IMSUT Hospital

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先端診療部

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Department of Advanced Medical Science was established in September 1997. Our aim is to contribute to the performance and the development of advanced therapeutic approach to the diseases. We have been participating in the potentially important clinical trials and the several projects in line with our principles. Our research projects are (1) Antigen-specific induction of allogeneic umbilical cord 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.

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

Fujita S. et al.

We have been focusing our effort on exploring the possibility of adoptive transfer of allogeneic umbilical cord blood-derived cytotoxic T lymphocytes (CTLs) to treat hematological malignancies and solid tumors. Using cryopreserved umbilical cord blood as the source of lymphocytes, we were able to induce the expansion of CTLs using combination of certain T cell growth factors and antigen-specific stimulation. Currently we are in the process of establishing an efficient protocol to induce HLA-restricted antigen-specific CTL using 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-ulcer patients.

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

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. 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

Lam Q.L.K. et al.

Recent reports including ours suggest a possible oncogenic role of leptin in malignant plasma cell development with implication in multiple myeloma pathophysiology (Lam et al., PNAS 107: 13812, 2010). Therefore in our proposal we aimed to analyze the effect of leptin in the survival and activity of myeloma cells and the bone marrow environment. On the other hand, we actively explored therapeutic strategies for hematological malignancies by performing parallel studies using available resources in our laboratory such as umbilical cord blood. We proposed that cytotoxic T lymphocytes derived from umbilical cord blood induced to exhibit tumor specificity may offer ideal treatment option. To this end, we have successfully developed methods to isolate and expand cytotoxic T lymphocytes from cryopreserved or fresh umbilical cord blood. Currently we are in the process of trying to induce antigen-specificity in these cytotoxic T lymphocytes in light of future clinical application to treat hematological malignancies including multiple myeloma.

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. Enrollment of patients will start at the beginning of January, 2013 and 50 to 60 patients will be analyzed annually.

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IMSUT Hospital

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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 360 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 a proteasome inhibitor for multiple myeloma. We extensively apply these molecular targeted therapies for in- and out-patients. 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. The impact of steroid use as a GVHD treatment or prophylaxis within 100 days after CBT

Kawakita T, Tsukada N, Takahashi S, Ooi J, Kato S, Tojo A

The incidence of severe graft-versus-host disease (GVHD) in cord blood transplantation (CBT) is generally low, but still exists. In our institute, we use cyclosporine (CsA) and short term methotrexate (MTX) as GVHD prophylaxis and minimally use steroid to avoid infection or

infection-related complications. In this study, we retrospectively analyzed the clinical data to clarify the impact of steroid use to the outcome of CBT. PATIENTS: We have performed 140 CBT after myeloablative conditioning using CsA with short term MTX as GVHD prophylaxis for adults at IMSUT between August 1998 and October 2008. The median age was 39 (range, 16-55) years and the median number of cryopreserved nucleated CB cells was 2.38 (range, 1.21-5.69)$\times 10^7$/kg. Although 82 of 140 patients (59%) suffered from grade II-IV aGVHD, only 31% patients received steroid after CBT. Steroid was used in 17 patients (12%) as a treatment for mainly GVHD and the dosage of prednisolone in the treatment group were 2 mg/kg (n = 7), 1 mg/kg (n = 8), and 0.5mg/kg (n = 2). Twenty-six patients (19%) changed CsA to steroid because of intolerability (20: renal dysfunction, 4: encephalopathy, 2: others) and received 1 mg/kg (n = 4) or 0.5mg/kg (n = 22) (alternative group). Overall survival in 5 years were 78% in the non-steroid use group, 71% in the treatment group, however 45% in the patients with alternative steroid use. The intolerability of CsA within 100 days after CBT seems to be a significant poor factor. We should modify the procedures including post-transplant immune modulation in such patients.

2. Treatment of multifocal Langerhans cell histiocytosis (LCH) in adults with the Special C regimen formulated by the Japan LCH Study Group.

Tojo A, Takahashi S, Morimoto A, Shimazaki C, Yoshikawa K, Nishimura R, Wakita H, Kobayashi Y, Kanegane H, Imamura T, Imashuku S; Japan LCH Study Group.

Little information is available regarding effective systemic therapies for adult Langerhans cell histiocytosis (LCH). The Japan LCH Study Group has formulated an ambulatory treatment regimen for adult patients with LCH. In total, 14 patients (median age 43 years, range 20-70 years) with multifocal LCH with biopsy-confirmed histology were enrolled. None had received cytoreductive agents for LCH previously. Four had single system (SS) and ten had multi system (MS) disease. All were treated with the Special C regimen, which consists of vinblastine/prednisolone and methotrexate with daily 6-mercaptopurine for 36 weeks. At the end of the therapeutic regimen, all SS patients achieved no active disease (NAD), and six of the ten MS patients showed a response (NAD in two, partial response in four). At the last follow-up (median 34?months), 11 patients were alive (NAD in eight and active disease in three). Of the three deceased, one died of hemorrhage during the Special C treatment, and two of infections during subsequent therapy. Although this study is limited by the small sample size, this ambulatory regimen shows signs of efficacy for adult LCH. This was particularly evident for patients with multifocal SS disease, but half of those with MS disease also benefited.

3. Strict monitoring of vancomycin serum trough concentrations for attenuating acute kidney injury after myeloablative cord blood transplantation in adults.

Mae H, Ooi J, Takahashi S, Kato S, Kawakita T, Tojo A.

Acute kidney injury (AKI) is a common medical complication after myeloablative allogeneic stem cell transplantation (SCT). We have previously performed a retrospective analysis of AKI after cord blood transplantation (CBT) in adults, and found that the maximum of vancomycin (VCM) trough levels were significantly higher in patients with AKI. Following these results, we have monitored VCM serum trough concentrations more strictly, to not exceed 10.0 mg/L, since 2008. In this report, we performed an analysis of AKI in a new group of 38 adult patients with hematological malignancies treated with unrelated CBT after myeloablative conditioning between January 2008 and July 2011. Cumulative incidence of AKI at day 100 after CBT was 34% (95% confidence interval 19-50). The median of the maximum value of VCM trough was 8.8 (4.5-12.2) mg/L. In multivariate analysis, no factor was associated with the incidence of AKI. No transplant-related mortality was observed. The probability of disease-free survival at 2 years was 83%. These findings suggest that strict monitoring of VCM serum trough concentrations has a beneficial effect on outcomes of CBT.

4. The CD3 versus CD7 plot in multicolor flow cytometry reflects progression of disease stage in patients infected with HTLV-I.

Seiichiro Kobayashi, Nobuhiro Ohno, Koichiro Yuji, Mayuko Tsuda, Arinobu Tojo, Kaoru Uchimaru

In a recent study to purify adult T-cell leukemia-lymphoma (ATL) cells from acute-type patients by flow cytometry, three subpopulations were observed in a CD3 versus CD7 plot (H: $CD3^{high}CD7^{high}$; D: $CD3^{dim}CD7^{dim}$; L: $CD3^{dim}CD7^{low}$). The majority of leukemia cells were enriched in the L subpopulation and the same clone was included in the D and L subpopulations, suggesting clonal evolution. In this study, we analyzed patients with indolent-type ATL and human T-cell leukemia virus type I

(HTLV-I) asymptomatic carriers (ACs) to see whether the CD3 versus CD7 profile reflected progression in the properties of HTLV-I-infected cells. Using peripheral blood mononuclear cells from patient samples, we performed multi-color flow cytometry. Cells that underwent fluorescence-activated cell sorting were subjected to molecular analyses, including inverse long PCR. In the D(%) versus L(%) plot, patient data could largely be categorized into three groups (Group 1: AC; Group 2: smoldering- and chronic-type ATL; and Group 3: acute-type ATL). Some exceptions, however, were noted (*e.g.*, ACs in Group 2). In the follow-up of some patients, clinical disease progression correlated well with the CD3 versus CD7 profile. In clonality analysis, we clearly detected a major clone in the D and L subpopulations in ATL cases and, intriguingly, in some ACs in Group 2. We propose that the CD3 versus CD7 plot reflects progression of disease stage in patients infected with HTLV-I. The CD3 versus CD7 profile will be a new indicator, along with high proviral load, for HTLV-I ACs in forecasting disease progression.

5. Investigation of consultation system for HTLV-1 asymptomatic carriers and patients with HTLV-1 related disease.

K. Uchimaru

Recently distribution of HTLV-1 carriers in Japan is altering as people continue to move to greater Tokyo area and other big cities such as Osaka and Nagoya. These cities previously were considered as non-endemic area of HTLV-1, so there was no systematic approach to establish consultation system for HTLV-1 asymptomatic carriers and HTLV-1 related disease patients. Supported by Ministry of health, labor, welfare, we started to investigate what ideal consultation system in each prefecture is. Health care centers are expected to be primary counseling institutions for HTLV-1 carriers, but majority of health care centers have no experience of counseling for HTLV-1 carriers. To encourage health care center activity of counseling for HTLV-1 carriers, prefecture government should organize consultation system for HTLV-1 carriers.

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IMSUT Hospital

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

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（先端医療研究センター感染症分野）

Founded in 1981, Department of Infectious Diseases and Applied Immunology (DIDAI) started HIV clinic in 1986. In 2012, 44 new patients with HIV infection have visited or been admitted to our hospital and 539 patients in total are currently under our clinical management. The total number of in-patients with HIV-infection during 2012 was 113, and about 8 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 for international infectious diseases such as malaria and typhoid 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, Shoichi Shimizu, Saho Takaya, Naoko Miyazaki[2], 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

44 new patients with HIV-1 infection visited our hospital this year (from January 1 to December 31, 2012), and 539 patients in total are under medical management in our outpatient clinic. The total number of HIV-infected inpatients during 2012 was 113. The number of total patients declined in 1997 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 459 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

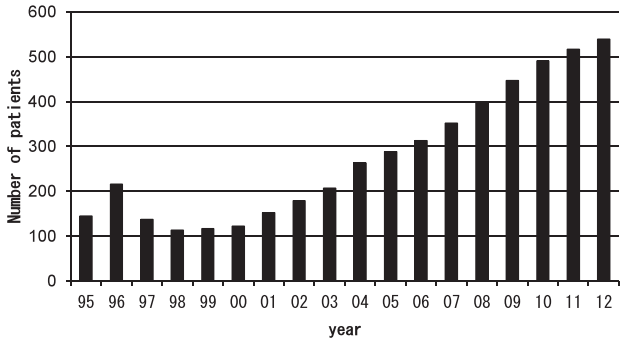

Figure 1. Number of HIV-infected outpatients in IMSUT Hospital

50 copies/ml in 94.7% of patients. Consequently, the clinical management of HIV-infected patients changed from how to treat opportunistic infections into how to control patients with ART.

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

Tomohiko Koibuchi, Michiko Koga[1], Eisuke Adachi, Shoichi Shimizu, Saho Takaya, Hitomi Nakamura[2], Tadashi Kikuchi[1], 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 central medical institution of the research group importing and providing these orphan drugs if needed, and colleting clinical data. This year, we imported and stored 19 orphan drugs and distributed required ones to 25 designated hospitals in all over Japan. 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 malaria (6 patients), dengue fever (3 patients), post-exposure prophylaxis of rabies (25 patients) and so on.

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

Tomohiko Koibuchi, Michiko Koga[1], Eisuke Adachi, Shoichi Shimizu, Saho Takaya, 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. 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.

4. *Shigella sonnei* outbreak among men who have sex with men in Tokyo.

Michio Okame, Eisuke Adachi, Hidenori Sato, Shoichi Shimizu, Tadashi Kikuchi[1], Naoko Miyazaki[2], Michiko Koga[1], Hitomi Nakamura[2], Masato Suzuki[3], Naoki Oyaizu[3], Takeshi Fujii, Aikichi Iwamoto[1] and Tomohiko Koibuchi: [1]Division of Infectious Diseases, The Advanced Clinical Research Center, [2]International Research Center for Infectious Diseases, [3]Department of Laboratory Medicine

Five patients of shigellosis were admitted in The IMSUT hospital in a short period; between September and November 2011. All of them were HIV-infected men who have sex with men (MSM). The range of their CD4 T-cell count was 168 to 415 cells/μL. Three of them have already received antiretroviral therapy (ART). All patients had abdominal pain and watery diarrhea (5-30 times/day), 3 had bloody stool, 4 had fever, and 1 had vomiting. *Shigella sonnei* was identified from stool culture of all patients. Their susceptibility patterns against antibiotics were identical. After receiving 5-day treatment of LVFX 500 mg/day, four patients recovered from diarrhea within several days. Only one patient who continued diarrhea following 5-day treatment of LVFX received extra LVFX 500 mg/day for 5 days. A mean duration of their symptom was 10 days (range 5 to 14 days). Trophozoites of *Entamoeba histolytica* was identified from one of the patients stool and metronidazole was added to the treatment. Pulsed-field gel electrophoresis (PFGE)

of all strains performed later demonstrated similar pattern, suggesting one strain of *Shigella sonnei* spread among MSM. For prevention of outbreak of *Shigella* species, practitioners and MSM need to be made aware of the risk of sexual transmission of orally transmitted agents.

5. Liver dysfunction in patients with early syphilis: a retrospective study.

Eisuke Adachi, Tomohiko Koibuchi, Michio Okame, Hidenori Sato, Tadashi Kikuchi[1], Michiko Koga[1], Hitomi Nakamura[2], Aikichi Iwamoto[1] and Takeshi Fujii: [1]Division of Infectious Diseases, The Advanced Clinical Research Center, [2]International Research Center for Infectious Diseases

Syphilis is one of the unrecognized etiologies of liver dysfunction. The incidence of syphilitic hepatitis is currently unknown. We conducted a retrospective study about causative agents of liver dysfunction at the time of diagnosis of early syphilis. Our study shows that 39% (44/112) of early syphilis patients have any liver enzyme abnormalities at the time of diagnosis, and that 2.7% (3/112) of patients are diagnosed with syphilitic hepatitis. Clinicians should include syphilitic hepatitis in the differential diagnosis for those patients with sexually transmitted diseases presenting with liver enzyme abnormalities.

6. The favorable outcome by treatment of mefloquine in combination with anti-retroviral therapy on progressive multifocal leukoencephalopathy in an HIV-infected patient

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

At present, the main approach to treatment of progressive multifocal leukoencephalopathy (PML) is to restore the host adaptive immune response to the JC virus (JCV). For HIV-infected PML patients, initiation or optimization of anti-retroviral therapy (ART) is the only therapy that has proven to be effective. However, PML still carries a significant mortality rate. Hence, the search for specific treatment targeting JCV is imperative. There was a report that mefloquine could inhibit replication of JCV in a cell culture system in 2009. Although the exact mechanisms by which mefloquine acts against JCV remain unclear, Phase I and II clinical trial has been in progress since September 2008 (ClinicalTrials.gov number, NCT00746941). Under the situation described above, we recently experienced a 33-year-old man who developed PML with HIV infection. The patient exhibited rapid decline in neurological status after initiation of ART, which was attributed to the PML-immune reconstitution inflammatory syndrome (PML-IRIS). We decided to add mefloquine after the permission from Institutional Review Board (IRB) (accession number: 21-32). Following the administration of mefloquine in combination with ART, the patient's neurological status improved substantially. This case suggests that the use of mefloquine might be effective in controlling PML in an HIV-infected patient.

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IMSUT Hospital

Department of Pediatric Hematology-Oncology
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Our major goal is to cure children suffering from a variety of life-threatening hematological disorders. Attempting to achieve it, we continue the commitment to treatment and follow-up care of such children, and to clinical and laboratory research 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 sundrome (MDS).

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

Yasuhiro Ebihara, Shohei Yamamoto, Shinji Mochizuki[1], Kohichiro Tsuji: [1]Division of Stem Cell Processing, Center for Stem Cell Biology and Regenerative Medicine

Although a standard regimen in hematopoetic stem cell transplatation (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-registant genes. Now we plan to extend our experience in nationwide collaborative studies.

2. Cooperative clinical trial for pediatric myelodysplastic syndrome

Kohichiro Tsuji, Yasuhiro Ebihara, Shohei Yamamoto, Shinji Mochizuki[1], Atsushi Manabe[2], Yuji Zaike[3]: [2]St. Luke's International Hospital, [3]Department of Laboratory Medicine, Research Hospital

Pediatric MDS is a rare disease, and only 50-100 children under the age of 16 suffer from the disease annually. The diagnosis and treatment have not been standardized and it should be determined in a nationwide manner. On behalf of the MDS committee of the Japanese Society of Pediatric Hematology, we began the pathologic central review in 1999 and reviewed all samples of patients suspected of hav-

ing MDS. At present, over 300 patients have been enrolled, and standard diagnostic criteria have been proposed for juvenile myelomonocytic leukemia (JMML), a subset of MDS. We also tested *in vitro* cell growth for patients with JMML using diagnostic samples. The results showed that spontaneous growth and hypersensitivity to granulocyte-macrophage colony-stimulating factor (GM-CSF) were observed in most children with JMML. We proposed a cooperative trial to establish the treatment for MDS (MDS99) and have enrolled over 100 patients from the whole country.

3. Novel approach to therapy in juvenile myelomonocytic leukemia

Shohei Yamamoto, Yasuhiro Ebihara, Shinji Mochizuki[1], Yoshitoshi Ohtsuka[4], Atsushi Manabe[2], Yuji Zaike[3], Kohichiro Tsuji: [4]Department of Pediatrics, Hyogo College of Medici

JMML is a clonal myeloproliferative/myelodysplastic disorder of early childhood with poor prognosis. 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 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.

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

Yasuhiro Ebihara, Shinji Mochizuki[1], Shohei Yamamoto, Satoshi Takahashi[5], Arinobu Tojo[5], Kohichiro Tsuji: [5]Division of Molecular Therapy, Advanced Clinical Research Center

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

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

Yasuhiro Ebihara, Shinji Mochizuki[1], Shohei Yamamoto, Seiko Kato[6], Toshiro Kawakita[7], Jun Ooi[6], Kazuaki Yokoyama[5], Fumitaka Nagamura[8], Satoshi Takahashi[5], Arinobu Tojo[5], Kohichiro Tsuji: [7]Division of Stem Cell Transplantation, Center for Stem Cell Biology and Regenerative Medicine, [6]Department of Hematology/Oncology, Research Hospital, [8]Department of Clinical Trial Safety Management, Research Hospital

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

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

Yasuhiro Ebihara, Shinji Mochizuki[1], Shohei Yamamoto, Hideyuki Takedani[9], Tokiko Nagamura-Inoue[10], Shigeyuki Wakitani[11], Arinobu Tojo[5], Hiromitsu Nakauchi[12], Kohichiro Tsuji: [9]Department of Joint Surgery, Research Hospital, [10]Department of Cell Processing and Transfusion, Research Hospital, [11]Department of Orthopedic Surgery, Osaka City University Graduate School of Medicine, [12]DivisioDevision of Stem Cell Therapy, Center for Stem Cell Therapy and Regenerative Medicine

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 syndromes, 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

Hirotoshi Tanaka, Noritada Yoshikawa, Noriaki Shimizu, Takako Maruyama, Akiko Souta-Kuribara, Ma Yanxia, Ryo Matsumiya, Osamu Hosono.

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

(i) Development of novel GR regulators

Despite the established role of glucocorticoids (GC) in controlling short-term inflammation, and despite emerging evidence supporting a disease-modifying role in various autoimmune disorders, concern for adverse events associated with GCs often limits their use. Activation of the GR by GC regulates hundreds of genes expression both positively and negatively. It has become quite widely accepted that transrepression accounts for the majority of therapeutic, anti-inflammatory effects of GC, whereas transactivation is responsible for most side effects. This "transrepression hypothesis" has arisen a set of ideas about how to discover novel anti-inflammatory drugs that do not carry the same burden of side effects as GC. We have explored unique GR regulators that have a different mode of action from classical GC. 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 muscles. 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 I_2, 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. Study on CD26 molecule in normal immune response and in patients with immune-mediated diseases

Osamu Hosono, Noritada Yoshikawa, Hiroshi Kawasaki, Ryo Matsumiya, Akiko Souta-Kuribara, Kei Ohnuma, Hirotoshi Tanaka, Chikao Morimoto.

CD26 is a T cell costimulatory molecule as well as an activation antigen with dipeptidyl peptidase IV (DPPIV) enzyme activity in its extracellular region that is preferentially expressed on memory T cells. The soluble form of CD26 (sCD26) is present in serum and recombinant soluble CD26 can enhance peripheral blood T cell proliferation induced by the recall antigen. We demonstrated that CD26 binds Caveolin-1 on antigen presenting cells, and that following CD26-caveolin-1 interaction on recall antigen-loaded monocytes, caveolin-1 is phosphorylated, with linkage to NF-κB activation, followed by upregulation of CD86. In addition, reduced caveolin-1 expression on monocytes inhibits CD26-mediated CD86 upregulation and abrogates CD26 effect on recall antigen-induced T cell proliferation, and immunohistochemical studies revealed an infiltration of CD26+ T cells in the sublining region of rheumatoid synovium and high expression of caveolin-1 in the increased vasculature and synoviocytes of the rheumatoid synovium. Taken together, these results strongly suggest that CD26-caveolin-1 interaction plays a role in the upregulation of CD86 on recall antigen-loaded monocytes and subsequent engagement with CD28 on T cells, leading to antigen-specific T cell activation such as the T-cell-mediated antigen-specific response in rheumatoid arthritis (RA).

(i) Research for CD26-targeting therapy for malignant tumors and immune-mediated diseases.

Currently we are focusing on the translational research of utilization of anti-CD26 monoclonal antibody (mAb) as well as recombinant soluble CD26 for treatment of malignant tumors, immune-mediated disorders and immune deficiency diseases. A

phase I/II, non-randomized, open-label, multi-center, dose-escalation study of YS110 (humanized anti-CD26 mAb which we developed) is being performed in patients with CD26-positive advanced refractory mesothelioma or CD26-positive solid tumors by Dr Eric Angevin as principal investigator (Institut Gustave Roussy, Villejuif, France). Hopefully we will perform phase I/II clinical trial utilizing humanized CD26 mAb for the treatment of the above diseases in Japan.

(ii) Soluble CD26/DPPIV in autoimmune and other immune-mediated disorders

Our previous studies demonstrated that CD26-caveolin-1 interaction plays a role in the upregulation of CD86 on recall antigen-loaded monocytes and subsequent engagement with CD28 on T cells, leading to antigen-specific T cell. CD26 could modulate function of several cytokines and chemokines such as RANTES (CCL5), SDF-1α (CXCL12) and glucagons-like peptide 1(GLIP-1) through its DPPIV enzyme activity. We have shown that the DPPIV enzyme activity of plasma sCD26 was low in HIV-1-infected individuals, and was inversely correlated with HIV-1 RNA, and that the in vitro addition of recombinant sCD26 could enhance purified protein derivative-induced lymphocyte proliferation. These DPPIV enzyme activity of sCD26 might contribute to the immunopathogenesis of HIV infection. Furthermore, we have shown that serum levels of sCD26 and its specific DPPIV activity were significantly decreased in SLE and were inversely correlated with SLE disease activity index score, but not with clinical variables or clinical subsets of SLE. Serum levels of sCD26 may be involved in the pathophysiology of SLE, and appear to be useful as a new disease activity measure for SLE. We had examined sCD26 and its specific DPPIV activity in serum of patients with inflammatory bowel diseases (IBD), such as Crohn's disease or ulcerative colitis in collaboration with Gastrointestinal Unit, School of Medicine, Keio University, and also in sera and synovial fluid from patients with RA. The DPPIV activity was reduced in patients with IBD and was significantly lower in patients with Crohn's disease compared to with ulcerative colitis ($P<0.05$). We found significant decrease of serum sCD26 and its specific DPPIV activity. These findings indicate that CD26 may be potentially important for the pathophysiology of IBD and RA. Furthermore, we have investigated autoantibodies against CD26 in serum using ELISA and Western blotting methods. We have not found anti-CD26 autoantibody which could reduce DPPIV activity so far. We plan to examine the effect of TNF-α blocking therapy (infliximab, etanercept, adalimumab, golimumab), IL-6 blocking therapy (tocilizumab) and costimulatory signal blocking therapy (abatacept) on serum levels of sCD26/DPPIV in patients with RA and its clinical significance.

(iii) Effect of humanized anti-CD26 mAb on measurement of soluble CD26/DPPIV

In our ELISA for measuring soluble CD26/DPPIV we used two different mouse anti-CD26 mAbs (5F8, 1F7) which could not interfere each other. Administration of our newly developed humanized anti-CD26 mAb (YS110) could form immune complex with sCD26, which might block binding of the detecting antibody (1F7) to serum sCD26. We confirm the interference of humanized anti-CD26 mAb with anti-CD26 mAb (1F7) for detecting sCD26 in our ELISA. Therefore, instead of 1F7 we selected another anti-CD26 mAb (9C11) which recognize the epitope different from humanized anti-CD26 mAb (YS110) and 5F8. In clinical trial utilizing humanized CD26 mAb (YSCMA-EU-0001) we could measure serum sCD26/DPPIV without interference of administered anti-CD26 humanized mAb (YS110).

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

Hirotoshi Tanaka[1], Noritada Yoshikawa[1], Ryo Matsumiya[1], Osamu Hosono[1], Shigeru Kiryu[2], Fumitaka Nagamura[3]: [1]Department of Rheumatology and Allergy, [2]Department of Radiology, [3]Department of Clinical Trial Safety Management.

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.

IV. Medical Genome Science Program and Global COE Program "Center of Education and Research for the Advanced Genome-Based Medicine"

Satoshi Iwata, Noritada Yoshikawa, Hiroshi Kawasaki, Osamu Hosono, and Hirotoshi Tanaka.

We participate in Medical Genome Science Program/Global COE Program. These programs include "Introduction of Medicine and Medical Ethics" and "Experience and Practice of Medicine", especially arranged for non-M.D. postgraduates. The former is a series of lectures outlining of medicine (history of medicine, internal medicine, surgery, nursing, nutrition, pharmacology, translational research, clinical psychology, and medical ethics), and the latter is a weekly round of IMSUT hospital. The attendants visit Department of Radiology, Laboratory Medicine, Blood Transfusion, Surgical Center, Nursing, Core Facility of Therapeutic vectors, Bio-Bank Japan, and participate in ward round in 1) Department of Hematology/Oncology, 2) Infectious Diseases and Applied Immunology, Rheumatology and Allergy, and Advanced Medical Science. These programs are indebted to educational hospitality of many persons working in IMSUT hospital.

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Professor	Yoshinori Murakami, M.D., Ph.D.	教	授	医学博士	村 上 善 則(併任)
Associate Professor	Tsuneo Ikenoue, M.D., Ph.D.	准教授		医学博士	池 上 恒 雄(併任)

Our department was established for the application of human genome information in clinics. For this purpose, we are carrying out three projects, 1) implementation of genetic analyses for hereditary diseases and human neoplasms, 2) development of new diagnostic approaches, and 3) genetic counsling providing appropriate medical information and psychological support for clients who may be associated with a hereditary disease.

1. Genetic analyses for hereditary diseases and human neoplasms

As a part of clinical service, we perform genetic analyses of human neoplasms such as leukemia and colorectal cancer. In 2012, 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. Genetic tests were additionally performed for clients who were suspicious of hereditary diseases.

2. Cancer genome analysis using next generation sequencer

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

We have started two projects using next generation sequencer (NGS); 1) the determination of germline mutations in patients suspicious of hereditary colorectal cancer, and 2) whole genome analysis of hematopoietic malignancies and colorectal tumors. For these two projects, we have established a highly secure system in collaboration with Human Genome Center. In this system, CPUs and storage in the supercomputer are theoretically separated, and desk-top computers accessible to the system were prepared in a secured room. Analytical pipelines are under construction. These projects are aimed to return the data of personal genome and/or cancer genome to the patients in IMSUT Hospital, and apply them to their diagnosis and treatment in near future.

3. Genetic counseling and related activities.

Yoshinori Murakami, Yoichi Furukawa, Reiko Sada, Momoyo Ohki[1], Kohichiro Tsuji[2], Koichiro Yuji[3], Noriko Fujiwara[4], Masae Ono[5], Shiro Ikegawa[6], Toshihiro Tanaka[6], Mayumi Tamari[6], Masahiko Suzuki[7], and Yusuke Nakamura[8]: [1]Bunkyo University, [2]Department of Pediatric Hematology-Oncology, [3]Department of Hematology-Oncology, [4]Department of Nursing, [5]Department of Pediatrics, Tokyo Teishin Hospital, [6]Center for

Genomic Medicine, RIKEN, [7]Department of Neurology, Jikei Medical University, [8]Laboratory of Molecular Medicine, Human Genome Center

In IMSUT Hospital, we provide genetic counseling and genetic tests to clients who are anxious about hereditary diseases. In 2012, we had a total of 28 cases including familial breast cancer, Lynch syndrome, familial polyposis of the colon, spinocerebellar ataxia, myotonic dystrophy, and Stickler dysplasia. In the counseling, we provided appropriate information of diseases and took psychological care of the clients in collaboration with a clinical psychologist. Genetic testing was performed in three cases with informed consent after thoughtful discussion about its merit and demerit.

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1. Yamamoto, S., Ebihara, Y., Mochizuki, S., Kawakita, T., Kato, S., Ooi, J., Tojo, A., Yusa, N., Furukawa, Y., Oyaizu, N., Watanabe, J., Sato, K., Kimura, F., and Tsuji, K. Quantitative PCR detection of CEP110-FGFR1 fusion gene in a patient with 8p11 syndrome. Leukemia & Lymphoma, in press.
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IMSUT Hospital

Department of Palliative Medicine
緩和医療科

Professor (Project)	Kohzoh Imai, M.D. D.M.Sc.	特任教授　医学博士	今　井　浩　三
Associate Professor	Mieko Chinzei, M.D., D.M.Sc.	准教授　医学博士	鎮　西　美栄子
Assistant Professor (Project)	Satoshi Iwase, M.D., D.M.Sc.	特任講師　医学博士	岩　瀬　　哲
Lecturer (Project)	Naoki Shimada, M.D., D.M.Sc.	特任助教　医師・農学博士	島　田　直　樹
Nurse Manager	Reiko Yamahana, R.N., C.N.S., M.Sc.	看護師長・専門看護師	山　花　令　子
Nurse Assistant Manager	Noriko Fujiwara, R.N., C.N.S., M.Sc.	看護副師長・専門看護師	藤　原　紀　子
Pharmacist	Aya Watanabe	薬剤師	渡　邊　　文
Part-time Assistant Professor	Kazutaka Ikeda, Ph.D.	非常勤講師	池　田　和　隆
Part-time Assistant Professor	Miwako Hosoda, Ph.D.	非常勤講師	細　田　満和子

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 cancer and other severe diseases, based on genomic analysis of the DNAs from the materials of each patient.

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IMSUT Hospital

Department of Radiology
放射線科

Associate Professor	Shigeru Kiryu, M.D., D.M.Sc.		准教授	医学博士	桐 生 茂
Senior Assistant Professor	Haruyasu Yamada, M.D., D.M.Sc.		講 師	医学博士	山 田 晴 耕
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.

Evaluation of liposomal contrast agent gadolisome for mouse MR imaging: comparison with gadofluorine M

Shigeru Kiryu, Yusuke Inoue[1], Kouhei Shimomura[2], Kohki Yoshikawa[2], and Kuni Ohtomo[3]: [1]Department of Diagnostic Radiology, Kitasato University School of Medicine, [2]Department of Radiotechnical Sciences, Faculty of Radiological Health Sciences, Komazawa University, [3]Department of Radiology, Graduate School of Medicine, University of Tokyo.

Liposomal contrast media, gadolisome, is equipped with gadolinium-labeled dendrons in the surface and acts as a positive MR contrast agent. Due to its large particle size, gadolisome also serve as a blood-pool agent. We investigated the kinetics of gadolisome in mice in comparison with a lipophilic micellar contrast agent, gadofluorine M, which enhanced the blood vessels for a long time. Mice were imaged under isoflurane anesthesia using a T1-weighted, three-dimensional fast low-angle shot sequence after intravenous injection of gadolisome or gadofluorine M, and the time course of the contrast effect of vessels and organs was examined. The visualization of vessels on maximum intensity projection (MIP) images was also assessed. A marked enhancement in the blood vessels was observed soon after injection of gadolisome, and decreased gradually. The spleen was also enhanced evidently after injection of gadolisome. The enhancement peaked 1 h after injection of gadolisome and decreased gradually. A slight enhancement was observed in the liver and kidneys. The liver enhancement was relatively constant over 6 h, and decreased slowly but was still evident at 3 weeks. The enhancement of kidneys was almost disappeared at 24 h. In comparison with gadolisome, contrast enhancement in the liver, kidney, and spleen was generally higher for gadofluorine M. The enhancement in the intestinal wall, and axially and inguinal lymph nodes was evident only after gadofluorine M injection. The degree and time course of blood enhancement after injection of gadofluorine M were similar to those after injection of gadolisome. On MIP images, the blood vessels were visualized soon after injection of gadolisome or gadofluorine M. The visualization of blood vessels on MIP images was evident still 6 h after injection

of gadolisome, however it became obscure after 1 h after injection of gadofluorine M with the increasing the enhancement of the background organs. The enhancement of the organs was generally lower after injection of gadolisome in comparison with gadofluorine M. The enhancement of blood vessels was evident both with gadolisome and gadofluorine M, however the visualization of blood vessels on MIP images was prolonged longer after injection of gadolisome, due to lower enhancement of the background organs.

Delayed hepatic signal recovery on ferucarbotran-enhanced magnetic resonance images: an experimental study in rat livers with gadolinium chloride-induced Kupffer cell damage.

Toshihiro Furuta, Masayuki Yamaguchi[4], Ryutaro Nakagami[4], Masaaki Akahane[3], Manabu Minami[5], Kuni Ohtomo[3], Noriyuki Moriyama[6], and Hirofumi Fujii[4]: [4]Division of Functional Imaging, Research Center for Innovative Oncology, National Cancer Center Hospital East, [5]Department of Radiology, Faculty of Medicine, University of Tsukuba, [6]Research Center for Cancer Prevention and Screening, National Cancer Center.

We investigated hepatic signal recovery in rats with gadolinium chloride-induced Kupffer cell (KC) damage. Hepatic signal recovery, rather than reduction, in ferucarbotran-enhanced magnetic resonance imaging (MRI) is a potential diagnostic marker of liver damage. Twelve rats received 8 μmol iron/kg of ferucarbotran 1 day after 0-7.5 mg/kg gadolinium chloride injection (experiment A). Another 12 rats received ferucarbotran followed by gadolinium chloride injection 6 h later (experiment B). In each experiment, three rats without gadolinium chloride ("no injury group") served as control. Another six rats received gadolinium chloride alone without ferucarbotran. Hepatic signals were assessed on T2*-weighted images for up to 29 days. Iron deposits were histologically examined on day 29. As a result, hepatic signal recovery was delayed in a gadolinium chloride dose-dependent manner in experiment A. Gadolinium chloride alone reduced hepatic signal 15 % during this experiment. Hepatic signal recovery was delayed only in rats that received 7.5 mg/kg gadolinium chloride in experiment B. Hepatic signals negatively correlated with iron deposits in KCs and hepatocytes. In conclusion, hepatic signal recovery on ferucarbotran-enhanced MRI was delayed in the context of gadolinium chloride-induced KC damage due to increased hepatic iron deposits. Hepatic signal recovery may be used as a clinical marker of KC damage in liver disorders, including radiation-induced hepatitis.

Quantitative MR image study in neuropsychiatric disorders: tract-specific and voxel-based analyses of diffusion tensor data sets.

Haruyasu Yamada[1], Osamu Abe[7], Hidenori Yamasue[8], and Kiyoto Kasai[8]: [7]Department of Radiology, School of Medicine, Nihon University, [8]Department of Psychiatry, Graduate School of Medicine, University of Tokyo.

Several studies have suggested that white matter integrity is disrupted in some brain regions in patients with neuropsychiatric disorders. Magnetic resonance (MR) diffusion tensor imaging (DTI) has been reported to be useful in evaluation of the normal appearing brain. DTI is a unique and relatively new technique to visualize and evaluate the cerebral white matter. The orientation of white matter tracts can be analyzed and tracked by the methods named as diffusion tensor tractography (DTT) or fiber tracking. Quantitative diffusion indices such as apparent diffusion coefficient (ADC) and fractional anisotropy (FA) have been used for evaluation of the normal appearing white matter in various diseases. Disruptions in connectivity may explain some of the symptoms in neuropsychiatric disorders such as schizophrenia. The purpose of our study is to investigate diffusion anisotropy in neuropsychiatric patients' brain by voxel-based analysis of DTI and voxel-based morphometry (VBM), using statistical parametric mapping (SPM), tract-based spatial statistics (TBSS), FreeSurfer, and other tools. Voxel-based analysis of the diffusion tensor data set allows a voxel-wise comparison encompassing the whole brain without operational bias or hypothesis. Our study suggests that the voxel-based diffusion tensor analysis may be robust enough to perceive changes in diffusion anisotropy in patients, and that changes in FA and ADC may be related to symptom or illness duration.

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桐生茂，大友邦．病期診断のための画像診断　臨床放射線腫瘍学（日本放射線腫瘍学会，日本放射線腫瘍学研究機構　編集）南江堂，東京, 17–21, 2012

IMSUT Hospital

Department of Surgery (Gastrointestinal and Breast Surgery)

外科(主として，大腸・胃・食道・乳腺領域)

Associate Professor	Masaru Shinozaki, M.D., Ph.D.		准教授	医学博士	篠崎　大
Lecturer	Giichiro Tsurita, M.D., Ph.D.		病院講師	医学博士	釣田義一郎
Assistant Professor	Keisuke Hata, M.D., Ph.D.		助　教	医学博士	畑　啓介
Assistant Professor	Kentaro Yazawa, M.D., Ph.D.		助　教	医学博士	谷澤健太郎

The mission of our department is to provide surgical service of malignancy and 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 are ready to start under cautious preparation.

1. Summary of surgical treatment in 2011

Masaru Shinozaki, Giichiro Tsurita, Kentaro Yazawa, Keisuke Hata, Yasuhiro Mizuno, Yuzo Nagai

It is notable that in 2012, the members in our Department decreased in number: In March, Dr. Hata went to the United States for research. In April, Dr. Mizuno opened his private office. Dr. Nagai was sent from the University of Tokyo Hospital and worked at our Department in April and May. He dedicated himself to the implementation of the Department in genuine way. However, after his return, only two doctors (M.S. and G.T) worked without substantial decrease, compared with that in the previous year, of in-patient and out-patient care in quality and quantity with great support of nurses, pharmacists, doctors of other departments, clerks, and other colleagues.

We performed various surgical operations. Malignancy is the top indication for operation, followed by benign diseases, such as inflammatory bowel disease (IBD) and hernia. Among the patients with malignancy, colorectum is by far the leading organ in number.

Dr. Sameshima and Dr. Kawamura are willing to help us when laparoscopic colorectal surgery is undergone. Recently, breast cancer has become a particular field only for highly specialized physicians bearing knowledge in the particular field. Dr. Sanuki, Dr. Tsuji and Dr. Fukatsu continued the out-patient clinic and assisted our breast cancer operations.

2. Summary of endoscopic examination in 2011

Giichiro Tsurita, Kentaro Yazawa, Masaru Shinozaki, Keisuke Hata, Yuzo Nagai, Yasuhiro Mizuno

Under cooperation with Department of Advanced Medical Science, we performed 705 (8% increase compared with the number last year) upper gastrointestinal endoscopies and 715 (16% 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 treatment and avoid operation as much as possible. Our two fellows (Y.N. and Y.M.) 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

Keisuke Hata, Masaru Shinozaki, Giichiro Tsurita

Recently, micro RNA (miRNA) had been known to play a crucial role in post-transcriptional regulation. In inflammatory bowel disease (IBD), its etiology has not been revealed yet. However, interaction between mucosa and intraluminal bacteria and immunological response are speculated to be included at least in the pathophysiology. There may be a possibility that abnormality in miRNA is involved. Furthermore, the patients with IBD are subject to suffer from colorectal cancer due to chronic inflammation. We investigate the possible relation between miRNA and carcinogenesis.

B. The problems including occurrence of cancer after eradication of H. pylori

Keisuke Hata, Hideki Ono, Masaru Shinozaki, Giichiro Tsurita

Recently, H. pylori is attributed to the main cause of gastric cancer. However, gastric cancer emerges even after eradication of H. pylori. We followed the patients after eradication and found cancer. We have sought the clinicopatological and molecular biological factors.

C. Whole genome sequencing of inflammatory bowel disease

Masaru Shinozaki, Yoichi Furukawa, Keisuke Hata, Giichiro Tsurita

The progress in nucleic acid sequencing 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.

D. Whole genome sequencing of colorectal cancer

Keisuke Hata, Yoichi Furukawa, Masaru Shinozaki, Giichiro Tsurita

We perform whole genome sequencing for colorectal cancer under various conditions.

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

Masaru Shinozaki, Keisuke Hata, Giichiro Tsurita

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 done like ulcerative colitis. However, in Japan, significant proportion of such cancer is located at perianal region, and the similar methodology does not seem sufficient for early detection. 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.

F. Cohort study for individualized postoperative adjuvant chemotherapy using pyrimidine analog in stage III colon cancer.

Giichiro Tsurita, Masaru Shinozaki, Keisuke Hata

Pyrimidine analog is the basic drug of colorectal cancer. However, the relationship between enzymatic profile of CRC concerning the metabolism of pyrimidine analog and the effect on the survival has not been revealed yet. Therefore, we conducted a prospective study where the activity of representative enzymes of pyrimidine analog, e.g. thymidylate sythetase, is measured in the postoperative patients who receive adjuvant chemotherapy.

4. Clinical research under development

We have been seeking for new projects in partnership with basic research departments in the Institute and outside.

5. Clinical trials under development

In 2010, Antibody and Vaccine Center has been developed at the Institute. We are planning to administer cancer related peptides under various situations to draw maximal effects. Moreover, noble therapy for ovarian cancer has been under consideration.

Publications

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2. 篠崎　大，畑　啓介，釣田義一郎．炎症性腸疾患に合併した小腸・大腸癌の特徴と外科治療．日本臨牀　70（増1）528–534，2012.

IMSUT Hospital

Department of Joint Surgery
関節外科

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

講 師 医学博士 竹 谷 英 之

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

Hideyuki Takedani

From 2006 to 2012, there are 133 surgical treatments for hemophilia (71 for hemophilia A, 16 for hemophilia B, 1 for deficiency factor VII patient, and 1 for Von Willebrand disease). 16 of them have the deficiency factor antibody.

In 2012, we were performed 19 surgical treatments (18 for hemophilia A, 1 for hemophilia B). Two of them have the deficiency factor antibody. 15 were performed total joint arthroplasties, one was arthroscopic synovectomy and three were other surgical treatments.

Publications

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2) Shimada K, Takedani H, Inoue K, Yamasaki K. Arthroscopic synovectomy of the elbow covered with rFVIIa in a haemophilia B juvenile with inhibitor. *Haemophilia* 2012; 18: e414-6.
3) 血友病性関節症の整形外科治療 竹谷英之 みんなに役立つ血友病の基礎と臨床 第２版 Page 202-210 試薬ジャーナル 大阪
4) 診療科を超えた連携と協力 整形外科の診断と管理 竹谷英之 血友病診察実践マニュアル Page 65-68 診断と治療社 東京
5) 【日常診療に必要な小児整形外科の知識―先天疾患から外傷まで―】下肢の疾患 血友病性関節症 竹谷英之 整形・災害外科55巻５号 Page 657-666

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. A preparation is underway to start clinical trials of G47Δ at IMSUT Hospital.

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 within the first year. 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. A clinical study to examine the efficacy of bevacizumab for recurrent malignant glioma or radiation-induced brain injury is ongoing.

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	医学士	柴　田　玲　子
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 (THA) in hemophilia patients.

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

2. Management of chronic intractable pain.

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

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

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

4. Risk management of medical electronic devices.

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

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

Publications

大島紀人，阿部祐太，浅沼充志，多田真由子，鎮西美栄子，石丸正吾。精神病院入院患者の転帰と退院後の生活環境による再入院・治療中断の頻度：第66回国立病院総合医学会　講演抄録集，p. 923，2012

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	医学博士　長　村　文　孝
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, Hisako Suyama, Makiko Tajima

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 go 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. Assistance and promotion of Clinical Trials/ TRs of Research Hospital

Noriko Fujiwara, Makiko Tajima, Fumitaka Nagamura.

To conduct clinical trials, especially for TRs, the support of the Clinical Research Coordinator (TRC in case of TRs), provision of regulatory information, assistance of design making and writing of protocol, consent form and the related documents are indispensable. One of the roles is to keep the quality of protocols on each clinical trial. To perform this task, we discuss and advise on a protocol with principal investigators, and made it a rule to submit a protocol and written consent form before submitting to the Institutional Review Board in case of TR. We have emphasized the importance of TRC, because TRC is the key to collect information on participants' feelings such as anger or disappoint-

ment when effects were not sufficient and status on their insufficient understandings on study protocols which we must supplement.

3. Stressor Scale for Clinical Research Coordinators: development and psychometric testing.

Matsumoto K, Sumino K, Fukahori H, Kamibeppu K, NagamuraF

Job stress is viewed as a situation where working conditions interact with individual worker characteristics and result in disruption of psychological or physiological homeostasis. Clinical research coordinators, also known as research nurses, are professionals who play a central role in clinical trials. They face various problems associated with their responsibilities; however, few studies have reported on their stress. To manage their stress, it is necessary to identify the sources of stress (i.e. stressors). The 56-item preliminary instrument was developed based on literature review and expert discussions. A total of 589 clinical research coordinators in 186 hospitals in Japan were surveyed in 2011. Statistical analyses on construct and concurrent validity, internal consistency, and test-retest reliability were performed. A six-factor solution with 23 items was selected using exploratory factor analysis: 'quantitative workload', 'conflict with investigators', 'ambiguity of work', 'conflict with other clinical research coordinators and with supervisors', 'demands from an affiliate other than the hospital', and 'difficulty in caring for trial participants'. Confirmatory factor analysis affirmed construct validity, with a demonstrated acceptable fit between the factor structure and the observed data. All factors had significant correlations with burnout and psychological distress, which indicated acceptable concurrent validity. Cronbach's alpha coefficients ranged from 0.73-0.82. Intra-class correlation coefficients indicated almost satisfactory test- retest reliability. Our new instrument has acceptable validity and reliability for evaluating job stressors for clinical research coordinators.

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

Noriko Fujiwara, Makiko Tajima, 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.

Publications

Mae H, Ooi J, Takahashi S, Kato S, Kawakita T, Ebihara Y, K Tsuji, Nagamura F, Echizen H, Tojo A. Acute kidney injury after myeloablative cord blood transplantation in adults: the efficacy of strict monitoring of vancomycin serum trough concentrations. Transpl Infect Dis 0: 1-6, 2012

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長村文孝　FDAにおける治験・承認審査の要点と傾向　稀少疾患/難病の診断・治療と製品開発　技術情報協会　255–260，2012

長村文孝　国内外のがんワクチンの開発動向と臨床からの期待　ワクチンの市場動向と開発・製造実務集　技術情報協会　673–689，2012

長村文孝　国内副作用情報報告からFDAへの英文副作用報告書を作成する　世界の薬事規制対応・承認申請　成功のコツ　技術情報協会　印刷中

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	Haruyasu Yamada, 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 cooperation beyond the framework of the hospital in recent years, and we are also planning support for the operation of the hospital.

1. 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.

2. 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.

3. 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.

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.
Lecturer Tokiko Nagamura-Inoue, M.D., D.M.Sc.

教 授 医学博士 東 條 有 伸
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. We have cooperated the cord blood (CB)-related projects with Tokyo Cord Blood Bank, whose cell processing has been established the first in IMSUT-Cell Resource Center (IMSUT-CRC), in 1997. Since 2008, we have started the research CB stem cell bank supported by MEXT. In research, we have developed the expansion system of regulatory T cell from CB and adult blood, and have studied the umbilical cord-derived mesenchymal stem cells for clinical use. In addition, we support the translational researches performed in IMSUT-CRC.

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 CD 25^{+}FOXP3^{+}regulatory T cells 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 (IMSUT-Cell Resource Center):

Nagamura-Inoue T, Yuzawa M, Yamamoto Y, Ogami K, 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 CB units that are non-conforming for clinical use, in processed and frozen or in fresh to world-wide researchers for research use via RIKEN Bioresource Center.

Visit our home page http://www.nbrp.jp/.

3. Exploring mesenchymal stem cells derived from Umbilical Cord:

Nagamura-Inoue T, Yuzawa M, Yamamoto Y, Tojo A.

Umbilical cord (UC) is a rich source of mesenchymal stem cells (MSCs). The UC is normally discarded after birth and its collection does not require an invasive procedure with ethical concerns. Moreover, UC-derived MSC (UC-MSC) possess many advantageous features, namely 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, for regenerative medicine and immunotherapy. Our final goal is to establish the 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, outcome data should be qualified. We support the collection of CBT data and the cleaning of the data for researchers in Japan.

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

Nagamura-Inoue T, Yamamoto Y, Yuzawa 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) Cord blood cell processing for banking (for Tokyo Cord Blood Bank and Research cord blood stem cell bank), 2) Dendritic cell therapies, 3) Regenerative therapy of alveolar bone derived from bone marrow mesenchymal cells, 4) Gene therapy for renal cancer.

Publications

Kurosawa S, Yakushijin K, Yamaguchi T, Atsuta Y, Nagamura-Inoue T, Akiyama H, Taniguchi S, Miyamura K, Takahashi S, Eto T, Ogawa H, Kurokawa M, Tanaka J, Kawa K, Kato K, Suzuki R, Morishima Y, Sakamaki H, Fukuda T. Changes in incidence and causes of non-relapse mortality after allogeneic hematopoietic cell transplantation in patients with acute leukemia/myelodysplastic syndrome: an analysis of the Japan Transplant Outcome Registry. Bone Marrow Transplant. In press 2012 Sep 10

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Kanda J, Ichinohe T, Kato S, Uchida N, Terakura S, Fukuda T, Hidaka M, Ueda Y, Kondo T, Taniguchi S, Takahashi S, Nagamura-Inoue T, Tanaka J, Atsuta Y, Miyamura K, Kanda Y. Unrelated cord blood transplantation vs related transplantation with HLA 1-antigen mismatch in the graft-versus-host direction. Leukemia. 27(2): 286-94, 2013

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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 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 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 on the facility and the equipments in CFTV has been performed to ensure cGMP compliance.

Production of clinical grade oncolytic HSV-1

A clinical lot of oncolytic herpes simplex virus type 1 (HSV-1) was manufactured in the vector production unit 2 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, MD, Ph.D.　病院講師　医学博士　磯　尾　直　之

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 correct 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, micoplasma, and endotoxin contaminations by using molecular and biochemical techniques.

2. Development of comprehensive diagnosis system for infections 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.

In this year, we started, by collaborations with

Tokyo Medical and Dental University, to extend this strategy and by applying multiplex PCR to detect all clinically significant infectious pathogens, which will be functioning "comprehensive infectious disease monitoring facilities".

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. Pathological evaluation of cancer immunotherapy

We have initiated the analysis of surgical specimen obtained from the patients under cancer immuno-therapy conducted in the research hospital. By applying sophisticated immunohistochemical techniques, we now are intensively analyzing materials from cases including GM-CSF-based gene therapy for renal cell carcinoma and dendritic cell-based or peptide-pulsed anti-melanoma immunotherapy. One of our goals is to evaluate the effectiveness of the therapies and to elucidate the mechanisms of anti-tumor immune response elicited by the therapy *in situ*.

5. Detection of target molecules expression in cancer tissues

Advances in understanding the molecular pathophysiology of cancer led to the development of molecular targeted drugs such as Herceptin, a monoclonal antibody that bind to her2 (human epidermal growth factor receptor 2). Thus it is crucial to detect the target molecule expression in the target cancer tissue and we are able to detect these molecules by immune-histochemical technique on tissue sections. We are routinely analyzing various chimeric molecules of hematopoietic neoplasm, such as bcr-abl gene expression in specimen from patients with CML and Ph1 + ve ALL by real-time PCR and nested RT-PCR techniques. In addition, we sequenced the amplified products to provide information for the molecular resistance to STI571 treatment. We are also examining the target molecules to non-hematological disorder, which includes c-kit, PDGF-R genes that is associated with gastro-intestinal stromal cell tumor (GIST).

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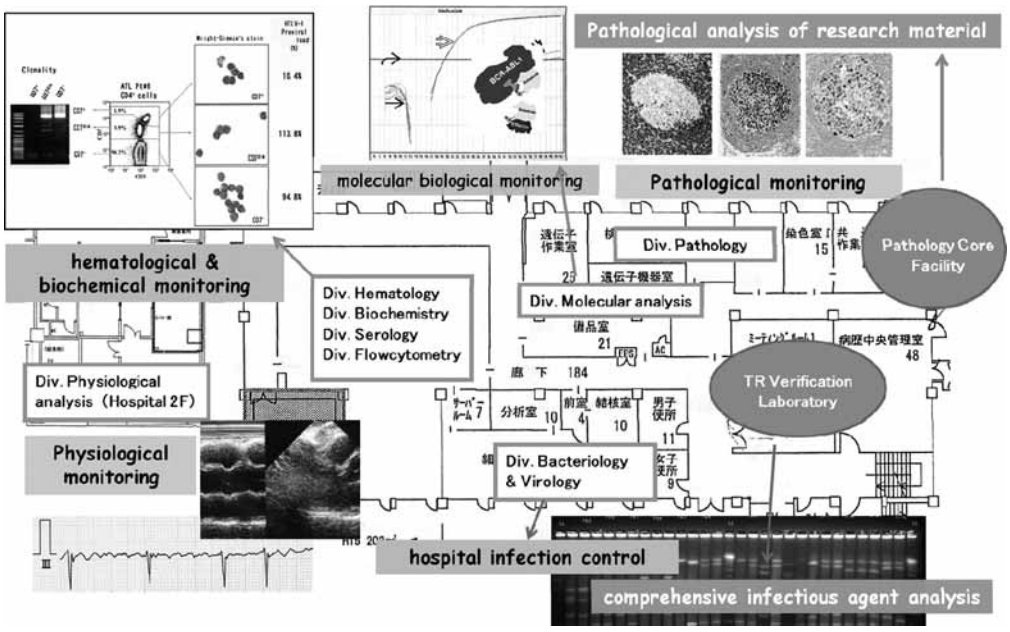

Department. Laboratory Medicine
functions as an integrated diagnosis and monitoring laboratory

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 (12 pharmacists) provides a drug distribution service, complete IV admixture hyperalimentation and chemotherapy preparation 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
	Hisako Suyama, RN.	看護師長		須 山 寿 子
	Keiko Kawasaki, RN.	看護師長		川 崎 敬 子
	Hatsuko Narita, RN.	看護師長		成 田 初 子
	Minayo Hisahara, RN, CNJRF.	看護師長	リウマチケア看護師	久 原 みな代
	Reiko Yamahana, RN, CNS, MHSc.	看護師長	がん看護専門看護師	山 花 令 子
	Tomoko Sato, RN.	看護師長		佐 藤 朋 子
	Satomi Torisu, RN.	看護師長		鳥 巣 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. Since the Career Ladder System for nurses was introduced in 2011, it keeps nurses motivated to continue learning and fulfill their career development as a nurse.

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. Nursing skills based on good knowledge and evidence is also very important in patient care. The online training tool "Nursing Skills Japan" was also launched in 2011 to enhance nurses' learning and to brush up their skills.

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

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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 侯 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 and an international collaborative project is proceeding toward a clinical trial of an AIDS vaccine using this system.

1. Impact of vaccination on CTL immunodominance and cooperation against SIV replication in rhesus macaques

Hiroshi Ishii, Miki Kawada, Tetsuo Tsukamoto, Hiroyuki Yamamoto[1], Saori Matsuoka[1], Teiichiro Shiino[1], Akiko Takeda[1], Makoto Inoue[2], Akihiro Iida[2], Hiroto Hara[2], Tsugumine Shu[2], Mamoru Hasegawa[2], Taeko K. Naruse[3], Akinori Kimura[3], Masafumi Takiguchi[4], and Tetsuro Matano: [1]AIDS Research Center, National Institute of Infectious Diseases, [2]DNAVEC Corporation, [3]Medical Research Institute, Tokyo Medical and Dental University, [4]Center for AIDS Research, Kumamoto University

Cytotoxic T lymphocyte (CTL) responses play a central role in viral suppression in human immunodeficiency virus (HIV) infections. Prophylactic vaccination resulting in effective CTL responses post-viral exposure would contribute to HIV control. It is important to know how CTL memory induction by vaccination affects post-exposure CTL responses. We previously showed vaccine based control of a simian immunodeficiency virus (SIV) challenge in a group of Burmese rhesus macaques sharing major histocompatibility complex class I (MHC-I) haplotype 90-120-Ia (A). $Gag_{206-216}$ and $Gag_{241-249}$ epitope specific CTL responses were responsible for viral control. In this study, we showed the impact of individual epitope specific CTL induction by prophylactic vaccination on post-exposure CTL responses. In the acute phase after SIV challenge, dominant $Gag_{206-216}$ specific CTL responses with delayed, naive-derived $Gag_{241-249}$ specific CTL induction were observed in $Gag_{206-216}$ epitope vaccinated animals with prophylactic induction of single $Gag_{206-216}$ epitope specific CTL memory, and vice versa in $Gag_{241-249}$ epitope vaccinated animals with single $Gag_{241-249}$ epitope specific CTL induction. $Gag_{206-216}$ epitope vaccinated animals selected for a $Gag_{206-216}$ specific CTL escape mutation by week 5 and showed significantly less decline of plasma viral loads from week 3 to week 5 than that in $Gag_{241-249}$ epitope vaccinated animals without escape mutations. Our results present evidence indicating significant effect of prophylactic vaccination on post-exposure CTL immunodominance and cooperation of vaccine antigen specific and non-vaccine antigen specific CTL responses, which affects viral control. These findings provide great insights into antigen design for CTL-inducing AIDS vaccines.

2. Host cell species specific effect of cyclosporine A on SIV replication

Hiroaki Tekuchi[5], Hiroshi Ishii, Tetsuya Kuwano,

Natsuko Inagaki, Hirofumi Akari[6], and Tetsuro Matano: [5]Department of Molecular Virology, Tokyo Medical and Dental University, [6]Primate Research Institute, The University of Kyoto

An understanding of host cell factors that affect viral replication contributes to elucidation of the mechanism for determination of viral tropism. Cyclophilin A (CypA), a peptidyl-prolyl *cis-trans* isomerase (PPIase), is a host factor essential for efficient replication of HIV-1 in human cells. However, the role of cyclophilins in SIV replication has not been determined. In this study, we examined the effect of cyclosporine A (CsA), a PPIase inhibitor, on SIV replication.

SIV replication in human CEM-SS T cells was not inhibited but rather enhanced by treatment with CsA, which inhibited HIV-1 replication. CsA treatment of target human cells enhanced an early step of SIV replication. CypA overexpression enhanced the early phase of HIV-1 but not SIV replication, while CypA knock-down resulted in suppression of HIV-1 but not SIV replication in CEM-SS cells, partially explaining different sensitivities of HIV-1 and SIV replication to CsA treatment. In contrast, CsA treatment inhibited SIV replication in macaque T cells; CsA treatment of either virus producer or target cells resulted in suppression of SIV replication. SIV infection was enhanced by CypA overexpression in macaque target cells.

CsA treatment enhanced SIV replication in human T cells but abrogated SIV replication in macaque T cells, implying a host cell species specific effect of CsA on SIV replication. Further analyses indicated a positive effect of CypA on SIV infection into macaque but not into human T cells. These results suggest possible contribution of CypA to the determination of SIV tropism.

3. Association of MHC-I haplotypes with disease progression after SIV challenge in Burmese rhesus macaques

Takushi Nomura, Hiroyuki Yamamoto[1], Teiichiro Shiino[1], Naofumi Takahashi, Taku Nakane, Nami Iwamoto, Hiroshi Ishii, Tetsuo Tsukamoto, Miki Kawada, Saori Matsuoka[1], Akiko Takeda[1], Kazutaka Terahara[7], Yasuko Tsunetsugu-Yokota[7], Naoko Iwata-Yoshikawa[8], Hideki Hasegawa[8], Tetsutaro Sata, Taeko K. Naruse[3], Akinori Kimura[3], and Tetsuro Matano: [7]Department of Immunology, National Institute of Infectious Diseases; [8]Department of Pathology; National Institute of Infectious Diseases

Nonhuman primate AIDS models are essential for analysis of AIDS pathogenesis and evaluation of vaccine efficacy. Multiple studies on HIV and SIV infection have indicated association of MHC-I genotypes with rapid or slow AIDS progression. Accumulation of macaque groups that share not only a single MHC-I allele but also a MHC-I haplotype consisting of multiple polymorphic MHC-I loci would largely contribute to progress of AIDS research. In this study, we investigated SIVmac239 infections in four groups of Burmese rhesus macaques sharing individual MHC-I haplotypes, referred to as A, E, B, and J, respectively. Out of twenty macaques consisting of A^+, E^+, B^+, and J^+, eighteen showed persistent viremia. Fifteen of them developed AIDS in 0.5 - 4 years, with the remaining three at 1 or 2 years under observation. A^+ animals including two controllers showed slower disease progression, whereas J^+ animals exhibited rapid progression. E^+ and B^+ animals showed intermediate plasma viral loads and survival periods. Gag specific CTL responses were efficiently induced in A^+ animals, while Nef specific CTL responses were in A^+, E^+, and B^+ animals. Multiple comparisons among these groups revealed significant differences in survival periods, peripheral CD 4^+ T cell decline, and SIV specific $CD4^+$ T cell polyfunctionality in the chronic phase. This study indicates association of MHC-I haplotypes with AIDS progression and presents an AIDS model facilitating analysis of virus-host immune interaction.

4. Immunogenicity of repeated Sendai viral vector vaccination in macaques

Kyoko Kurihara, Yusuke Takahara, Takushi Nomura, Hiroshi Ishii, Nami Iwamoto, Naofumi Takahashi, Makoto Inoue[2], Akihiro Iida[2], Hiroto Hara[2], Tsugumine Shu[2], Mamoru Hasegawa[2], Chikaya Moriya, and Tetsuro Matano

Induction of durable cellular immune responses by vaccination is an important strategy for the control of persistent pathogen infection. Viral vectors are promising vaccine tools for eliciting antigen-specific T cell responses. Repeated vaccination may contribute to durable memory T cell induction, but anti-vector antibodies could be an obstacle to its efficacy. We previously developed a Sendai virus (SeV) vector vaccine and showed the potential of this vector for efficient T cell induction in macaques. In this study, we examined whether repeated SeV vector vaccination with short intervals can enhance antigen specific CTL responses. Four rhesus macaques possessing the MHC-I haplotype A were immunized three times with intervals of three weeks. For the vaccination, we used replication-defective F-deleted SeV vectors inducing CTL responses specific for SIV $Gag_{206-216}$ and $Gag_{241-249}$, which are dominant epitopes restricted by A-derived MHC-I molecules. All four animals showed higher $Gag_{206-216}$ and $Gag_{241-249}$ specific CTL responses after the third vaccination than those after

the first vaccination, indicating enhancement of antigen specific CTL responses by the second/third SeV vector vaccination even with short intervals. These results suggest that repeated SeV vector vaccination can contribute to induction of efficient and durable T cell responses.

5. A novel protective MHC-I haplotype not associated with dominant Gag-specific CTL responses in SIVmac239 infection of Burmese rhesus macaques

Naofumi Takahashi, Takushi Nomura, Yusuke Takahara, Hiroyuki Yamamoto[1], Teiichiro Shiino[1], Akiko Takeda[1], Makoto Inoue[2], Akihiro Iida[2], Hiroto Hara[2], Tsugumine Shu[2], Mamoru Hasegawa[2], Hiromi Sakawaki[9], Tomoyuki Miura[9], Tatsuhiko Igarashi[9], Yoshio Koyanagi[9], Taeko K. Naruse[3], Akinori Kimura[3], and Tetsuro Matano: [9]Institute for Virus Research, Kyoto University

Several MHC-I alleles are associated with lower viral loads and slower disease progression in HIV and SIV infections. Immune-correlates analyses in these MHC-I-related HIV/SIV controllers would lead to elucidation of the mechanism for viral control. Viral control associated with some protective MHC-I alleles is attributed to CTL responses targeting Gag epitopes. We have been trying to know the mechanism of SIV control in multiple groups of Burmese rhesus macaques sharing MHC-I genotypes at the haplotype level. Here, we found a protective MHC-I haplotype, *90-010-Id* (D), which is not associated with dominant Gag specific CTL responses. Viral loads in five D^+ animals became significantly lower than those in our previous cohorts after 6 months. Most D^+ animals showed predominant Nef specific but not Gag specific CTL responses after SIV challenge. Further analyses suggested two Nef epitope specific CTL responses exerting strong suppressive pressure on SIV replication. Another set of five D^+ animals that received a prophylactic vaccine using a Gag-expressing SeV vector showed significantly reduced viral loads compared to unvaccinated D^+ animals at 3 months, suggesting rapid SIV control by Gag specific CTL responses in addition to Nef specific ones. These results present a pattern of SIV control with involvement of non-Gag antigen specific CTL responses.

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).

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IMSUT Hospital

Center for Antibody and Vaccine Therapy
Division of Antibody and Targeting Therapy
Division of Rheumatology

抗体・ワクチンセンター
抗体・分子標的分野
免疫病治療学分野

Professor (Project)	Kohzoh Imai, M.D., D.M.Sc.	特任教授	医学博士	今井浩三
Professor	Hirotoshi Tanaka, M.D., D.M.Sc.	教授	医学博士	田中廣壽
Associate Professor (Project)	Hiroaki Taniguchi, M.D., D.M.Sc.	特任准教授(兼)	医学博士	谷口博昭
Senior Assisitant Professor (Project)	Hiroshi Yasui, M.D., D.M.Sc.	特任講師(兼)	医学博士	安井寛

This center was established in April 1st, 2012, in the memory of Professor Shibasaburo Kitazato, 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 an ordinal 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 the special 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.

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