fraction of leukemic cells from a cohort of patients with HTIL-1 infection by flow cytometry. By using sophisticated gating technique, we are successfully quantitating ATL (adult T-cell leukemia) cells at the subclinical stage, hence enable us to detect very early stage of overt leukemia and initiate proper therapies.

4. Construction of an assay system of HB-EGF-related peptides as prognostic factors for patients with malignancy

A clinical study is ongoing in IMSUT hospital to investigate the effect of CRM197 on ovarian cancer targeting HB-EGF. Recent study revealed that further processing of sHB-EGF by MT1-MMP is crucial for cancer growth. To examine the level of processed sHB-EGF in the peripheral blood or ascites, we are trying basic study in animals for an immunological assay combined with ultrafiltration using a novel polyclonal antibody which recognizes the bioactive HB-EGF related peptides.

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

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

6. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma

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

7. Other new findings.

We report other new findings by many case reports.

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IMSUT Hospital

DEPARTMENT OF PHARMACY
薬剤部

Director　Yosuke Kurokawa

薬剤部長　　黒　川　陽　介

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

IMSUT Hospital

Department of Nursing
看護部

Director	Yukie Takemura, RN, CNA, PhD.	看護部長	保健学博士・認定看護管理者	武	村 雪 絵
Deputy Director	Hiroko Sato, RN, CNA, MSc.	副看護部長	認定看護管理者	佐	藤 博 子
Nurse Manager	Mika Kogayu, RN, PNIPC.	看護師長	感染制御実践看護師	小	粥 美 香
	Aki Muraoka, RN.	看護師長		村	岡 亜 紀
	Keiko Kawasaki, RN.	看護師長		川	崎 敬 子
	Hisako Suyama, RN.	看護師長		須	山 寿 子
	Minayo Hisahara, RN, CNJRF.	看護師長	リウマチケア看護師	久	原 みな代
	Tomoko Sato, RN.	看護師長		佐	藤 朋 子
	Hatsuko Narita, RN.	看護師長		成	田 初 子
	Satomi Kiriyama, RN.	看護師長		桐	山 里 美

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

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

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

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

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

Publications

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井部俊子・笠松由佳・倉岡有美子・佐々木菜名代・渡邉綾子・武村雪絵・手島恵・吉田千文．看護管理者を対象としたコンピテンシー・ベースのトレーニング・プログラムの開発．第17回日本看護管理学会学術集会．東京ビッグサイト．2013. 8. 24–25.
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島田直樹，岩瀬哲，渡邊文，藤原紀子，山花令子，春田淳志，鎭西美栄子，今井浩三．積極的治療適応がなくなった入院患者の在宅移行の実際．第18回日本緩和医療学会学術大会．パシフィコ横浜．2013. 6. 21–22.

IMSUT Hospital

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

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

教授(委嘱) 医学博士 俣 野 哲 朗

We are working on Microbiology and Immunology to elucidate the immune mechanism for viral control in vivo. For development of an effective AIDS vaccine, we are studying virus-host interaction in non-human primate AIDS models. We developed a recombinant Sendai virus vector vaccine system eliciting cytotoxic T lymphocyte responses. An international collaborative clinical trial phase I of an AIDS vaccine using this system has started in Rwanda, Kenya, and U.K.

1. IL-21-producer CD4$^+$ T cell kinetics during primary simian immunodeficiency virus infection

Shoi Shi, Sayuri Seki, Tetsuro Matano, and Hiroyuki Yamamoto[1]: [1]AIDS Research Center, National Institute of Infectious Diseases

IL-21 signaling is important for T cell and B cell-mediated clearance of chronic viral infections. While non-cognate follicular helper CD4+ T cells (TFH) are indicated to be pivotal in providing IL-21-mediated help to activated B cells within germinal centers, how this signaling may be disrupted in early AIDS virus infection is not clear. In this study, we assessed the lineage and kinetics of peripheral blood IL-21-producing CD4$^+$ T cells in primary simian immunodeficiency virus (SIV) infection of rhesus macaques. After SIV challenge, antigen-nonspecific IL-21 production was observed in Th1, Th2 and Th17 cells with Th1 dominance. While IL-21$^+$ Th2 and IL-21$^+$ Th17 showed variable kinetics, an increase in total IL-21$^+$ CD4$^+$ T cells and IL-21$^+$ Th1 from week 3 to week 8 was observed, preceding plasma SIV-specific IgG development from week 5 to week 12. SIV Gag-specific IL-21$^+$ CD4$^+$ T cells detectable at week 2 were decreased in frequencies at week 5. Results imply that kinetics of IL-21$^+$ CD4$^+$ T cells comprised of multiple lineages, potentially targeted by SIV with a bias of existing frequencies during their precursor stage, associate with availability of cooperative B-cell help provided through a proportionate precursor pool developing into TFH and subsequent anti-SIV antibody responses.

2. Limited impact of passive non-neutralizing antibody immunization in acute SIV infection on viremia control in rhesus macaques

Taku Nakane, Takushi Nomura, Shoi Shi, Midori Nakamura, Taeko K. Naruse[2], Akinori Kimura[2], Tetsuro Matano, and Hiroyuki Yamamoto[1]: [2]Medical Research Institute, Tokyo Medical and Dental University

Antiviral antibodies, especially those with neutralizing activity against the incoming strain, are potentially important immunological effectors to control human immunodeficiency virus (HIV) infection. While neutralizing activity appears to be central in sterile protection against HIV infection, the entity of inhibitory mechanisms via HIV and SIV-specific antibodies remains elusive. The recent HIV vaccine trial RV144 and studies in nonhuman primate models have indicated controversial protective efficacy of HIV/SIV-specific non-neutralizing binding antibodies (non-NAbs). While reports on HIV-specific non-NAbs have demonstrated virus inhibi-

tory activity *in vitro*, whether non-NAbs could also alter the pathogenic course of established SIV replication *in vivo*, likewise via neutralizing antibody (NAb) administration, has been unclear. Here, we performed post-infection passive immunization of SIV-infected rhesus macaques with polyclonal SIV-specific, antibody-dependent cell-mediated viral inhibition (ADCVI) competent non-NAbs.

Ten lots of polyclonal immunoglobulin G (IgG) were prepared from plasma of ten chronically SIV_{mac239}-infected, NAb-negative rhesus macaques, respectively. Their binding capacity to whole SIV_{mac239} virions showed a propensity similar to ADCVI activity. A cocktail of three non-NAb lots showing high virion-binding capacity and ADCVI activity was administered to rhesus macaques at day 7 post-SIV_{mac239} challenge. This resulted in an infection course comparable with control animals, with no significant difference in set point plasma viral loads or immune parameters.

Despite virus-specific suppressive activity of the non-NAbs having been observed *in vitro*, their passive immunization post-infection did not result in SIV control *in vivo*. Virion binding and ADCVI activity with lack of virus neutralizing activity were indicated to be insufficient for antibody-triggered non-sterile SIV control. More diverse effector functions or sophisticated localization may be required for non-NAbs to impact HIV/SIV replication *in vivo*.

3. Control of SIV replication by vaccine induced Gag- and Vif-specific $CD8^+$ T cells

Nami Iwamoto, Naofumi Takahashi, Sayuri Seki, Takushi Nomura, Hiroyuki Yamamoto[1], Makoto Inoue[3], Tsugumine Shu[3], Taeko K. Naruse[2], Akinori Kimura[2], and Tetsuro Matano: [3]DNAVEC Corporation

For development of an effective T cell-based AIDS vaccine, it is critical to define the antigens that elicit the most potent responses. Recent studies have suggested that Gag-specific and possibly Vif/Nef-specific $CD8^+$ T cells can be important in control of the AIDS virus. Here, we tested whether induction of these $CD8^+$ T cells by prophylactic vaccination can result in control of SIV replication in Burmese rhesus macaques sharing the MHC-I haplotype *90-010-Ie* associated with dominant Nef-specific $CD8^+$ T-cell responses. In the first group vaccinated with Gag-expressing vectors (n = 5), three animals that showed efficient Gag-specific $CD8^+$ T-cell responses in the acute phase post-challenge controlled SIV replication. In the second group vaccinated with Vif- and Nef-expressing vectors (n = 6), three animals that elicited Vif-specific $CD8^+$ T-cell responses in the acute phase showed SIV control, whereas the remaining three with Nef-specific but not Vif-specific $CD8^+$ T-cell responses failed to control SIV replication. Analysis of eighteen animals consisting of seven unvaccinated non-controllers and the eleven vaccinees described above revealed that the sum of Gag- and Vif-specific $CD8^+$ T-cell frequencies in the acute phase was inversely correlated with plasma viral loads in the chronic phase. Our results suggest that replication of the AIDS virus can be controlled by vaccine-induced subdominant Gag/Vif epitope-specific $CD8^+$ T cells, providing a rationale for the induction of Gag- and/or Vif-specific $CD8^+$ T-cell responses by prophylactic AIDS vaccines.

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

A project for a clinical trial of an AIDS vaccine using Sendai virus vectors is proceeding in collaboration with DNAVEC Corp. and International AIDS Vaccine Initiative (IAVI). A phase I trial (S001) has started in Rwanda, Kenya, and U.K.

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

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IMSUT Hospital

Center for Antibody and Vaccine Therapy
Division of Antibody and Targeting Therapy
Division of Immunotherapy
Division of Vaccine and Targeting Therapy
Division of Translational Research

抗体・ワクチンセンター
抗体・分子標的分野
免疫治療分野
ワクチン・分子標的分野
橋渡し研究分野

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This center was established in April 1st, 2012, in the memory of Professor Shibasaburo Kitasato, the founder and the first director of our institute, because the year 2012 was 120th anniversary of our institute which was built in 1892. Prof Kitazato was keen to utilize "serum therapy" for patients with infectious diseases and actually prepared several kinds of sera from horses at that time. Now, we can use monoclonal antibody to growth factor receptor on cancer cells for cancer patients and to TNF molecule in the case of patients with rheumatoid arthritis in anordinal clinical setting. The aim of this center is to investigate novel immunological therapy including monoclonal antibody, targeting molecule and peptide vaccine for patients with malignant and autoimmune diseases. Part of the funding for this center was supported by thespecial grant from the Ministry of Education, Culture, Sports, Science and Technology, Japan from 2013-2017. We welcome any collaborative study with other facilities to create novel personalized therapy to above mentioned patients.

1. Development of novel therapeutics targeting cancer stem cells

Hiroaki Taniguchi, Kohzoh Imai

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

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

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

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

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

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

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

In this last setting, KLF2 transfection was also associated with decreased dissemination and lower mortality rate. In EZH2-depleted cells, which characteristically have lower tumorigenicity, the induction of KLF2 depletion 'rescued' partially the oncogenic phenotype, suggesting that KLF2 repression has an important role in EZH2 oncogenesis.

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

B) PR domain-containing protein, PRDM14

PRDM have been linked to human cancers. To explore the role of the PR domain family genes in breast carcinogenesis, we examined the expression profiles of 16 members of the PRDM gene family in a panel of breast cancer cell lines and primary breast cancer specimens using semiquantitative real-time PCR. We found that PRDM14 mRNA is overexpressed in about two thirds of breast cancers. Moreover, immunohistochemical analysis showed that expression of PRDM14 protein is also up-regulated. PRDM14 are known as a key transcription factor required for the maintenance of hESC identity and the reacquisition of pluripotency in human somatic cells.

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

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

2. Clinical activities of the Division of Immunotherapy

Osamu Hosono[1], Noritada Yoshikawa[1], Hiroshi Kobayashi[1], Masaaki Uehara[1], Hirotoshi Tanaka: [1]Department of Rheumatology and Allergy, IMSUT Hospital, University of Tokyo

Rheumatologists at our division provide state-of-the-art diagnosis and treatment for diseases that affect the body's connective tissue. Physicians in the specialty see nearly 1,000 patients each year. Our physicians have active basic and clinical research projects and also are involved in training of rheumatology specialists. Our rheumatologists treat many types of arthritis, including common diseases such as rheumatoid arthritis and osteoarthritis, and rare diseases such as relapsing polychondritis and multicentric reticulohistiocytosis. Additionally physicians offer consultative and continuing care for patients with regional musculoskeletal disorders such as shoulder pain, hip pain, and knee pain.

Preoperative evaluation and recommendations

for patients considering joint replacement and arthritis-related reconstructive surgeries are also provided.

Rheumatologic services offered at IMSUT include:

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

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

3. Research activities of the Division of Immunotherapy

Noritada Yoshikawa, Noriaki Shimizu[1], Takako Maruyama[1], Akiko Souta-Kuribara[1], Ma Yanxia[1], Ryo Matsumiya[1], Hiroshi Kobayashi, Osamu Hosono, Hirotoshi Tanaka

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

(i) Development of novel GR regulators

Despite the established role of glucocorticoids (GC) in controlling short-term inflammation, and despite emerging evidence supporting a disease-modifying role in various autoimmune disorders, concern for adverse events associated with GCs often limits their use. Activation of the GR by GC regulates hundreds of genes expression both positively and negatively. It has become quite widely accepted that transrepression accounts for the majority of therapeutic, anti-inflammatory effects of GC, whereas transactivation is responsible for most side effects. This "transrepression hypothesis" has arisen a set of ideas about how to discover novel anti-inflammatory drugs that do not carry the same burden of side effects as GC. We have explored unique GR regulators that have a different mode of action from classical GC. We have recently shown that not only synthetic GC but also certain bile acids could differentially modulate GR function in such a way that preserves transrepression but not transactivation function. Moreover, the effects of those compounds are ascribed to the ligand binding domain of the receptor. 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. On the other hand, receptor specificity is another important aspect of novel GR regulators. In this line, we have shown that cortivazol is extremely specific for GR and does not bind to mineralocorticoid receptor.

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

We have studied the molecular basis for the receptor specificity of the ligand using cortivazol as a model and develop 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 cardiac muscles and skeletal muscles. We discovered a novel desirable effect of GC and are now tackling their undesirable side effects.

Cardiac muscles We found that the expression of genes that encode 2 key enzymes in a common pathway of prostaglandin biosynthesis were upregulated by GCs via the GR in cardiomyocytes: phospholipase A2 group IVA (Pla2g4a; encoding cytosolic calcium-dependent phospholipase A2 [cPLA2]) and prostaglandin-endoperoxide synthase 2 (Ptgs2; encoding COX2). Importantly, aldosterone did not have similar stimulatory effects on these genes. The induction of Pla2g4a and Ptgs2 by GR is specific for cardiomyocytes, since GR has been shown to transrepress the activation of these proinflammatory genes in most cells. Therefore, we sought to investigate the major types of prostanoids produced in cardiomyocytes after exposure to glucocorticoids and to clarify the roles of these products in cardiac physiology. Among the genes for PGH2 isomerases, expression of Ptgds, which encodes lipocalin-type prostaglandin D synthase (L-PGDS), was selectively upregulated by a GR-specific ligand. Consistent with this result, PGD2 was the most prominently induced prostaglandin by GR-specific ligand stimulation of cultured cardiomyocytes and in vivo hearts. Using isolated Langendorff-perfused hearts and cultured cardiomyocytes, we demonstrated that the activation of L-PGDS-mediated production of PGD2 was crucial for the cardioprotection against ischemia/reperfusion conferred by GC-GR signaling. Our results suggest a novel interaction between GC-GR signaling and the arachidonic acid cascade-mediated cardiomyocyte survival pathway. Recently, we have characterized the cardiac receptor for PGD2 and more precisely analyzed the role of GR in cardiac muscles by developing cardiomyocyte-specific GR knockout mice in collaboration with the Department of Cardiology, Keio University School of Medicine.

Skeletal muscle Muscle comprises ~40% of body mass and contributes not only to the structure and movement of the body but also to nutrient storage and supply. Excessive loss of muscle mass is associated with poor prognosis in several diseases, including myopathies and muscular dystrophies, as well as in systemic disorders such as cancer, diabetes, sepsis, heart failure, and glucocorticoid excess. Muscle atrophy also occurs in aging that is called sarcopenia and recently thought to be one of core features of "Locomotive Syndrome". The maintenance of healthy muscles is crucial for preventing metabolic disorders, maintaining healthy aging and providing energy to vital organs during stress conditions. Recent analyses revealed that the resulting loss of muscle mass in the catabolic states involves a common transcriptional program, resulting in a general acceleration of proteolysis and a decrease in protein synthesis. Atrophy-related genes (atrogenes) induced most dramatically during atrophy are two muscle-specific ubiquitin ligases, atrogin-1 and MuRF-1, which are regulated by the FoxO transcription factors. On the other hands, in growing muscles, FoxOs are maintained in an inactive state by the IGF-1/phosphoinositide 3-kinase (PI3K)/Akt/mTOR signaling cascade. This pathway plays a key role in the regulation of muscle mass and promotes fiber hypertrophy by stimulating overall protein synthesis and suppressing proteolysis.

The involvement of FoxO transcription factors is reported in the gene regulation of atrogin-1 and MuRF1 under the presence of excess of GC, the biochemical role of GR in the transcriptional regulation of muscle tissue has not yet been determined. Therefore, 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. REDD1 is known to be induced by various stressors, including glucocorticoid, and to inhibit mTOR activity via the sequestration of 14-3-3 and the increase of TSC1/2 activity. We clearly identified the functional GRE via the promoter analysis of REDD1 gene. On the other hand, KLF15 is a recently discovered transcription factor that is involved in several metabolic processes in skeletal muscle; e.g., KLF15 transcriptionally upregulates the gene expression of branched-chain aminotransferase 2 (BCAT2), a mitochondrial enzyme catalyzing the first reaction in the catabolism of branched-chain amino acids (BCAA) to accelerate BCAA degradation and alanine production in skeletal muscle. Moreover, phenotypic analysis of cardiac-specific KLF15 knockout mice revealed marked left ventricular hypertrophy, indicating the negative regulatory role of KLF15 on muscle mass. We here demonstrated that KLF15 participates in muscle catabolism via the transcriptional regulation of atrogin-1 and MuRF1. Moreover, KLF15 affects mTOR through BCAA degradation and negatively modulates myofiber size. mTOR activation inhibits GR-mediated transcription by suppressing GR recruitment onto target genes, strongly suggesting a mutually exclusive crosstalk between mTOR and GR. Pharmacological activation of mTOR with BCAA attenuated GR-mediated gene expression, leading to the substantial restoration of muscle in glucocorticoid-treated rats. We, therefore, indicate the critical importance of the interaction of GR and mTOR in the regulation of metabolism-volume coupling in skeletal muscle. Recently, we have created skeletal muscle-specific GR knockout mice (mGRKO) and revealed that mGRKO show significant increase of their myofiber size and muscle mass. Given this, we have just started the clinical trial in IMSUT hospital to verify our scenario in glucocorticoid-treated patients.

(iii) Development of a novel therapy for pulmonary hypertension associated with collagen vascular disease

Pulmonary hypertension (PH) associated with collagen vascular disease causes fatal right ventricular hypertrophy (RVH). To further improve the outcome of those patients, it may be effective to directly interrupt hypertrophy and irreversible remodeling of RV. Hexamethylene bis acetamide inducible protein 1 (HEXIM1) is a negative regulator of positive transcription elongation factor b (P-TEFb), which activates RNA polymerase II (RNAPII)-dependent transcription and whose activation is strongly associated with left ventricular hypertrophy. We revealed that, in the mouse heart, HEXIM1 is highly expressed in the early postnatal period and its expression is gradually decreased, and that prostaglandin I2, a major therapeutic drug for PH, increases HEXIM1 levels in cardiomyocytes, suggesting that HEXIM1 might possess negative effect on cardiomyocyte growth and take part in cardiomyocyte regulation in RV. Using adenovirus-mediated gene delivery to cultured rat cardiomyocytes, we revealed that overexpression of HEXIM1 prevents endothelin-1-induced phosphorylation of RNAPII, cardiomyocyte hypertrophy, and mRNA expression of hypertrophic genes, whereas a HEXIM1 mutant lacking central basic region, which diminishes P-TEFb-suppressing activity, could not. Moreover, we created cardiomyocyte-specific HEXIM1 transgenic mice and revealed that HEXIM1 ameliorates RVH and prevents RV dilatation in hypoxia-induced PH model. Taken together, these findings indicate that cardiomyocyte-specific overexpression of HEXIM1 inhibits progression to RVH under chronic hypoxia, most possibly via inhibition of P-TEFb-mediated enlargement of cardiomyocytes. We conclude that P-TEFb/HEXIM1-dependent transcriptional regulation may play a pathophysiological role in RVH and be a novel

therapeutic target for mitigating RVH in PH.

4. Novel therapeutic target discovery for solid cancers

Yataro Daigo, Atsushi Takano, Koji Teramoto

To identify molecules involved in human carcinogenesis and those which could be applied for the development of new molecular therapies and/or biomarkers, we had established a systematic screening system as follows; i) identification of overexpressed genes in the majority of solid cancers (lung, esophagus etc.) by genome-wide screening using the expression microarray in the combination of enrichment of tumor cell populations from cancer tissues by laser microdissection, ii) verification of no or little expression of each of candidate molecules in normal tissues by northern-blot analyses, iii) validation of the clinicopathological significance of its higher expression with tissue microarray containing hundreds of archived solid cancers, iv) verification of a critical role of each target gene in the growth or invasiveness of cancer cells by RNAi and cell growth/invasion assays, v) evaluation of their usefulness as targets for passive immunotherapy using specific antibodies and/or as a serum 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). In fact, this systematic approach identified more than 30 molecules including CDCA1, LY6K, and JMJD2A that appear to fall into the category of oncoantigens whose overexpression is an important feature of the malignant nature of cancer cells and that have very high immunogenicity to induce antigen-specific CTLs in cancer patients. We further validated these molecules identified as potential targets for the development of antibodies, small-molecular compounds, growth-suppressive cell-permeable peptides, and cancer vaccines that could have a more specific and strong anti-cancer effect with minimal risk of adverse events.

5. Development of anti-cancer cell-permeable peptide therapy

Yataro Daigo, Atsushi Takano, Koji Teramoto

Selective killing of cancer cells with no or minimum adverse effect on normal cells by targeting interaction of tumor-specific molecules is one of the most reasonable treatments to cancer patients. We screened interaction of several combinations of oncogenic proteins whose interaction played pivotal roles in growth of cancer cells through the immunoprecipitation using antibodies to these proteins and mass spectrometric analyses. We found that Ras and EF-hand domain containing (RASEF) interacted with extracellular signal-regulated kinase (ERK) 1/2 and enhanced ERK1/2 signaling in lung cancer cells. Importantly, inhibiting the interaction between RASEF and ERK1/2 using a cell-permeable peptide that corresponded to the ERK1/2-interacting site of RASEF, suppressed growth of lung cancer cells. In addition, RASEF expression is associated with poor prognosis for lung cancer patients. RASEF may play an important role in lung carcinogenesis and could serve as a candidate biomarker and target for novel molecular therapies.

6. Screening of small-molecular compounds for cancer therapy

Yataro Daigo, Atsushi Takano, Koji Teramoto

Through the gene expression profile analysis of lung cancers, we identified TTK (TTK therine threonine kinase; alias monopolar spindle 1 (Mps1)) that was overexpressed in the majority of lung cancers, but its expression was hardly detectable in normal tissues except testis. As TTK kinase is an attractive cancer drug target due to the important role in the centrosome duplication, the spindle assembly checkpoint and the maintenance of chromosomal stability, we performed high throughput screening and found lead compounds that inhibited the TTK kinase activity. A design based on JNK inhibitors with aminopyridine scaffold and subsequent modifications identified diaminopyridine (compound No. 9) with an IC50 of 37 nM. An X-ray structure of compound No. 9 revealed that the Cys604 carbonyl group of the hinge region flips to form a hydrogen bond with the aniline NH group in compound No. 9. Further optimization of compound No. 9 led to compound No. 12 with improved cellular activity, suitable pharmacokinetic profiles and good in vivo efficacy in a mouse A549 xenograft model. TTK can serve as a promising target for the development of anticancer drugs.

7. Development of therapeutic cancer vaccine

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

Using the systematic screening system shown above, we identified concoantigens which were overexpressed in the majority of lung cancers and essential for the growth and/or survival of cancer cells, as targets for therapeutic cancer vaccine treatment against solid cancer. We screened dozens of 9- or 10-amino-acid epitope peptides recognized by human HLA-A*0201 and/or A*2402-restricted CTL by ELISPOT assay. In collaborative hospitals, Inter-

national 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.

8. Management and enforcement of the investigator-initiated clinical trials under an Investigational New Drug Application

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We are conducting two investigator-initiated clinical trials under an Investigational New Drug Application for the development of the academia-oriented innovative drug. The first trial is "the second phase trial of BK-UM against HB-EGF in combination with gemcitabine in patients with advanced or recurrent ovarian cancer". We play the role of the site management with the department of clinical trial safety management, as well as the enforcement with the department of surgery, radiology, laboratory medicine, and the surgical center.

The second trial is "the multi-center double-blind parallel-group placebo-control Phase II study on the efficacy of survivin-2B peptide vaccine therapy for patients with advanced or recurrent pancreatic cancer, and for which there is no effective treatment". We play the role of the site management with the department of clinical trial safety management, as well as the enforcement with the department of surgery, radiology, laboratory medicine, and cell processing and transfusion. We study to conduct clinical trials to promote translational research more efficiently in IMSUT hospital through these investigations.

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