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 were (1) Adaptive transfer of allogeneic umbilical cord blood -derived cytotoxic lymphocytes, (2) Analysis of the gradient expression of genes in human colonic mucosa, (3) Analysis of the effect of Helicobacter pylori eradication on non-ulcer patients, (4) Effect of H. pylori eradication on the expression of microRNAs in gastric mucosa, (5) Analysis of the role of Dnm3os, a non-coding RNA in skeletal development, (6) Analysis on the mechanisms of cardiac outflow tract development and (7) Analysis of the role of leptin in the pathophysiology of multiple myeloma.

1. Adoptive transfer of allogeneic umbilical cord blood-derived cytotoxic lymphocytes

Fujita S., et al.

We have been making a continuous effort on investigating the possibility of adoptive transfer of allogeneic umbilical cord blood-derived cytotoxic T lymphocytes (CTLs) for the treatment of hematological malignancies and solid tumors. Using cryopreserved or fresh umbilical cord blood as the source of lymphocytes, certain combination of T cell growth factors and antigen-specific stimulation were found to be able to induce massive expansion of CTLs. Further analysis of HLA-restricted tetramers with flow cytometry revealed the functional maturation of ex vivo expanded CTLs. Currently we are in the process of establishing an efficient protocol on antigen-specific CTL induction in light of acquiring an international patent at the University of Tokyo for future clinical use.

2. Analysis of the gradient expression of genes in human colonic mucosa

Ohno H et al.

Ulcerative colitis is characterized by continuous inflammation extending from rectum to oral colonic mucosa. We speculate that the gradient expression of genes in human colonic mucosa might be related to the disease development and progression. We evaluated the expression levels of genes throughout the GI tract and in other tissues by micro array and northern blot analysis. As a result of these analyses, some genes showed the expression gradient to increase toward the distal colon. We are currently investigating the expression changes of these genes in

human intestinal diseases.

3. 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.

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 Dnm3os, a non-coding RNA in skeletal development

Nakaoka T. et al.

Dnm3os, a non-coding RNA, contains three micro RNAs; miR-199a, miR-199a* and miR-214, whose functions remain entirely unknown in mammals. We generated Dnm3os knock-out (KO) mouse in collaboration with Department of Physiological Chemistry and Metabolism, Division of Biochemistry and Molecular Biology, University of Tokyo. Dnm3os KO mice exhibited several skeletal abnormalities, including craniofacial hypoplasia, defects in dorsal neural arches, and osteopenia. Importantly, the expression of miR-199a, miR-199a*, and miR-214 was significantly down-regulated in Dnm3os KO embryos, supporting the assumption that Dnm3os serves as a precursor of these three miRNAs. Now, we are investigating the molecular mechanisms responsible for the skeletal abnormalities observed in Dnm3os KO mice.

6. Analysis on the mechanisms of cardiac outflow tract development

Nakaoka T. et al.

Malformations of the cardiovascular system in the human account for most of the premature deaths caused by congenital abnormalities and, most often, are linked to abnormalities in the formation of the cardiac outflow tract. The heart defect (hdf) mouse is a recessive lethal mutation that arose from a LacZ reporter containing a transgene insertional mutation. The most striking feature of the hdf homozygous embryo is the immature formation of the outflow tract. We are analyzing the second heart field and the neural crest cells, which actively contribute to the formation of the cardiac outflow tract in hdf mouse embryos.

7. Analysis of the role of leptin in the pathophysiology of multiple myeloma

Lam Q.L.K. et al.

Leptin, originally discovered as an endocrine hormone, has recently been identified as an important cytokine in modulating the immune function. Leptin shares high structural similarity to IL-6, while leptin receptor is related to the gp-130 signal-transducing subunit of the IL-6-type cytokine receptors. Our recent report showed that leptin promotes survival of peripheral B cells via the induction of Blc-2 and Cyclin D1 gene expression, and activates STAT3, Akt and NF-kappaB pathways in B cells, supporting a specific role for leptin in B cell physicology (Lam et al., PNAS 107: 13812, 2010). Furthermore, myeloma cells were recently found to express leptin and the leptin receptor, suggesting a possible oncogenic role of leptin in malignant plasma cell development. This evidence altogether pointed us to analyze the potential role of leptin in the survival and activity of myeloma cells, and how it might regulate the bone marrow environment. The anticipated results will facilitate a better understanding on leptin's role in multiple myeloma pathophysiology.

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IMSUT Hospital

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内科（血液腫瘍内科）

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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 350 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.

1. Unrelated cord blood transplantation after myeloablative conditioning in adults with advanced myelodysplastic syndromes.

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

We analyzed the disease-specific outcomes of adult patients with advanced myelodysplastic syndrome (MDS) treated with cord blood transplantation (CBT) after myeloablative conditioning. Between August 1998 and June 2009, 33 adult patients with advanced MDS were treated with unrelated CBT. The diagnoses at transplan-

tation included refractory anemia with excess blasts (n=7) and MDS-related secondary AML (sAML) (n=26). All patients received four fractionated 12 Gy TBI and chemotherapy as myeloablative conditioning. The median age was 42 years, the median weight was 55 kg and the median number of cryopreserved nucleated cells was 2.51×10^7 cells per kg. The cumulative incidence of neutrophil recovery at day 50 was 91%. Neutrophil recovery was significantly faster in sAML patients (P=0.04). The cumulative incidence of plt recovery at day 200 was 88 %. Plt recovery was significantly faster in CMV seronegative patients (P<0.001). The cumulative incidence of grade II-IV acute GVHD (aGVHD) and extensive-type chronic GVHD was 67 and 34%, respectively. Degree of HLA mismatch had a significant impact on the incidence of grade II-IV aGVHD (P=0.021). TRM and relapse at 5-years was 14 and 16%, respectively. The probability of EFS at 5 years was 70%. No factor was associated with TRM, relapse and EFS. These results suggest that adult advanced MDS patients without suitable related or unrelated BM donors should be considered as candidates for CBT.

2. 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)$\times10^7$/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 0.5 mg/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 0.5 mg/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.

3. Aberrant CD3/CD7 expression in CD4+ T cells of HTLV-1 carriers

Kobayashi S, Ohno N, Tsuda M, Uchimaru K, Tojo A

In our recent study to purify adult T-cell leukemia-lymphoma (ATL) cells of acute-type patients by flow cytometry, three subpopulations were observed in CD3 *vs* CD7 plot (P: CD $3^{posi}CD7^{posi}$, D: $CD3^{dim}CD7^{dim}$ and N: $CD3^{dim}CD7^{neg}$). Majority of leukemia cells were enriched in the N subpopulation and the same clone was included in the D and N subpopulations, suggestive of clonal evolution. In this study we analysed patients of indolent-type ATL and human T-cell leukemia virus type I (HTLV-I) asymptomatic carrier (AC) to see whether the CD3 *vs* CD7 profile reflects progressive property of HTLV-I infected cells. In D(%) *vs* N(%) plot, each patient data could be mainly categorized into three groups (Group 1: AC, Group 2: smoldering- and chronic-type ATL and Group 3: acute-type ATL). Intriguingly there were some exceptions (*e.g.* AC in Group 2). In follow-up of some patients, clinical disease progression correlated well with the CD3 *vs* CD7 profile. Further molecular (proviral load and clonality) and clinical data analyses lead us to propose that the CD 3 *vs* CD7 plot reflects progression of disease stage of HTLV-I infected patients. The CD3 *vs* CD7 profile will be a new indicator, along with high proviral load, for HTLV-I AC to forecast disease progression. (manuscript in preparation)

4. Nation-wide survey of the management of adult T-cell leukemia and HTLV-1 carrier

Uchimaru K

Adult T-cell leukemia (ATL) is endemic in south-western Japan, especially in Kyushu and Okinawa islands, whereas it is considered as a rare disease in the other areas of Japan. ATL is one of the most intractable hematological malignancies and various therapeutic approaches could be applicable. We performed nation-wide survey for the management of ATL and HTLV-1

asymptomatic carrier to investigate whether inter-district and/or inter-hospital difference exists. We sent questionnaires to 1310 hematology and dermatology departments in allover Japan and 462 replies were recovered (35.2%). Therapeutic approach to ATL was significantly variable especially in acute/lymphoma, high-risk chronic type and smoldering type with skin lesion. In Kyushu district, low dose chemotherapies other than intensive chemotherapies were introduced to acute/lymphoma type ATL in more than half of the hospitals whereas the proportion of those were only 29% in the other areas. Ninety-two percent and 74% of low-risk chronic ATL patients were followed without therapy in Kyushu and the other areas respectively. Hematopoietic stem cell transplantation (SCT) was considered to acute/lymphoma type ATL patients in almost all the hospitals but upper limit of applicable age for SCT was significantly variable (range 45-75). These differences could greatly affect therapies for ATL patients. Approximately 60% of the hospitals regarded high-risk chronic ATL as applicable to SCT. The approach to high-risk chronic ATL is most variable in ATL subtypes. The results of the dermatology departments will also be reported.

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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 2011, 41 new patients with HIV infection have visited or been admitted to our hospital and 517 patients in total are currently under our clinical management. The total number of in-patients with HIV-infection during 2011 was 46, and about 10 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 and clinical research on HIV infection and related diseases.

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

Takeshi, Fujii, Tomohiko Koibuchi, Michiko Koga[1], Syoichi Shimizu, Kentaro Imai, Eisuke Adachi, Michio Okame, Hidenori Sato, Toshiyuki Miura[1], Hitomi Nakamura[1], Tadashi Kikuchi[1], Takashi Odawara, and Aikichi Iwamoto1: [1]Division of Infectious Diseases, The Advanced Clinical Research Center.

41 new patients with HIV-1 infection visited our hospital this year (from January 1 to December 31, 2011), and 517 patients in total are under medical management in our outpatient clinic. The total number of HIV-infected inpatients during 2011 was 46. 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 420 HIV-

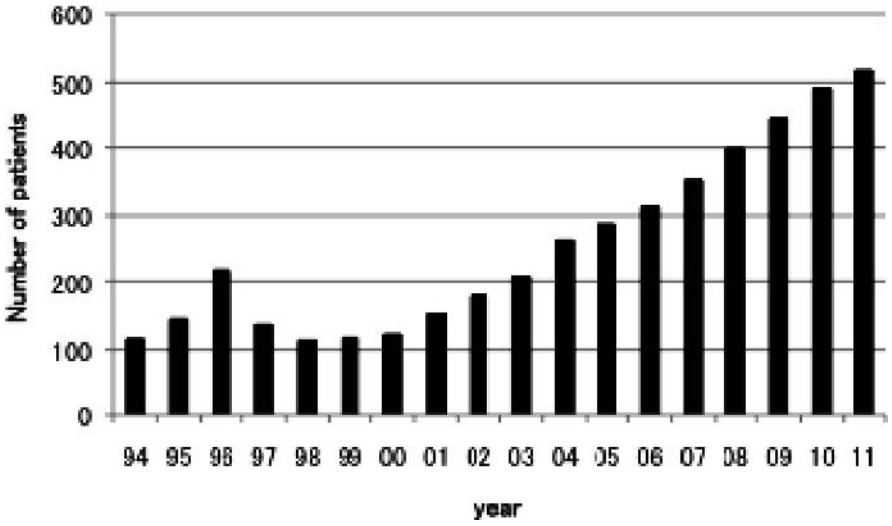

Figure 1. Number of HIV-infected outpatients in IMSUT Hospital

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 40 copies/ml in more than 90% of patients, and their CD4 cell counts increase by approximately 200/μL in average. Consequently, the clinical management of HIV-infected patients changed from how to treat opportunistic infections into how to control patients with ART.

2. Treatments and Clinical Research of Tropical Diseases

a. Treatment of Tropical Diseases in IMSUT hospital

Takeshi, Fujii, Tomohiko Koibuchi, Michiko Koga[1], Syoichi Shimizu, Kentaro Imai, Eisuke Adachi, Michio Okame, Hidenori Sato, Toshiyuki Miura[1], Hitomi Nakamura[1], Tadashi Kikuchi[1], Takashi Odawara, and Aikichi Iwamoto[1]: [1]Division of Infectious Diseases, The Advanced Clinical Research Center.

Dozens of important medicines essential for treatment of tropical or parasitic diseases are not licensed in Japan. For instance, artesunate and injectable quinine for falciparum malaria, 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 hundred of 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, dengue, typhoid fever, amebiasis, post-exposure prophylaxis of rabies and so on.

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

Tomohiko Koibuchi, Takeshi, Fujii, Michiko Koga[1], Toshiyuki Miura[1], Hitomi Nakamura[1], Takashi Odawara, and Aikichi Iwamoto[1]: [1]Division of Infectious Diseases, The Advanced Clinical Research Center.

The Japanese guidelines for treatment of HIV-infected patients have been established since 1998 with support from Ministry of Health, Labor and Welfare. The representatives from our department have played critical roles in development of the current practice guidelines in Japan. It is vital to create practice guidelines that are specific for the unique genetic and social backgrounds of the HIV-infected population in Japan. In collaboration with other Japanese HIV-experts, the physicians from our department update the practice guidelines annually, as we deem necessary. The guidelines are available at http://www.haart-support.jp/guideline.htm and used widely by Japanese clinicians. 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. Hepatitis B virus co-infection in HIV-infected Patients in IMSUT hospital

Tomohiko Koibuchi, Takeshi, Fujii, Michiko Koga[1], Toshiyuki Miura[1], Hitomi Nakamura[1], Takashi Odawara, and Aikichi Iwamoto[1]: [1]Division of Infectious Diseases, The Advanced Clinical Research Center.

The rate of Hepatitis B virus (HBV) co-infection is higher in HIV-infected patients compared with that in the general population because of common transmission routes. The percentage of HBV surface antigen (HBsAg) positive HIV-infected patients in IMSUT hospital is around 5%. On the other hand, HBsAg positive rate in Japanese population is estimated 1.0%. HBV co-infection of HIV-infected patients accelerates development of cirrhosis. Prevention of HBV infection is therefore essential for HIV-infected patients. However, HIV-infected patients respond poorly to HBV vaccination even if the patients' CD4 T-cell count is high. We recently reported the low response rates of HBV vaccination in HIV-infected Japanese patients; out of 12 patients received HBV vaccination at standard schedule (0-, 1-, 6-month) in IMSUT hospital, only one was a responder (HBsAb ≧10 IU/L). Our data support that the strategy of improving the efficacy of HBV vaccination in HIV-infected patients is urgently needed.

5. Kinetics of serumβ-D-glucan after Pneumocystis pneumonia treatment in patients with AIDS.

Michiko Koga[1], Tomohiko Koibuchi, Tadashi Kikuchi[1], Hitomi Nakamura[1], Toshiyuki Miura[1], Aikichi Iwamoto[1] and Takeshi Fujii: [1]Division of Infectious Diseases, The Advanced Clinical Research Center.

The serum β-D-glucan has been demonstrated as a reliable, adjunct diagnostic marker for PCP, but its kinetics after PCP treatment is poorly understood. To evaluate the correlation between the levels of β-D-glucan and the clinical response, we investigate the individual transition of the serum β-D-glucan levels after the initiation of PCP treatment. Seventeen PCP patients with AIDS admitted in our hospital were analyzed. All subjects showed the serum β-D-glucan levels above the cutoff value, and the median level was 224 pg/ml〔IQR: 78-597〕at the time of PCP diagnosis. There were no correlations between serum β-D-glucan levels and CRP, LDH, or AaDO2 at room air. Although there was a downward trend of serum β-D-glucan level as PCP treatment was initiated, a significant number of subjects experienced marked increase in the serum β-D-glucan levels despite their evident clinical improvement. Serum β-D-glucan level does not reflect the severity and prognosis of PCP infection, and they may not be suitable for monitoring response to treatment.

6. Long-term successful control of super-multi-drug resistant Human Immunodeficiency Virus type I infection by a novel combination therapy of Raltegravir, Etravirine and boosted-Darunavir.

Hitomi Nakamura[1], Naoko Miyazaki, Noriaki Hosoya, Michiko Koga[1], Takashi Odawara, Tadashi Kikuchi[1], Tomohiko Koibuchi, Ai Kawana-Tachikawa[1], Takeshi Fujii, Toshiyuki Miura[1], Aikichi Iwamoto[1]: [1]Division of Infectious Diseases, The Advanced Clinical Research Center

Drug-resistant virus infection has been a major hurdle in the management of human immunodeficiency virus type 1 (HIV-1) infection. Recently, three novel antiretrovirals [raltegravir (RAL), etravirine (ETR), and darunavir (DRV)] were introduced into the market almost simultaneously, and salvage regimens containing these three antiretrovirals have been reported to exhibit strong potency against drug-resistant HIV-1 infection. However, the sustainability of such regimens remains unclear, particularly for patients infected with multidrug-resistant viruses. Here we report a case of super-multidrug-resistant HIV-1 infection which has been successfully controlled by novel combination therapy including RAL, ETR, and DRV for over 2 years, indicating that the novel combination could become an ultimate weapon against drug-resistant HIV infection and could alter the landscape of HIV salvage therapy.

7. Cerebral schistosomiasis due to Schistosoma haematobium confirmed by PCR analysis of the brain specimen.

Kentaro Imai, Tomohiko Koibuchi, Takashi Kumagai[2], Takuya Maeda[3], Yoshio Osada[4], Nobuo Ohta[2], Michiko Koga[1], Hitomi Nakamura[1], Toshiyuki Miura[1], Aikichi Iwamoto[1], and Takeshi Fujii: [1]Division of Infectious Diseases, The Advanced Clinical Research Center, [2]Section of Environmental Parasitology, Department of International Health Development, Division of Public Health, Tokyo Medical and Dental University, [3]Department of Infectious Diseases and Pulmonary Medicine, National Defense Medical College, [4]Department of Immunology and Parasitology, University of Oc-

cupational and Environmental Health.

The case of a 25-year-old Japanese male who had cerebral schistosomiasis by *Schistosoma haematobium* is reported here. Although serum antibody tests showed cross-reaction with other helminths and no ova were excreted in urine or feces, the existence of *Schistosoma haematobium* in the brain was confirmed by PCR analysis.

8. A case of secondary syphilis presenting with unusual complications: syphilitic proctitis, gastritis and hepatitis.

Eisuke Adachi, Tomohiko Koibuchi, Michio Okame, Hidenori Sato, Kentaro Imai, Shoichi Shimizu, Giichiro Tsurita[2], Naoki Oyaizu[3], Aikichi Iwamoto[1] and Takeshi Fujii: [1]Division of Infectious Diseases, The Advanced Clinical Research Center, [2]Department of Surgery, Research Hospital of The Institute of Medical Science, [3]Department of Laboratory Medicine, Research Hospital of The Institute of Medical Science

We report the first known case of syphilis with simultaneous manifestations of proctitis, gastritis, and hepatitis. The diagnosis of syphilitic proctitis and gastritis was established by the demonstration of spirochetes with anti-Treponema pallidum antibody staining in biopsy specimens. Unusual manifestations of secondary syphilis completely resolved after 4 weeks of antibiotic therapy.

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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

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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, Shinji Mochizuki[1], Shohei Yamamoto, 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 having 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

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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

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As mentioned above, adolescents and young adults with hematologic malignancies are distinct in terms of their therapeutic requirements compared to adults or children. However, there have been no data 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

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Hemophilia is a congenital disease with a lack of coagulation factors. Arthropathy is a major cause of morbidity in the patients with hemophilia. Approximately one third of the patients need the mobility assistance. Although the pathogenesis of hemophilic arthropathy (HA) still have 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, in Japan is performed by Department of Joint Surgery in our hospital. So far, however, the efficacy of the treatment has been insufficient. Recently it has been shown that BM contains MSC, which can differentiate into various mesenchymal tissue cells, osteocytes, adipocytes and chondrocytes. Although the mechanism by which MSC are committed to differentiate into each mesenchymal tissue, the environment surrounding MSC plays an important role in the commitment. We are then preparing for the clinical trial of the transplantation of autologous culture-expanded BM-derived MSC into the articular cartilage defect in the HA patients.

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We 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. Study on CD26 molecule in normal immune response and in patients with immune-mediated diseases

Osamu Hosono, Kei Ohnuma, Noritada Yoshikawa, Hiroshi Kawasaki, Hirotoshi Tanaka, Chikao Morimoto. (Department of Rheumatology and Allergy), Akiko Souta-Kuribara, (Division of Clinical Immunology)

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 CD 26-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).

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.

a. Clinical significance of soluble CD26/DPPIV in various disease conditions

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

Our previous studies demonstrated that CD 26-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. Possible substrates of CD26/DPPIV include several critical cytokines and chemokines. CD26 could modulate function of several cytokines and chemokines such as RANTES (CCL5), SDF-1 α (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 in HIV-1-infected individuals contributes to the immunopathogenesis of HIV infection. Furthermore, we have shown that serum levels of sCD 26 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), 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.

(ii) Soluble CD26/DPPIV in malignancies associated with asbestos exposure

CD26 /DPPIV is able to cleave selected biological factors to alter their functions and regulates topoisomerase II α level in hematologic malignancies, affecting sensitivity to doxorubicin and etoposide. Expressed on various tissues, CD 26 is involved in the development of certain human cancers. We have shown CD26 is highly expressed on the cell surface of malignant mesothelioma and that a newly developed humanized anti-CD26 mAb has an inhibitory effect on malignant mesothelioma cells in both in vitro and in vivo experiments.

We examined sCD26 and its specific DPPIV activity in serum and pleural effusion of patients with asbestosis in collaboration with Okayama Rosai Hospital. Serum levels of sCD26 and its specific DPPIV activity was significantly reduced in patients with both malignant mesothelioma and primary lung cancer associated with asbestos exposure compared to patients with pleural plaque. As there seems to be a relationship between pleural CD26/DPPIV and prognosis in mesothelioma, we have done the measurement of more samples and serial studies to confirm their clinical significance. We are now analyzing their clinical significance, especially their association with prognosis of mesothelioma.

(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).

b. CD26-based molecular target therapy for graft-versus-host disease in hematopoietic stem cell transplantation

Graft-versus-host disease (GVHD) remains a major cause of morbidity and mortality in allogeneic hematopoietic stem cell transplantation (alloHSCT). In GVHD, mature donor T cells that accompany the stem cell graft attack recipient tissues, especially the skin, liver, gastrointestinal tract, and lung. Therefore, all patients undergoing alloHSCT receive GVHD prophylaxis to impair T cell function; however, treatment to prevent GVHD can be deleterious since mature donor T cells play a critical role in mediating reconstitution of the adaptive immune system. Recipients of alloHSCT are thus at great risk for infections, particularly when prolonged immunosuppression is required for treatment of GVHD. Although the role of CD26/DPPIV in GVHD needs to be studied in more detail, treatment with a murine antibody against human CD26 was reported to have an effect in patients with steroid-resistant acute GVHD following alloSCT (Bacigalupo A., et al., Acta Haematol 1985:73:185, de Meester, et al., Immunobiology 1993:188:145). To examine the efficacy of CD26-targeting therapy in GVHD more profoundly, we established mouse GVHD model using human peripheral blood lymphocytes (huPBL) (xenograft GVHD mouse model; x-GVHD). After NOD/LtSz-scid or NOD/Cg-Prkdcscidil2 rgtm1Sug/Jic mice were injected with appropriate numbers of huPBL, mice show symptoms of GVHD such as loss of weight, loss of hair, deterioration of activity, and thinning of ear pads. Histopathological examination revealed that CD 3+CD26+ human lymphocytes were infiltrated in the skin, intestinal mucosa, salivary gland, lung and liver of the x-GVHD mice. In this mouse model, humanized anti-CD26 monoclonal antibody (mAb) was injected two weeks later of onset of x-GVHD, and the symptoms of GVHD were improved after ten injections of humanized anti-CD26 mAb. Moreover, x-GVHD was observed to be suppressed when humanized anti-CD26 mAb was prophylactically administered. Taken together, it may be possible that the full therapeutic potential of alloSCT will be realized by approaches that aim to minimize GVHD by targeting CD26-mediated T cell regulation.

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

Hirotoshi Tanaka, Noritada Yoshikawa (Department of Rheumatology and Allergy), Noriaki Shimizu, Takako Maruyama, Chikao Morimoto (Division of Clinical Immunology).

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. Our recent achievement is now been applied in clinical settings in the IMSUT Hospital.

Glucocorticoid hormones are effective in controlling inflammation and immunity, but underlying mechanisms are largely unknown. It has been shown that both positive and negative regulation of gene expression is necessary for this process. The genes whose activity is negatively modulated in the anti-inflammatory process code for several cytokines, adhesion molecules. Most of them do not carry a classical binding site for regulation by the GR, but have instead regulatory sequences for transcription factors such as AP-1 or NF-κB. Considering various severe side effects of glucocorticoids, it may be pharmacologically important to dissociate these negative regulatory function of the GR from induction of genes for metabolic enzymes, expression of which have been shown to be positively regulated by the GR. We propose that a certain class of compounds (surprisingly, some of them are non-steridal chemicals) may dissociate transactivation and transrepression function of the GR and offer opportunities for the design of such compounds that could function more effectively as antiinflammatory drugs. In this line, we are developing novel therapeutic strategy. On the other hand, we have developed an efficient system to screen out the target genes of GR in glucocorticoid-responsive tissues, and are working with clarification of tissue-specific effects of glucocorticoids.

(i) Development of Dissociating Ligand for the GR

The GR function could be differencially regulated by ligands. We have recently shown that not only synthetic glucocorticoids but also certain bile acids could differentially modulate GR function. Moreover, the effects of those compounds are indicated to be ascrived to the ligand binding domain of the receptor. In this line, we are going to isolate the dissociating ligand that preferencially promotes transrepression function of the GR. Recently we have demonstrated that certain ligands can modulate in-

terdomain 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 regulator. In this line, we have shown that cortivazol is extremely specific for GR and does not bind to MR. We are studying the molecular basis for this receptor specificity of the ligand using cortivazol as a model. Our recent microarray study demonstrated that GR and MR have differential role in homeostatic regulation in non-classical corticosteroid target tissues including the heart. Notably, collaboration with Professor Miyano's laboratory greatly contributed to development of this program.

(ii) Molecular biology of small nuclear RNA binding protein HEXIM1

Expression of HEXIM1 is induced by treatment of vascular smooth muscle cells with a differentiation inducer hexamethylane bisacetamide. It is shown that HEXIM1 binds 7SK snRNA and inhibits P-TEFb-mediated transcriptional elongation process. Physiological significance of HEXIM1 is studied using newly generated transgenic mice. HEXIM1 Tg mice show cardiac resistance to elevation in pulmonary arterial pressure with less hypertrophic response, suggesting that HEXIM1 might be a therapeutic candidate of pulmonary hypertension in connective tissue diseases.

(iii) Clarification of tissue-specific effects of glucocorticoids

We performed target gene identification and clarification of their biological significance in cardiac muscles and skeletal muscles.

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 glucocorticoids via the GR in cardiomyocytes: phospholipase A2 group IVA (*Pla2g4a*; encoding cytosolic calcium-dependent phospholipase A2 [cPLA 2]), which belongs to the class of cPLA2s that preferentially cleave arachidonic acid from membrane phospholipids; and prostaglandin-endoperoxide synthase 2 (*Ptgs2*; encoding COX2), which converts arachidonic acid into PGH2. Importantly, ALD 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 glucocorticoid-GR signaling. Our results suggest a novel interaction between glucocorticoid-GR signaling and the arachidonic acid cascade-mediated cardiomyocyte survival pathway. Recently, we have characterized the cardiac receptor for PGD2 and clinical application of this study is now ongoing in collaboration with the Department of Cardiology, Keio University School of Medicine.
2. Skeletal muscle. Muscle comprises ~40% of body mass and contributes not only to the structure and movement of the body but also to nutrient storage and supply. In adult mammals, skeletal muscle hypertrophy/atrophy is characterized by an increase/decrease in the size (as opposed to the number) of individual myofibers, respectively. The control of muscle mass is believed to be determined by a dynamic balance between anabolic and catabolic processes. Mammalian target of rapamycin (mTOR) is a crucial component of the anabolic machinery for protein synthesis. Prototypically, insulin/IGF-1 activates mTOR via the PI3K-Akt pathway. Protein degradation in skeletal muscle cells is essentially mediated by the activity of two conserved pathways: the ubiquitin-proteasomal pathway and the autophagic/lysosomal pathway. The ubiquitin-proteasomal pathway is responsible for the turnover of the majority of soluble and myofibrillar muscle proteins. The activity of this pathway is markedly increased in atrophying muscle due to the transcriptional activation of a set of E3 ligase-encoding genes, e.g., atrogin-1 and MuRF1. Autophagy also plays an important role in the degradation of skeletal muscle, and is indicated to be a consequence of an ordered transcriptional program involving a battery of genes, e.g., LC3 and Bnip3. These positive and negative pathways are balanced in a highly coordinated manner for the determination of myofiber size and total muscle volume; however, distortion

of this balance with a relative increase in degradation results in the generalized decrease of myofiber size and muscle atrophy (Hoffman and Nader, Nat. Med. 2004). Pioneering studies demonstrated that muscle atrophy is a result of active processes that are transcriptionally controlled through the expression of a particular gene set; the forkhead box O (FoxO) transcription factors are common components of a number of atrophy models and act as critical liaison molecules for protein degradation and autophagy via the transcriptional regulation of, for example, atrogin-1, MuRF1, LC3, and Bnip3 (Mammucari et al., 2007; Sandri et al., 2004; Stitt et al., 2004; Zhao et al., 2007). In clear contrast, it is evident that each disease has proper signaling pathways to FoxOs and that other components of the cellular machinery often participate in the progression of atrophy. Therefore, for the development of therapies against muscle atrophy, it should be addressed how the transcriptional program triggered by a particular atrophy pathway is orchestrated and how the balance of muscle protein synthesis and degradation is distorted in each disease.

Typically, glucocorticoid-induced muscle atrophy is characterized by fast-twitch type II glycolytic muscle fiber loss with reduced or no impact on type I fibers. The mechanism of such fiber specificity is yet unknown. Previous reports suggested that the glucocorticoid-GR system has anti-anabolic and catabolic effects and promotes degradation via the induction of a set of genes including atrogin-1, MuRF1, and myostatin. Although the involvement of FoxO transcription factors is reported in the gene regulation of atrogin-1 and MuRF1 under the presence of excess glucocorticoids, the biochemical role of GR in the transcriptional regulation of muscle tissue has not yet been determined. Therefore, we investigated how GR-mediated gene expression coordinately modulates anti-anabolic and catabolic actions to understand the functional coupling of metabolism and volume regulation in muscle.

We identified REDD1 and KLF15 genes as direct targets of GR. REDD1 is known to be induced by various stressors, including glucocorticoid, and to inhibit mTOR activity via the sequestration of 14-3-3 and the increase of TSC1/2 activity. We clearly identified the functional GRE via the promoter analysis of REDD1 gene. On the other hand, KLF15 is a recently discovered transcription factor that is involved in several metabolic processes in skeletal muscle; e.g., KLF15 transcriptionally upregulates the gene expression of branched-chain aminotransferase 2 (BCAT2), a mitochondrial enzyme catalyzing the first reaction in the catabolism of branched-chain amino acids (BCAA) to accelerate BCAA degradation and alanine production in skeletal muscle. Moreover, phenotypic analysis of cardiac-specific KLF15 knockout mice revealed marked left ventricular hypertrophy, indicating the negative regulatory role of KLF15 on muscle mass. We here demonstrated that KLF15 participates in muscle catabolism via the transcriptional regulation of atrogin-1 and MuRF1. Moreover, KLF15 affects mTOR through BCAA degradation and negatively modulates myofiber size. mTOR activation inhibits GR-mediated transcription by suppressing GR recruitment onto target genes, strongly suggesting a mutually exclusive crosstalk between mTOR and GR. Pharmacological activation of mTOR with BCAA attenuated GR-mediated gene expression, leading to the substantial restoration of muscle in glucocorticoid-treated rats. We, therefore, indicate the critical importance of the interaction of GR and mTOR in the regulation of metabolism-volume coupling in skeletal muscle. Given this, we have just started the clinical trial in IMSUT hospital to verify our scenario in glucocorticoid-treated patients.

III. Clinical Trial & Survey

Osamu Hosono, Kei Ohnuma, Noritada Yoshikawa, Hiroshi Kawasaki, Hirotoshi Tanaka, Chikao Morimoto

We have participated the post-marketing survey (Orencia®: abatacept) since 2010 to evaluate its safety in clinical use in patients with rheumatoid arthritis (RA). We had already performed post-marketing survey of biologics for treatment of rheumatoid arthritis (Remicade®, Enbrel® and Humira®). The post-marketing survey of Orencia® finished in 2011. We are going to participate SECURE (Safety of Biologics in Clinical Use in Japanese Patients with Rheumatoid Arthritis in the Long Term) study.

We have also participated another post-marketing survey (Rheumatrex®: methotrexate, MTX) to evaluate the safety and efficacy of MTX dose up in RA patients treated with 8mg of MTX per week.

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

Satoshi Iwata (Division of Clinical Immunology), Noritada Yoshikawa, Kei Ohnuma, Hiroshi Kawasaki, Osamu Hosono, Hirotoshi Tanaka, and Chikao Morimoto.

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, BioBank 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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がん細胞の生物学～がん幹細胞とは　山崎裕人，森本幾夫　Medical Bio，8，40–43，2011.

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IMSUT Hospital

Department of Applied Genomics
ゲノム診療部

Professor Yoichi Furukawa M.D., Ph.D.
Professor Yusuke Nakamura M.D., Ph.D.
Professor Yoshinori Murakami M.D., Ph.D.

教 授 医学博士 古 川 洋 一(併任)
教 授 医学博士 中 村 祐 輔(併任)
教 授 医学博士 村 上 善 則(併任)

Our department was established for the application of human genome information in clinics. In 2011, we incorporated the genetic testing laboratory in the IMSUT hospital.

1. Genetic tests for the patient with malignant neoplasm

We reconstructed a system to perform genetic tests for patients with leukemia. In the last six months, we performed more than two hundreds of genetic tests including qualitative and quantitative evaluation of leukemic cells in the patients. In addition, we have established a system to determine c-MPL, NPM, and KRAS mutations, and *CEP110/FGFR1* fusion gene. These genetic tests are contributing to precise diagnosis of malignant diseases and effect of treatment to the patients.

2. Genetic testing using next generation sequencer

Masao Nagasaki[1], Satoru Miyano[2]: [1]Functional Genomics, [2]Laboratory of DNA Information Analysis, Human Genome Center

We started a project, the determination of germ-line mutations in patients suspected for familial colorectal cancer, using next generation sequencer. This project was approved by institutional review board in 2011. One patient was enrolled in this study. The patient was diagnosed as familial polyposis of the colon, but conventional PCR-direct sequence method identified no pathogenic mutations of *APC*. This project is aimed to detect mutations that are undetectable by Sanger sequence method, and to identify novel genetic alterations associated with familial tumor.

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 tests to clients who are anxious about

genetic issues associated with hereditary diseases. In 2011, we had a total of 16 cases including familial breast cancer, Peutz-Jeghers syndrome, familial polyposis of the colon, spinocerebellar degeneration, ornithine transcarbamylase deficiency, and retinitis pigmentosa. In the counseling, we provided correct information of the diseases and took psychological care of the clients in collaboration with clinical psychologists. Genetic testing was performed in four cases at clients' request after thoughtful discussion about its merit and demerit, and written informed consent.

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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
Lecturer	Haruyasu Yamada, M.D., D.M.Sc.	講　師	医学博士	山　田　晴　耕
Assistant Professor	Makoto Watanabe, M.D., D.M.Sc.	助　教	医学博士	渡　邉　　慎

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.

Interstitial Magnetic Resonance Lymphography in Mice: Comparative Study of Gadofluorine 8, Gadofluorine M, and Gadofluorine P

Shigeru Kiryu, Yusuke Inoue[1], Fugeng Sheng[2], Makoto Watanabe, Kohki Yoshikawa[3], Morio Shimada[3], and Kuni Ohtomo[4]: [1]Department of Diagnostic Radiology, Kitasato University School of Medicine, [2]Department of Radiology, Affiliated Hospital of The Academy of Military Medical Sciences, Beijing, China, [3]Department of Radiotechnical Sciences, Faculty of Radiological Health Sciences, Komazawa University, [4]Department of Radiology, Graduate School of Medicine, University of Tokyo.

We investigated the characteristics and capability of interstitial MR lymphography in mice using gadofluorine 8, gadofluorine M, and gadofluorine P. Healthy mice were injected with 0.5 μmol Gd gadofluorine 8, gadofluorine M, or gadofluorine P subcutaneously into the right rear footpad, and the time courses of contrast enhancement in the lymph nodes were assessed. Moreover, we assessed the lymphatic pathway from the right and left rear feet or tail using gadofluorine M. Contrast enhancement was demonstrated for the right popliteal, right sacral, and right iliac lymph nodes in all mice 5 min after the injection of each of the three agents, and then decreased gradually. Enhancement in the lymph nojdes was still detectable 30 min after the injection of gadofluorine 8 or gadofluorine M, it became obscure sooner after gadofluorine P injection. In comparison with gadofluorine P, the other two contrast agents showed mildly stronger enhancement in the lymph nodes. Clear differences were found in the hepatobiliary and urinary kinetics of the three agents. The injection of gadofluorine M into various sites delineated the lymphatic pathway from the respective injection site. Interstitial MR lymphography using gadofluorine 8, gadofluorine M, and gadofluorine P offered clear visualization of the lymphatic pathway in healthy mice during a sufficient imaging time window. This technique allowed for repeated assessment of the lymphatic pathway in a given mouse, helping to reveal the mouse lymphatic system.

Long-term assessment of contrast effects of gadofluorine M and gadofluorine P in magnetic resonance imaging of mice.

Fugeng Sheng[2], Yusuke Inoue[1], Shigeru Kiryu, Makoto Watanabe, and Kuni Ohtomo.[4]

We investigated the long-term time course of the contrast effects after the intravenous injection of gadofluorine M or gadofluorine P in mice. Magnetic resonance images were acquired longitudinally after intravenous injection of 0.1 μmol Gd/g gadofluorine M into BALB/c mice. The contrast effects were also assessed in C57BL /6J mice injected with gadofluorine M, BALB/c mice injected with gadofluorine P, and BALB/c mice injected with a double dose of gadopentetate dimeglumine. The injection of gadofluorine M into BALB/c mice caused prolonged contrast effects in the blood and other organs. The liver enhancement was especially long-lasting and still evident 6 days after injection. Strain-related differences in contrast kinetics of gadofluorine M were not observed between BALB/c mice and C57BL/6J mice. In comparison with gadofluorine M, clearances from the blood, liver, and kidney were more rapid and contrast enhancement in the spleen was generally lower for gadofluorine P. The enhancement in the gallbladder cavity, indicating biliary excretion, was evident only after gadofluorine P injection. Blood enhancement at 10 min was much weaker for gadopentetate dimeglumine. Both gadofluorine M and gadofluorine P appear to be applicable to blood pool imaging and liver imaging in mice.

Distortion correction in whole-body imaging of live mice using a 1-Tesla compact magnetic resonance imaging system.

Shigeru Kiryu, Yusuke Inoue[1], Yoshitaka Masutani[4], Tomoyuki Haishi[5], Kohki Yoshikawa[3], Makoto Watanabe, and Kuni Ohtomo[4]: [5]MRTechnology.

We investigated a distortion correction applicable to whole-body imaging of live mice. All magnetic resonance imaging (MRI) scans were acquired on a compact 1-T permanent magnet unit for mouse imaging using a T1-weighted, three-dimensional (3D) fast low-angle shot sequence. We assessed geometric distortion in MR images of a small 3D grid phantom and determined 3D image transformations for distortion correction. The developed distortion correction was applied to MR images of the 3D grid phantom acquired on another day, and the correction was validated. A two-dimensional (2D) grid phantom was imaged with a mouse to investigate the applicability of the distortion correction to whole-body mouse imaging. Obvious geometric distortion was observed in the MR images of the 3D grid phantom. The application of the developed 3D phantom-based distortion correction reduced distortion in the images of the 3D grid phantom acquired on another day. Geometric distortion was observed in the MR images of the 2D grid phantom acquired together with the mouse. The 3D phantom-based correction decreased the distortion substantially, regardless of mouse positioning. The developed distortion correction can reduce distortion in whole-body imaging of live mice and may enhance the capabilities of MRI in small animal experiments.

Gaussia luciferase for bioluminescence tumor monitoring in comparison with firefly luciferase.

Yusuke Inoue[1], Fugeng Sheng[2], Shigeru Kiryu, Makoto Watanabe , Harnprasopwat Ratanakanit[6], Kiyoko Izawa[6], Arinobu Tojo[6], and Kuni Ohtomo[4]: [6]Division of Molecular Therapy, Advanced Clinical Research Center, University of Tokyo.

Gaussia luciferase (Gluc) is a secreted reporter, and its expression in living animals can be assessed by in vivo bioluminescence imaging (BLI) or blood assays. We characterized Gluc as an in vivo reporter in comparison with firefly luciferase (Fluc). Mice were inoculated subcutaneously with tumor cells expressing both Fluc and Gluc and underwent Fluc BLI, Gluc BLI, blood assays of Gluc activity, and caliper measurement. In Gluc BLI, the signal from the tumor peaked immediately and then decreased rapidly. In the longitudinal monitoring, all measures indicated an increase in tumor burden early after cell inoculation. However, the increase reached plateaus in Gluc BLI and Fluc BLI despite a continuous increase in the caliper measurement and Gluc blood assay. Significant correlations were found between the measures, and the correlation between the blood signal and caliper volume was especially high. Gluc allows tumor monitoring in mice and should be applicable to dual-reporter assessment in combination with Fluc. The Gluc blood assay appears to provide a reliable indicator of viable tumor burden, and the combination of a blood assay and in vivo BLI using Gluc should be promising for quantifying and localizing the tumors.

Quantitative MR image study in neuropsychiatric disorders: voxel-based analysis of diffusion tensor data sets.

Haruyasu Yamada, 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.

Magnetic resonance diffusion tensor imaging (DTI) has been reported to be useful in evaluation of the normal appearing brain in neuropsychiatric disorders. 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 or fiber tracking. Quantitative diffusion indices such as apparent diffusion coefficient and fractional anisotropy 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, using statistical parametric mapping, tract-based spatial statistics, 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.

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渡辺慎，桐生茂，大友邦 術後合併症．画像診断．

学研メディカル秀潤社　31：706–714，2011
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IMSUT Hospital

Department of Surgery (Gastrointestinal and Breast Surgery)

外科(主として，大腸・胃・食道・乳腺領域)

Associate Professor	Masaru Shinozaki, M.D., Ph.D.		准教授	医学博士	篠崎　大
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

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, Keisuke Hata, Yasuhiro Mizuno, Junko Takei

We performed various surgical operations. Malignancy is the leading 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 continued the outpatient clinic and assisted our breast cancer operations. Dr. Tsuji and Dr. Fukatsu who belong to the University of Tokyo Hospital (Hongo), started to assist our breast clinic in 2011.

2. Summary of endoscopic examination in 2011

Giichiro Tsurita, Keisuke Hata, Masaru Shinozaki, Yasuhiro Mizuno, Junko Takei

Under cooperation with Department of Advanced Medical Science, we performed 650 (9% increase compared with the number last year) upper gastrointestinal endoscopies and 639 (27 % increase) colonoscopies without major complications. Dr. Tsurita has been the chief of Division of Endoscopy and played the crucial role in examinations. For the patients' satisfaction, we aggressively perform endoscopic treatment and avoid operation as much as possible. Our two fellows (Y.M. and J.T.) have learned gastrointestinal endoscopic technique and have been making 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. The comparison between step biopsy and target biopsy at surveillance colonoscopy in long-standing ulcerative colitis: a randomized control study

Keisuke Hata, Masaru Shinozaki, Yasuhiro Mizuno, Giichiro Tsurita

Patients with long-standing ulcerative colitis have increased risk of colorectal cancer. The prognosis of symptomatic patients is extremely poor, and surveillance colonoscopy with multiple biopsies is recommended for such patients. However, the methods of biopsies are different between the Western countries and Japan: Numerous (more than 32) blind biopsies are recommended in the former countries, whereas target biopsied with restricted number are favored in Japan. Although the detection rates of dysplasia, which is known as a precancerous lesion as well as a marker of invasive cancer, seem to be substantially similar, when studies were executed separately, no direct comparison has been attempted yet. We have included five patients, who were randomized to the two groups, without any complications.

F. 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.

G. 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.

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.

Publications

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2. Shuno Y, Hata K, Sunami E, Shinozaki M, Kawai K, Kojima T, Tsurita G, Hiyoshi M, Tsuno NH, Kitayama J, Nagawa H. Is surveillance endoscopy necessary after colectomy in ulcerative colitis? ISRN Gastroenterol. 2011; 2011: 509251.
3. Shinozaki M, Hata K, Matsukura M, Mizuno Y, Takei J, Tsurita G. Portal vein thrombosis and pulmonary artery thromboembolism after laparoscopic colectomy. Minim Invasive Ther Allied Technol. 2011; 20(5): 301-6.
4. Hata K, Shinozaki M, Toyoshima O, Toyoshima A, Matsumoto S, Saisho T, Tsurita G. Impact of family history of gastric cancer on colorectal neoplasias in young Japanese. Colorectal Disease. (in press)
5. 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（in press）

IMSUT Hospital

Team Violet, Department of Surgery
外科（主に肝臓，胆のう，膵臓）

Lecturer	Akihiko Itoh, M.D.	講　師	伊　藤　精　彦
Professor	Hideaki Tahara, M.D., D.M.Sc.	教　授　医学博士	田　原　秀　晃
Assistant Professor	Akira Kanamoto, M.D., D.M.Sc.	助　教　医学博士	金　本　　彰

We have been engaged in the surgical treatment of solid tumors and the immunotherapy of various malignancies. We have also been offering diagnostic services, including endoscopic examination on upper and lower intestines. One of the goals of our team is to provide evidence-based standard therapies including surgery, chemo-therapy, and radiation for cancer patients. However, additional emphasis has been put on the development of the novel immunological and gene therapies in intimate collaboration with the Division of Bioengineering, Advanced Clinical Research Center and Core Facility for Therapeutic Vectors of Research Hospital. We have conducted multiple early-phase clinical trials (Phase I and II) for cancer patients at Research Hospital utilizing its fundamental functions enabling clinical research of high quality.

I. Summary of surgical treatment and other procedures performed in 2011

Akihiko Itoh, Akira Kanamoto, Hideaki Tahara,

Team Violet has been newly established in an independent group of the Department of Surgery on June 1st of 2010. This team has been treating the patients with the diseases of gastrointestinal organs having the focus on, but not limited to, hepato-biliary system and pancreas.

Surgical operations have been performed by the team personnel on 47 cases under general anesthesia and spinal or epidural and/or local anesthesia in 2011. As shown in Table 1, major operations were performed in 4 patients with malignant diseases and in 8 patients with benign diseases.

Table 1. Major operations performed in 2011

Malignant Diseases		Benign Diseases	
hepato-biliary organs and pancreas			
Hepatectomy	1 (GIST: 1)	Cholecystecyomy	5 (laparoscopic; 2)
Colon and rectum			
colo-rectal resection	2		
Miscellaneous			
LN biopsy	1	Miscellaneous procedures	3
TOTAL	4		8

Table 2. Other Surgical Treatment for Malignancy in 2011

hepato-biliary organs and pancreas	
TACE	16
(HCC: 14, metastatic liver cancer: 2)	
PTCD	3
LN biopsy	8
TOTAL	27

Publications

1. Kutsuna, N., Yamazaki S, Kaiga T, Inagaki. Y, Hayashi Y, Okada S, Kanamoto A, and Takayama T.: Partial MHC matched Donor CD8+ T-Cells are Indispensable to Switch Splenocytic Chimera. Journal of Surgical Research (2011 Mar 12.)
2. Yamano T, Watanabe S, Hasegawa H, Suzuki T, Abe R, Tahara H, Nitta T, Ishimaru N, Sprent J, and Kishimoto H. Ex-vivo expanded DC induce donor-specific central and peripheral tolerance and prolong the acceptance of donor skin allografts. Blood (2011 Mar 3; 117 (9): 2640-8.)
3. Hikichi M, Kidokoro M, Haraguchi T, Iba H, Shida H, Tahara H & Nakamura T. MicroRNA regulation of vaccinia virus for enhanced oncolytic activity and reduced pathogenicity in oncolytic virotherapy. Molecular Therapy (2011 Jun; 19 (6): 1107-15.)

IMSUT Hospital

Department of Joint Surgery
関節外科

Lecturer 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 2011, there are 113 surgical treatments for hemophilia (57 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 2011, we were performed 22 surgical treatments (15 for hemophilia A, 6 for hemophilia B, and 1 for Von Willebrand disease). 5 of them have the deficiency factor antibody. 17 were performed total joint arthroplasties, 1 was arthroscopic synovectomy and 4 were other surgical treatments.

Publications

1) Takedani, H., Fujii, T., Kobayashi, N., Haga, S., Tatsunami, T. and Fujii, T. Inter-observer reliability of three different radiographic scores for adult haemophilia . Haemophilia. 17: 134-138, 2011.

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

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. New clinical protocols to test the efficacy of G47Δ are also in preparation.

Outpatient clinic

The outpatient clinic of the Department of Surgical Neuro-Oncology opened in October 2011. Patients with newly diagnosed glioblastoma have been treated with high dose or standard dose radiation therapy and concomitant chemotherapy. Clinical study protocols for recurrent or newly diagnosed malignant glioma patients are in preparation.

Publications

1. Ogura, M., Todo, T., Tanaka, M., Nannya, Y., Ichikawa, M., Nakamura, F. and Kurokawa, M.: Temozolomide may induce therapy-related acute lymphoblastic leukemia. Br J Haematol 154: 663-665, 2011.
2. Koga, T., Maruyama, K., Tanaka, M., Ino, Y., Saito, N., Nakagawa, K., Shibahara, J. and Todo, T.: Extended field stereotactic radiosurgery for recurrent glioblastoma. Cancer (published online 16 DEC 2011 | DOI:10.1002/

cncr.27372).

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	Yuki Ito		臨床工学技士	伊藤 友紀

Our clinical practice and clinical studies have been focused on (1) anesthetic management in patients undergoing major surgery including joint arthroplastic surgery for hemophilia patients, (2) management of chronic intractable pain or improving the quality of life of patients with life-threatening illness (3) assessment of the impact of anesthesia and surgery on autonomic nervous activity, and (4) risk management of medical electronic devices in Research Hospital.

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

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

2. Management of chronic intractable pain.

We organized a palliative care support team 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

Oshima N, Numao S, Chinzei M. Effectiveness of a relaxation technique at the workplace evaluated by autonomic nervous activity and psychological mood. J Jpn Soc Balneol Climatol Phys Med. 74(4): 256-262, 2011

IMUSUT 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

Division of Clinical Trial Safety Management (DCTSM) owes two major missions. 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 right of 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 have engaged in the risk management and the protection of medical incidents/accidents at RH. We have promoted the report system on medical incidents and accidents, and quick corresponding scheme such as "Medical Accident-Response Meeting" and "Council of Risk Management in the RH". We take place at least two seminars for staffs of RH on medical safety every year. Participation to these seminars is the obligation of workers of RH. We have created manuals on the risk management and Standard Operating Procedures (SOP) on operations of RH and revised quickly when required.

2. Assistance and oversight of Clinical Trials/ TRs at Research Hospital

Kazufumi Matsumoto, Kumiko Sumino, Noriko Fujiwara, Minako Kohno, Makiko Tajima, Fumitaka Nagamura

The assistance of Translational (Clinical) Research Coordinators is indispensable for the conduct of clinical trials, especially for TR. In 2011, we assisted the conduct of 15 clinical trials including TR. Number of the protocols are summarized in Table 1. Table 2 shows the number of patients enrolled into clinical trials at RH in 2011.

Table 1.

Number of protocol	Started in 2011	Continuation before 2011	Total
TR	2	0	2
Clinical trials from pharmaceutical companies	3	1	4
Multi-center studies	2	7	9
	7	8	15

Table 2.

Number of patients	Enrolled in 2011	Continuation before 2011	Total
TR	2	0	2
Clinical trials from pharmaceutical companies	1	0	1
Multi-center studies	2	11	13
	5	11	16

3. The Development of the Scholastic Program for the Graduate Students of Nurses in the Area of Translational Research.

Kazufumi Matsumoto, Makiko Tajima, Kumiko Sumino, Noriko Fujiwara, Fumitaka Nagamura

Translational Research (TR) is the early phase of clinical trials, which applied the developments of basic researches for patients with incurable and/or life-threatening diseases. High-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 two-weeks 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 in accordance with the qualitative method. Six students participated in the program and we evaluated the reports and the questionnaires. Students could understand the role of research nurse and the necessary ability and organization to play this role appropriately. They were satisfied with the content and the quality of lectures and role-plays, however, the experiences of the actual operations did not meet their demands due to the less acquisition of the practical expertise. 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.

4. Education and training for ethics board members: Is e-learning the solution?

Makiko Tajima, Fumitaka Nagamura

The Japanese Ministry of Health, Labour and Welfare recently revised the Ethical Guidelines for Clinical Studies. The revised guidelines require education and training for members of a research ethics committee (REC). Some training programs on ethics are offered in an e-learning format for added convenience to learners. E-learning, also called online learning, web-based learning, or distance learning, has potential to be an effective training tool. We conducted a literature and internet search to assess the feasibility of e-learning in REC member training. E-learning is suitable for studying bioethical principles as well as laws and regulations relevant to clinical research. It is also useful to share criteria for protocol review and to update information on science and technology. E-learning is especially effective when the same training courses are offered repeatedly and when members are unable to assemble at the same location and same time due to geographical and temporal limitations. E-learning materials are shared among REC members, faculty, staff, and students, and may be open to the public. Disadvantages of e-learning include a high dropout rate due to lack of social interaction and the requirement for additional human and financial resources. To overcome these disadvantages, conventional methods such as lectures, workshops, and on-the-job training (OJT) should be incorporated into the training program. E-learning that includes the use of learning networks, such as online discussion forums, may provide results similar to those of workshops and OJT.

E-learning can be a valuable tool for REC member training. Combining different types of training media, or blended learning, is recommended to conduct effective training.

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

Kazufumi Matsumoto, Kumiko Sumino, Fumitaka Nagamura

Job stress is viewed as a situation in which working conditions interact with individual worker characteristics and result in disruption of psychological or physiologic homeostasis. Clinical research coordinators, also known as re-

search 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 to 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.

Publications

Matsumoto K, Nagamura F, Ogami Y, Yamashita N, Kamibeppu K. Difficulties of Nursing Staff Involved in Phase 1 Oncology Trials in Japan. Cancer Nur 34(5): 369-75, 2011.

Sato A, Ooi J, Takahashi S, Tsukada N, Kato S, Kawakita T, Yagyu T, Nagamura F, Iseki T, Tojo A, Asano S. Unrelated cord blood transplantation after myeloablative conditioning in adults with advanced myelodysplastic syndromes. *Bone Marrow Transplant* 46(2): 257-61, 2011.

Matsumoto K, Sumino K, Fukahori H, Kitaoka, Kamibeppu K, Nagamura F. Stressor Scale for Clinical Research Coordinators: development and psychometric testing. J Advanced Nursing (in press)

Ebihara Y, Takahashi S, Mochizuki S, Kato S, Kawakita T, Ooi J, Yokoyama K, Nagamura F, Tojo A, Asano S, Tsuji K. Unrelated cord blood transplantation after myeloablative conditioning regimen in adolescent patients with hematologic malignancies: a single institute analysis. *Leukemia Res (in press)*

中島和江，本間覚，玉木長良，金子道夫，名川弘一，原田賢治，長村文孝，大川淳，倉林亨，鳥谷部真一，後藤百万，相馬孝博，武田裕，高橋りょう子，森崎市治郎，前田潔，江原一雅，富永隆治．国立大学附属病院における「診療行為に関連した死亡の調査分析モデル事業の利用経験とその評価」医療の質・安全学会誌　6⑶：332–345，2011．

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長村文孝　トランスレーショナルリサーチにおける医学と心理学の連携　心理学ワールド50回記念誌　215–220，2011．

長村文孝　臨床安全情報(有害事象)が原因で中止となった薬剤の分析　月刊ファームステージ　2：3–5，2011．

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長村文孝　NICEにおける抗がん剤および抗体技術の価値評価動向　がんの新しいバイオマーカー／予測因子による個別化医療時代に求められる抗がん剤開発　技術情報協会　31–38，2011．

長村文孝　FDA対応におけるQ&A解説集　情報機構　9–10，11–13，15–20，2011．

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 is established in 1990, in order to manage the transfusion medicine and cell processing for hematopoietic stem cell transplantation. We have cooperated on a clinical and research cord blood banking with Tokyo Cord Blood Bank, whose cell processing and cryopreservation facility was established the first in IMSUT 'Room for Clinical Cellular Technology (RCCT)', in 1997. Now we have developed RCCT as IMSUT-Cell Resource Center (IMSUT-CRC) to facilitate and support the advanced cell therapy projects including the regenerative medicine. Also we have been engaged to the studies for the development of various cell therapy projects together with other departments, as follows.

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

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

Regulatory T cells harbored the immunosuppressive effects and were related to the pathogenesis of graft-versus-host disease (GVHD), rejection of organ transplantation and autoimmune disease. We developed the system of *ex vivo* expansion of $CD25^{+}FOXP3^{+}$regulatory T cells from the small amount of 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, Ishige I, Yuzawa M, Tamura T, Ogami K, Tojo A

"Research Cord Blood Stem Cell Bank" (former named 'Research Stem Cell Resource Bank') was established by the support of 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. The research CB bank provides CB units that are non-conforming for clinical use, in processed and frozen or in fresh to domestic researchers for research use via RIKEN Bioresource Center.
Visit our home page http://scb.ims.u-tokyo.ac.jp/

3. Exploring mesenchymal stem cells derived from Umbilical Cord:

Nagamura-Inoue T, Yuzawa M, Tamura T, Tojo A

We have explored the umbilical cord as a new mesenchymal stem cells (MSC) source. We studied the differentiation ability of cord-derived MSC including osteocytic, chondrocytic, adipocytic, and also hepatic cell differentiation.

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

Nagamura-Inoue T, Miki Yuzawa, Ogami K, Tojo A

To promote the cell therapy related to translational research, RCCT 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. In 2010, we developed and changed the name 'Room for Clinical Cellular Technology (RCCT)' to 'IMSUT-CRC' as for more functional broad units for cell therapy.

Publications

Kanda J, Hishizawa M, Utsunomiya A, Taniguchi S, Eto T, Moriuchi Y, Tanosaki R, Kawano F, Miyazaki Y, Masuda M, Nagafuji K, Hara M, Takanashi M, Kai S, Atsuta Y, Suzuki R, Kawase T, Matsuo K, Nagamura-Inoue T, Kato S, Sakamaki H, Morishima Y, Okamura J, Ichinohe T, Uchiyama T. Impact of graft-versus-host disease on outcomes after allogeneic hematopoietic cell transplantation for adult T-cell leukemia: a retrospective cohort study. Blood. 119: 2141-8, 2012

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Kato K, Yoshimi A, Ito E, Oki K, Hara J, Nagatoshi Y, Kikuchi A, Kobayashi R, Nagamura-Inoue T, Kai S, Azuma H, Takanashi M, Isoyama K, Kato S; for the Japan Cord Blood Bank Network. Cord Blood Transplantation from Unrelated Donors for Children with Acute Lymphoblastic Leukemia in Japan: The Impact of Methotrexate on Clinical Outcomes. Biol Blood Marrow Transplant. 17: 1814-21, 2011

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Sakabe S, Iwatsuki-Horimoto K, Takano R, Nidom CA, Le MQ, Nagamura-Inoue T, Horimoto T, Yamashita N, Kawaoka Y. Cytokine production by primary human macrophages infected with highly pathogenic H5N1 or pandemic H1N1 2009 influenza viruses. J Gen Virol. 92,1428-34, 2011

Yuzawa M, Nagamura-Inoue T, Ishige I, Ogami K, Tamura T, Takahashi A, Kodo H, Yamaguchi S, Tojo A. Time from cord blood collection to processing and temperature influence the quality of mononuclear cell products isolated using a density-gradient protocol. Jap J Trans Cell Ther. 57: 139-45, 2011

IMSUT Hospital

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

Professor	Hideaki Tahara, M.D., D.M.Sc.		教授(室長)	医学博士	田 原 秀 晃(併)
Project Associate Professor	Takafumi Nakamura, Ph.D.		特任准教授	生命科学博士	中 村 貴 史
Project Assistant Professor	Hisako Katano, D.D.S., Ph.D.		特任助教	歯学博士	片 野 尚 子

The primary function of the Core Facility for Therapeutic Vectors (CFTV) is to support clinical trials that require the genetic modification and/or ex vivo manipulation of patients' tissue or cells under current Good Manufacturing Practice (cGMP) conditions defined by FDA of USA. The CFTV is the first facility established in Japanese academia to produce genetic or cellular vectors of clinical grade. Using this facility, the adenoviral vector and herpes vector were prepared in CFTV for clinical use in 2011 and 2008 respectively.

1. Preparation of Standard Operating Procedures (SOPs)

The cGMP compliance is maintained using written SOPs prepared by ourselves. The SOPs codify all aspects of laboratory activities including facility design and operations of the personnel. The SOPs enables the staff not only to produce the reagents with high quality in the stable manners but also to help identify areas for improvement.

2. Adoption of ISO

In order to continuously improve our activities, quality management system of the CFTV has been assessed and found 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.

3. 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 Class 10,000. There are many features incorporated into the design of this CFTV to minimize the risk of cross-contamination between products; i. e., unidirectional traffic flow, individual airlocks to each production suite, single-pass HEPA filtered supply air, 100 percent exhaust from the biological safety cabinets through dedicate ducts, among others. Periodical validation has been performed on the facility and the equipments in CFTV to ensure cGMP compliance.

4. Projects in CFTV

Four projects are now in progress in the CFTV.

I. Cancer gene therapy using dendritic cells transfected with IL-12 genes

Takafumi Nakamura, Hisako Katano, Akira Kanamoto*, Marimo Sato*, Hideaki Tahara:

[*]**Division of Bioengineering, Advanced Clinical Research Center**

•Preparation of the Clinical Lot

We have been preparing the replication-defective recombinant adenoviral vector encoding human interleukin-12, which is an immune-stimulatory cytokine. The backbone of this vector is based on the E1- and E3-deleted serotype 5 adenovirus with a modified fiber, harboring an integrin-binding CDCRGDCDC-motif within the HI-loop of its knob protein. The IL-12 genes are driven by a CA promoter (CMV-IE enhancer with the chicken β-actin promoter). The master virus seed stock (MVSS) and purified final material have been successfully prepared following the optimization of purified method for the production of high-titer vector.

II. Vaccine therapy with peptide-loaded dendritic cells for advanced melanoma

Hisako Katano, Takafumi Nakamura, Akira Kanamoto[*], Marimo Sato[*], Hideaki Tahara: [*]Division of Bioengineering, Advanced Clinical Research Center

•Preparation of Peptide-Loaded Dendritic Cells (DCs)

We have been supporting phase I clinical trials against melanoma. Based on the results of the basic research performed in Division of Bioengineering, the SOPs of the DC preparation have been written and used. The cellular reagents have been successfully prepared in the Cell Unit and offered for clinical trials without serious problems.

III. Oncolytic viral therapy using genetically engineered herpes simplex viruses for malignant brain tumors.

Tomoki Todo[**], Yasushi Ino[**], Takafumi Nakamura, Hisako Katano, Hideaki Tahara: [**]Department of Neurosurgery, Graduate School of Medicine, The University of Tokyo

•Manufacture of the viral vector

In collaboration with the research team, we have been preparing oncolytic herpes simplex virus. We have supported the establishment of the master and working cell banks of Vero cells to produce genetically engineered herpes simplex viruses. The cGMP compliant MVSS, which contains a replication-competent herpes simplex virus type 1 vector defective for the α47 gene, was successfully produced. The purified final products have been successfully prepared, approved for clinical use by the authorities and are now used in phase I clinical trial for brain cancer patients.

IV. Development of robotized cell culture system

Shigeyuki Wakitani[***], Marimo Sato[*], Takafumi Nakamura, Hisako Katano, Hideaki Tahara: [***]Department of Orthopedics, Graduate School of Medicine, Osaka City University

In collaboration with Kawasaki Heavy Industries, Inc., we are developing robotized cell culture system which could be applied to a variety of procedures including virus production as a funded project by NEDO.

V. Treatment of malignan pleural mesothelioma using replication-defective recombinant adenoviral vector expressing the suppressor of cytokine signaling 3 (SOCS 3).

Tetsuji Naka[#], Hiroyuki Mizuguchi[##], Takafumi Nakamura, Hisako Katano, Hideaki Tahara: [#]Laboratory for Immune Signal, National Institute of Biomedical Innovation, Osaka, Japan, [##]Laboratory of Biochemistry and Molecular Biology, Graduate School of Pharmaceutical Sciences, Osaka University

•Manufacture of the viral vector for preclinical studies in non-human primates

In collaboration with the research team, we have been preparing the replication-defective recombinant adenoviral vector expressing the suppressor of cytokine signaling 3 (SOCS3) for treatment of malignant pleural mesothelioma. We have supported the vector production using the master and working cell banks of 293 cells, which we established previously. The purified final products are to be used for preclinical study in monkey.

5. Financial Support

This CFTV has been supported in large by Coordination, Support and Training Program for Translational Research from Ministry of Education, Culture, Sports, Science and Technology (2007-2011), and Advanced Clinical Research Center of IMSUT.

Publications

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IMSUT Hospital

Department of Pathology and Laboratory Medicine
検査部

Associate Professor Naoki Oyaizu, M.D, Ph.D
Research associate Naouki Isoo, MD, Ph.D.

准教授 部長 医学博士 小柳津 直 樹
助 教 医学博士 磯 尾 直 之

The Department of Pathology and Laboratory Medicine consists of eight divisions - clinical physiology, hematology, biochemistry, serology, bacteriology, molecular diagnosis and pathology, and a division of flow cytometrical analysis. This Department engages in the laboratory analysis and provides information which is critical for patient care. While facilitating the ongoing translational research projects in the research hospital, the Department functions as an integrated diagnosis & monitoring laboratory that evaluates the safety and effectiveness 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. Establishment of GMP-based biosafety examination laboratory (TR verification laboratory):

Funded by the Ministry of Education, Culture, Sports, Science and Technology (MEXST), we have established a laboratory, in which we examine safeties of material for Translational Research (TR) clinical applications, such as the products for gene therapy and cell therapy, under GMP-based standards. It is now officially called TR verification laboratory. For the present time, we are able to examine bacteria, fungi, micoplasma, and endotoxin contaminations by using molecular and biochemical techniques. We are planning to extend this strategy and will conduct "all-inclusive infectious agents examination" facility.

2. 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 immuno-therapy. 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*.

3. Quantitative Evaluation of a fraction of leukemia cell by flow cytometry

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

4. Detection of the new target molecules for advanced cancer therapy by immune-histochemical technique: :

In recent years, advances in understanding the molecular pathophysiology of cancer led to the development of molecular target-based drugs such as *Herceptin*, a monoclonal antibody that binds to her2 (human epidermal growth factor receptor 2). Thus it is critical to detect the target-molecule expression in target cancer tissue and we are able to detect these molecules by sophisticated immune-histochemical techniques.

5. Immunopathogical analysis of hematopoietic cell transplantation

A number of allogeneic hematopoietic stem cell transplantation (HSCT), mainly cord blood transplantation, has been performed for the treatment of hematological malignancies. Graft-versus-host disease (GVHD), a life-threatening complication, occurs as a complication of allogeneic HSCT. We are also intending to develop a new way to detect GVHD and make an accurate evaluation of GVHD at our laboratory.

Publications

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IMSUT Hospital

Department of Nursing
看護部

Director	Yukie Takemura, R.N., Ph.D.	看護部長	保健学博士	武　村　雪　絵
Deputy Director	Kisako Sato, R.N.	副看護部長		佐　藤　喜佐子
Nurse Manager	Reiko Yamahana, R.N., C.N.S., M.Sc.	看護師長	専門看護師	山　花　令　子
	Hisako Suyama, R.N.	看護師長		須　山　寿　子
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	Taeko Koyane, R.N.	看護師長		小屋根　たえ子
	Satomi Torisu, R.N.	看護師長		鳥　巣　里　美
	Mika Kogayu, R.N.	看護師長		小　粥　美　香

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. The Carrier Ladder System introduced in 2011 supports continuous learning and carrier development of nurses.

One of our missions is "to bring a difference to patient outcome by the power of nursing." We hope to provide high-quality care so that patients can receive treatment without anxiety or pain, and are empowered to live valuable life. We also make efforts to prevent infection, pressure ulcer or other complications.

In 2011, we introduced the carrier ladder system to support active learning and development of nurses. Nursing skills based on good knowledge and evidence are also very important in patient care. The online training tool "Nursing Skills Japan" is also introduced in 2011 to support nurses' learning and brushing up their skills.

Publications

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IMSUT Hospital

Department of Pharmacy
薬剤部

Director　Yosuke Kurokawa

薬剤部長　　黒　川　陽　介

The Department of Pharmacy provides pharmaceutical care services. The present staff (9 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 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
Lecturer	Haruyasu Yamada, M.D., D.M.Sc.	講師	医学博士	山田晴耕	
Assistant Professor	Makoto Watanabe, M.D., D.M.Sc.	助教	医学博士	渡邉	慎

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, Makoto Watanabe, 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, Makoto Watanabe.

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, Makoto Watanabe

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.

Publications

None.