

11. 当該遺伝子治療臨床研究の実施施設の状況

当該遺伝子治療臨床研究は筑波大学附属病院遺伝子・細胞治療室にて行う。この治療室内にはクラス II 安全キャビネット、遠心器や高圧滅菌器を備えており、その物理的封じ込めレベルは P2 である(別添 11)。

12. 当該遺伝子治療臨床研究に関連する国内外の研究状況

現在まで欧米(イタリア、フランス、イギリス、ドイツ、オランダ、アメリカ)を中心に当該遺伝子治療が計画され、一部の国で実行されている。詳細な臨床経過は「7-3 これまでの遺伝子治療臨床研究の成果」で示され、当該遺伝子治療臨床研究は極めて有効な治療法として報告されている。さらには同様の遺伝子治療は add-back 法や固形腫瘍に対する治療にも取り入れられており、その対象疾患は今後も拡大してゆくものと思われる。

13. 研究者の略歴、研究業績

長澤 俊郎

略歴: 昭和 44 年 東京医科歯科大学医学部卒業
昭和 48 年 東京医科歯科大学医学部 第一内科 助手
昭和 50 年 ブラウン大学 Pawtucket Memorial Hospital 血液科
フェロー
昭和 53 年 筑波大学臨床医学系・講師
平成 5 年 筑波大学臨床医学系・助教授
平成 11 年 筑波大学臨床医学系・教授(血液内科)

専門: 血液内科学、巨核球-血小板の分化、造血幹細胞移植

研究業績:

- 1) Thrombopoietin induces megakaryocyte differentiation in hematopoietic progenitor FDC-P2 cells. *J. Biol. Chem.* 270: 19673-19675, 1995.
- 2) Aprotinin inhibits plasma-induced platelet activation during cardiopulmonary bypass. *Circulation* 96: 569-574, 1997.
- 3) Serum thrombopoietin level is mainly regulated by megakaryocyte mass rather than platelet mass in human subjects. *Brit. J. Haematol.* 101: 242-244, 1998.
- 4) Tec is involved in G protein-coupled receptor- and integrin-mediated signalings in human blood platelets. *Oncogene* 16: 2773-2779, 1998.
- 5) Role of GATA-1 in proliferation and differentiation of definitive erythroid and megakaryocytic cells in vivo. *Blood* 92: 434-442, 1998.

小野寺 雅史

略歴: 昭和 61 年 北海道大学医学部卒
平成 6 年 米国国立衛生研究所勤務
平成 10 年 科学技術振興事業団研究員
平成 13 年 筑波大臨床医学系・講師(血液内科)
平成 10 年 日本遺伝子治療学会評議委員

専門: 原発性免疫不全症、小児血液学、遺伝子治療

研究業績:

- 1) Overexpression of retinoic acid receptor alpha suppresses myeloid cell differentiation at the promyelocyte stage. *Oncogene* 11:1291-1298, 1995.
- 2) A simple and reliable method for screening retroviral producer clones without selectable markers. *Hum Gene Ther* 8:1189-1194, 1997.
- 3) Successful peripheral T-lymphocyte-directed gene transfer for a patient with severe combined immunodeficiency caused by adenosine deaminase deficiency. *Blood* 91:30-36, 1998.
- 4) Development of improved adenosine deaminase (ADA) containing retroviral vectors. *J Virol* 72: 1769-1774, 1998.
- 5) Gene therapy for severe combined immunodeficiency caused by adenosine

deaminase deficiency: Improved retroviral vectors for clinical trials. Acta Haematol 101: 89-96, 1999.

小島 寛

略歴： 昭和 59年 筑波大学医学専門学群卒業
平成 2年 筑波大学大学院医学研究科修了
平成 2年 筑波大学臨床医学系・講師(血液内科)
平成 4-5年 Blood Center of Southeastern Wisconsin 研究員
平成 13年 筑波大学臨床医学系・助教授(血液内科)

専門：血液内科学、造血器悪性腫瘍

研究業績：

- 1) Production and characterization of transformed B-lymphocytes expressing the membrane defect of Scott syndrome. J. Clin Invest 94: 2237-2244, 1994.
- 2) Modulation of platelet activation in vitro by thrombopoietin. Thromb Haemost 74: 1541-1545, 1995.
- 3) Aprotinin inhibits plasmin-induced platelet activation during cardiopulmonary bypass. Circulation 96: 569-574, 1997.
- 4) Tec is involved in G protein-coupled receptor- and integrin-mediated signalings in human blood platelets. Oncogene 16: 2773-2779, 1998.
- 5) Priming with G-CSF effectively enhances low-dose Ara-C-induced in vivo apoptosis in myeloid leukemia cells. Exp Hematol 27: 259-265, 1999.

松井 陽

略歴： 昭和 50年 東京大学医学部卒業
昭和 54年 英国 Kins's College Hospital 小児科 Honorary Registrar
昭和 57年 自治医科大学小児科・助手
昭和 58年 自治医科大学小児科・講師
平成 2年 自治医科大学小児科・助教授
平成 9年 筑波大学臨床医学系・教授(小児科)

専門：小児科学、肝臓学、新生児

研究業績

- 1) Loss of circulating hepatitis C virus in children who developed a persistent carrier state after mother-to-baby transmission. Pediatr Res 42: 263-27, 1997.
- 2) Natural course of HGV infection in haemophiliacs. Brit. J. Haematol. 102: 616-621, 1998.
- 3) Persistence and clinical outcome of hepatitis G virus infection in pediatric bone marrow transplant recipients and children treated for hematological malignancy. Blood 93: 721-727, 1999.
- 4) Linkage and association of atopic asthma to markers on chromosome 13 in the Japanese population. Hum Mol Genet 8: 1487-1490, 1999.
- 5) Significant evidence for linkage of febrile seizures to chromosome 5q14-q15. Hum Mol Genet 9: 87-91, 2000.

長谷川 雄一

略歴: 昭和 61 年 筑波大学医学専門学群卒業
平成 5 年 筑波大学臨床医学系・助手
平成 8 年 筑波大学臨床医学系・講師(血液内科)

専門:血液内科学、造血幹細胞移植

研究業績:

- 1) Effects of anti-platelet glycoprotein Ib and/or IIb/IIIa autoantibodies on the size of megakaryocytes in patients with immune thrombocytopenia. Eur J Haematol 55: 152-157, 1995.
- 2) Complement-induced procoagulant alteration of red blood cell membranes with microvesicle formation in paroxysmal nocturnal haemoglobinuria (PNH): implication for thrombogenesis in PNH. Brit. J Haematol 106: 224-231, 1999.
- 3) Hodgkin disease with subsequent transformation to CD30 positive non-Hodgkin lymphoma in six patients. Cancer 85: 970-979, 1999.

向井 陽美

略歴: 平成 2 年 筑波大学医学専門学群卒業
平成 8 年 筑波大学大学院博士課程医学研究科卒業
平成 12 年 筑波大学臨床医学系・講師(血液内科)

専門:血液内科学、造血幹細胞移植

研究業績:

- 1) Major basic protein binding to thrombomodulin potentially contributes to the thrombosis in patients with eosinophilia. Brit J Haematol 90: 892-899, 1995.
- 2) Serum thrombopoietin (TPO) levels in patients with amegakaryocytic thrombocytopenia are much higher than those with immune thrombocytopenic purpura. Thromb Haemost. 76: 675-678, 1996.
- 3) Elevated serum levels of eosinophil major basic protein in patients with myeloproliferative disorders without eosinophilia. Int J Hematol 66: 197-202, 1997.
- 4) High-dose chemotherapy with peripheral blood stem cell rescue in blastoid natural killer cell lymphoma. Leuk Lymphoma. 32: 583-588, 1999.
- 5) Nasal natural killer cell lymphoma in a post-renal transplant patient. Transplantation. 69: 1501-1503, 2000.

須磨崎 亮

略歴: 昭和 52 年 東京医科歯科大学医学部卒業
昭和 58 年 筑波大学臨床医学系・講師
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昭和 63 年 筑波大学臨床医学系・講師

平成 11 年 筑波大学臨床医学系・助教授(小児科)

専門: 感染免疫学、ウイルス感染症、小児血液学、小児肝臓病学
研究業績

- 1) Successful treatment of invasive thoracopulmonary mucormycosis in a patient with acute lymphoblastic leukemia. *Cancer* 76: 895-899, 1995.
- 2) Rapidly progressive hepatitis C in a patient with common variable immunodeficiency. *Eur. J. Pediatr* 155: 532-534, 1996.
- 3) Natural course of HGV infection in haemophiliacs. *Brit. J. Haematol.* 102: 616-621, 1998.
- 4) Transfusion transmitted virus. *The Lancet* 352: 1308-1309, 1998.
- 5) Persistence and clinical outcome of hepatitis G virus infection in pediatric bone marrow transplant recipients and children treated for hematological malignancy. *Blood* 93: 721-727, 1999.

福島 敬

略歴: 昭和 62 年 筑波大学医学専門学群卒業

平成 4 年 茨城西南医療センター病院小児科科長

平成 9 年 茨城県立こども病院小児科医員

平成 12 年 筑波大学臨床医学系・講師(小児科)

専門: 小児科学、血液学(白血病・血液幹細胞移植)

研究業績

- 1) Successful treatment of invasive thoracopulmonary mucormycosis in acute lymphoblastic leukemia. *Cancer* 76: 895-899, 1995.
- 2) Multicolor flow-cytometric, morphologic, and clonogenic analysis of marrow CD10-positive cells in children with leukemia in remission or nonmalignant diseases. *J Pediatric Hematol/Oncol* 20: 222-228, 1998.
- 3) Engraftment of human myelodysplastic syndrome delivered cell line in transgenic severe combined immunodeficient (TG-SCID) mice expressing human GM-CSF and IL-3. *Eur J Haematol* 61: 93-99, 1998.
- 4) Persistence and clinical outcome of hepatitis G virus infection in pediatric bone marrow transplant recipient and children treated for hematological malignancy. *Blood* 93: 721-717, 1999.
- 5) A magnetic resonance abnormality correlating with permeability of blood-brain barrier in a child with chemical meningitis during central nervous system prophylaxis for acute leukemia. *Ann. Hematol.* (in press)

清水 崇史

略歴: 平成 4 年 東海大学医学部卒業

平成 11 年 米国ピッツバーグ大学勤務

平成 13 年 東海大学医学部小児科学教室 助手

平成 15 年 筑波大学臨床医学系 講師

専門 血液学、小児科学

研究業績

- 1) A simple and efficient purification of transduced cells by using green fluorescent protein gene as a selection marker. *Acta Paediatrica Japonica* 40:586-592, 1998.
- 2) Interleukin-12 transduced dendritic cells induce regression of established murine neuroblastoma. *J. Pediatric Surgery* 36:1285-1292, 2001.
- 3) Efficient lentiviral transduction of human cord blood CD34+ cells followed by their expansion and differentiation into dendritic cells. *Experimental Hematology* 29:1210-1217, 2001.
- 4) Interleukin-10 promotes the maintenance of antitumor CD8+ T-cell effector function in situ. *Blood* 98:2143-2151, 2001.

大塚 藤男

経歴： 昭和 49年 東京大学医学部医学科卒業
昭和 50年 東京大学助手
昭和 56年 アメリカ合衆国国立衛生研究所 (NIH)癌研究所
皮膚科訪問研究員
昭和 59年 東京大学医学部・講師
昭和 61年 東京大学医学部・助教授
平成 3年 筑波大学臨床医学系・教授(皮膚科)

専門：高発癌性皮膚疾患、皮膚腫瘍、神経皮膚症候群、皮膚脂質
研究業績

- 1) A novel donor splice site mutation in the C1 inhibitor gene of a patient with type 1 hereditary angioneurotic edema. *J Invest Dermatol* 110: 837-839, 1998.
- 2) Linkage and association of an interleukin 4 gene polymorphism with atopic dermatitis in Japanese families. *J Med Genet* 35: 502-504, 1998.
- 3) Effects of interferons on tumor necrosis factor alpha production from human keratinocytes. *Cytokine* 10: 500-505, 1998.
- 4) A novel gene "Niban" upregulated in renal carcinogenesis: Cloning by the cDNA-amplified fragment length polymorphism approach. *Jpn J Cancer Res* 91: 869-874, 2000.
- 5) Pemphigoid nodularis with IgA autoantibodies against the intercellular domain of desmoglein 1. *Brit J Dermatol* 142: 143-147, 2000.

野口 雅之

略歴： 昭和 57年 筑波大学医学専門学群卒業
昭和 62年 国立がんセンター研究所病理部研究員
平成 4年 国立がんセンター研究所病理部
第3組織病理研究室長
平成 8年 筑波大学基礎医学系・教授(病理学)

専門:人体腫瘍病理学、外科病理学

研究業績:

- 1) DNA methylation and expression of p16INK4A gene in pulmonary adenocarcinoma and anthracosis in background lung. *Int J Cancer (Pred Oncol)* 84: 609-613, 1999.
- 2) Amplotyping of microdissected, methanol fixed lung carcinoma by arbitrarily primed polymerase chain reaction. *Int J Cancer* 89:19-25, 2000.
- 3) Clonal proliferation of B lymphocytes in the germinal center of human reactive lymph nodes: Possibility of overdiagnosis of B cell clonal proliferation. *Diagn Mol Pathol* 9:132-136, 2000.
- 4) Application of the p53 and K-ras gene mutation patterns for cytologic diagnosis of recurrent lung carcinomas. *Cancer (Cancer Cytopathol)* 90:258-263, 2000.
- 5) Loss of heterozygosity on 10q23.3 and mutation of the tumor suppressor gene PTEN in benign endometrial cyst of the ovary: Possible sequence progression from benign endometrial cyst to endometrioid carcinoma and clear cell carcinoma of the ovary. *Cancer Res* (in press).

松井 良樹

略歴:	昭和 46 年	東京医科歯科大学医学部医学科卒業
	昭和 52 年	東京医科歯科大学医学部助手
	昭和 54 年	ハーバード大学医学部病理学リサーチフェロー
	昭和 61 年	ハーバード大学医学部病理学インストラクター
	昭和 61 年	筑波大学臨床医学系・講師
	平成 4 年	筑波大学臨床医学系・助教授(輸血学)

専門:輸血学、臨床血液学、臨床免疫学、膠原病・リウマチ学

研究業績:

- 1) Differential expression of T cell differentiation antigens and major histocompatibility antigens on activated T cells during the cell cycle. *Eur J Immunol.* 16: 248 - 251, 1986.
- 2) Effects of frequent and sustained platelet apheresis on peripheral blood mononuclear cell populations and lymphocyte functions of normal volunteer donors. *Transfusion* 26: 446 - 452, 1986.
- 3) Interferon-gamma modulates messenger RNA levels of c-sis (PDGF- β chain), PDGF- α chain, and IL-1 β genes in human vascular endothelial cells. *Am J Pathology* 134: 35 - 43, 1989.
- Characterization of genomic polymorphism of an activation-associated antigen, Blast-1. *Immunogenetics* 31: 188 - 190, 1990.
- Interleukin-1 receptor antagonist gene polymorphism in Japanese patients with systemic lupus erythematosus. *Arthritis and Rheumatism* 40: 389-390, 1997.

大津 真

略歴： 平成元年 北海道大学医学部医学科卒業
平成 5年 癌研究会化学療法センター分子生物治療研究部
研究員
平成 10年 米国国立衛生研究所、NHGRI, Visiting Fellow
平成 14年 財団法人医療機器センターリサーチレジデント
(受入研究機関：北海道大学大学院医学研究科遺
伝子治療講座
平成 15年 筑波大学臨床医学系・講師

専門：血液学、小児科学、免疫学

研究業績：

- 1) Otsu M, Hershfield MS, Tuschong LM, Muul LM, Onodera M, Ariga T, Sakiyama Y, Candotti F. Flow cytometry analysis of adenosine deaminase (ADA) expression: a simple and reliable tool for the assessment of ADA-deficient patients before and after gene therapy. *Hum Gene Ther.* 2002;13:425-432.
- 2) Otsu M, Sugamura K, Candotti F. Lack of dominant-negative effects of a truncated gamma(c) on retroviral-mediated gene correction of immunodeficient mice. *Blood.* 2001;97:1618-1624.
- 3) Otsu M, Anderson SM, Bodine DM, Puck JM, O'Shea JJ, Candotti F. Lymphoid development and function in X-linked severe combined immunodeficiency mice after stem cell gene therapy. *Mol Ther.* 2000;1:145-153.
- 4) Otsu M, Sugamura K, Candotti F. In vivo competitive studies between normal and common gamma chain-defective bone marrow cells: implications for gene therapy. *Hum Gene Ther.* 2000;11:2051-2056.
- 5) Ohtsu M, Sakai N, Fujita H, Kashiwagi M, Gasa S, Shimizu S, Eguchi Y, Tsujimoto Y, Sakiyama Y, Kobayashi K, Kuzumaki N. Inhibition of apoptosis by the actin-regulatory protein gelsolin. *EMBO J.* 1997;16:4650-4656.

金子 新

略歴： 平成 7年 筑波大学医学専門学群卒業
平成 10年 筑波大学医学研究科

専門：血液内科学、造血器悪性腫瘍、遺伝子治療
研究業績：

- 1) Down-regulation of CXCR4 by human herpesvirus 6 (HHV-6) and HHV-7. *J Immunol* 162: 5417-5422, 1999.
- 2) Fas-independent and nonapoptotic cytotoxicity mediated by a human CD4(+)T-cell clone directed against an acute myelogenous leukemia-associated DEK-CAN fusion peptide. *Blood* 93: 925-935, 1999.
- 3) CD4(+) cytotoxic T-cell clones specific for bcr-abl b3a2 fusion peptide augment. *Blood* 92: 3355-3361, 1998.
- 4) Simplified Retroviral Vector GCsap with Murine Stem Cell Virus Long Terminal Repeat Allows High and Continued Expression of Enhanced Green Fluorescent

Protein by Human Hematopoietic Progenitors Engrafted in Nonobese Diabetic/Severe Combined Immunodeficient Mice. Hum Gene Ther 12: 35-44, 2001

中内 啓光

略歴: 昭和 53 年 横浜市立大学医学部卒業
昭和 58 年 スタンフォード大学医学部研究員
昭和 59 年 順天堂大学医学部免疫学講座助手・講師
昭和 62 年 理化学研究所ライフサイエンス筑波研究センター研究員・チームリーダー
平成 5 年- 筑波大学基礎医学系・教授(免疫)
平成 5 年- 日本遺伝子治療学会幹事・評議委員
平成 14 年 東京大学医科学研究所・教授

専門:免疫学、血液学

研究業績:

- 1) Retrovirus-mediated gene transfer of human pyruvate kinase (PK) cDNA into murine hematopoietic cells: Implications for gene therapy of human PK deficiency. Blood 83: 2305-2310, 1994.
 - 2) Presence of hematopoietic stem cells in the adult liver. Nature Medicine 2: 198-203, 1996.
 - 3) Loss of ganciclovir sensitivity by exclusion of thymidine kinase gene from transplanted proinsulin-producing fibroblasts as a gene therapy model for diabetes. Gene Therapy 3: 230-234, 1996.
 - 4) Long-term lymphohematopoietic reconstitution by a single CD34 negative hematopoietic stem cell. Science 273: 242-245, 1996.
- The hematopoietic stem cells. Are they CD34 positive or CD34 negative? News and Views. Nature Medicine 4:1009-1010, 1998.

坂巻 壽

略歴:昭和 49 年 東京医科歯科大学医学部卒業
昭和 50 年 東京都立墨東病院 内科伝染科医員
昭和 55 年 獨協医科大学第三内科 助手
昭和 58 年 獨協医科大学第三内科 講師
昭和 61 年 東京都立駒込病院 内科医長
平成 10 年 東京都立駒込病院 内科部長

専門:血液内科学、造血幹細胞移植

研究業績:

- 1) Rapid detection cytomegalovirus pneumonia in recipients of bone marrow transplant: evaluation and comparison of five survey methods for bronchoalveolar lavege fluid. Bone Marrow Transplant 17: 855-860, 1996.
- 2) Comparison of cytomegalovirus (CMV) antigenemia and CMV in

- bronchoalveolar lavage fluid for diagnosis of CMV pulmonary infection after bone marrow transplantation. Bone Marrow Transplant 20: 143-147, 1997.
- 3) Risk factors for hepatic veno-occlusive disease after bone marrow transplantation: retrospective analysis of 137 cases at a single institution. Bone Marrow Transplant 20: 397-402, 1997.
 - 4) Plasma thrombopoietin (TPO) levels and expression of TPO receptor on platelets in patients with myelodysplastic syndromes. Brit J Haematol 103: 778-784, 1998.
 - 5) Augmented proliferation of human alveolar macrophages after allogeneic bone marrow transplantation. Blood 93: 667-673, 1999.

大橋 一輝

略歴: 平成 4年 東京医科歯科大学大学院博士課程内科学系修了
 平成 6年 東京医科歯科大学第一内科助手
 平成 9年 東京都立駒込病院血液内科医員

専門: 血液内科学、造血幹細胞移植

研究業績:

- 1) Primary structure of human thromboxane synthase determined from the cDNA sequence. J Biol Chem 267: 789-793, 1992.
- 2) Enhanced prostacyclin synthesis in endothelial cells by retrovirus-mediated gene transfer of prostaglandin H synthase cDNA. J Clin Invest 91: 1843-1849, 1993.
- 3) Characterization of the promoter region of human BCL6 gene. Biochem Biophys Res Commun 214: 461-467, 1995.
- 4) Molecular remission in adult T cell leukemia after autologous CD34+ peripheral blood stem cell transplantation. Bone Marrow Transplant 24: 219-221, 1999.
- 5) Mannose trimming targets mutant α 2-plasmin inhibitor for degradation by the protease. J Biol Chem 275: 4981-4987, 2000.

土田 昌宏

略歴: 昭和 47年 東京大学医学部卒業
 昭和 51年 シンシナチ大学小児病院クリニカルフェロー
 昭和 53年 虎の門病院小児科医員
 昭和 55年 東邦大学小児科助手
 昭和 61年 茨城県立こども病院小児科部長
 平成 6年 同医務局次長

専門: 小児科学一般、小児血液腫瘍学、小児病理学、造血幹細胞移植研究業績:

- 1) Therapy related acute leukemia associated with t(11q23) after primary acute myeloid leukemia: A report of two cases. Blood 86: 3613-3617, 1995.
- 2) Translocation in Myelodysplastic Syndrome Fuses the MLL Gene to the CGP Gene. Blood 89: 384-3850, 1997.
- 3) Myelodysplastic Syndrome and Acute Myelogenous Leukemia as a Late Clonal

- Complication in Children With Acquired Aplastic Anemia. *Blood* 90: 1009-1013, 1997.
- 4) Gianotti-Crosti syndrome associated with unrelated donor bone marrow transplantation. *Bone Marrow Transplantation* 20: 691-693, 1997.
 - 5) Multicolor flow-cytometric, morphologic, and clonogenic analysis of marrow CD10-positive cells in children with leukemia in remission or nonmalignant diseases. *J. Pediatr Hematol/Oncol* 20: 222-228, 1998.

小池 和俊

略歴: 昭和 61 年 筑波大学医学専門学群卒、小児科研修医
平成 5 年 茨城県立こども病院小児科医員

専門: 小児科学、小児血液腫瘍学、造血幹細胞移植
研究業績:

- 1) Gianotti-Crosti syndrome associated with unrelated donor bone marrow transplantation. *Bone Marrow Transplantation*. 20: 691-693, 1997.
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