Department of Obstetrics and Gynecology

Outline and Research Objectives

The goal we aim at is the improvement of holistic women's health. To achieve it, we integrate all the knowledge in the field of reproductive medicine, perinatal medicine and gynecological oncology, which has been established on the basis of our history more than hundred years, and will develop them.

Faculties and Students

Professor and Chair	Yuji Taketani, MD, PhD (from 1994)
Associate Professor	Shiro Kozuma
Lecturer	Toshiyuki Kojima
	Koji Kugu

Associate.....15
Postdoctoral Fellow 2
Graduate Student.....2
Research Student 15
Secretary 2

Past Research and Major Accomplishments

Professor Taketani has led the clinical and basic research on reproductive endocrinology in Japan. Especially, he is the distinguished leader in the research field of endometriosis, and has achieved many valuable studies. He has also conducted the research which went into the broad range in obstetrics and gynecology by his prominent leadership in the department. There are more than 250 papers which he directed in these two decades.

Current Research

We have a highly organized infertility clinic, where every patient is systemically examined and after diagnosis of underlying infertility factor(s) appropriate treatment is performed following our protocol. Once it turns out higher level of treatment is necessary, ART is applied to such cases. We have been engaged in in vitro fertilization and embryo transfer (IVF-ET) as a main axis of ART for fifteen years. Conventional IVF-ET is mainly indicated to cases with tubal factor, mild male factor, immunological factor or of unexplained infertility factor. In case of severe male factor or other fertilization disorder intracytoplasmic sperm injection (ICSI) is performed. Now we have about 300 cases of IVF-ET every year, which conventional IVF-ET and ICSI share almost equally. The pregnancy rate of conventional IVF-ET is around 25% per embryo transfer cycle, which is comparable with that of ICSI. Other ART techniques such as embryo cryopreservation and assisted zona hatching are also under way.

Total number of delivery cases is 426 per year. Recently cases of obstetrical emergencies like abruptio placentae, eclampsia and uterine ruptures transported from neighboring hospitals have been increasing. Our service is an important part of Tokyo Metropolitan Service System for Maternal Welfare and Perinatal Medicine.

Primary care for peri/post-menopausal women is becoming more and more important. We have already established the primary care system for women focusing on climacteric syndrome and osteoporosis. Hormone replacement therapy (HRT) is employed for the purpose.

In basic research section, a couple of projects as follows are under way, some of which have already yielded interesting findings; 1) the mechanism of folliculogenesis and follicular apoptosis in the ovary, 2) the functions of gynecologic hormones such as gonadotropins and ovarian steroids, 3) the biochemical evaluation of early embryos and establishment of a new procedure of embryo cryopreservation, 4) the genetic mechanism in gamete formation and development and 5) effect of sex steroid on bone metabolism.

Future Prospects

To improve the pregnancy rate in the infertility clinic, the basic research on both the embryo and the endometrium, ovarian function and its regulatory mechanism must be proceed. To take the precautions in the infertility treatment, the development of the safe protocol and secure system is also demanded.

The validity of hormone replacement therapy for managing peri/post-menopausal women is becoming a subject of discussion. To seek the answer this problem, we are studying on the various protocols in clinical and by experiments.

In the obstetrical field, the researches on the immunological feto-maternal interaction are going on.

In vivo study of fetal physiology using sheep model are in progress, expected to provide valuable knowledge for clinical field.

Research Grants

Grant-in-Aid for Scientific Research, Japan Society for the Promotion of Science: Scientific Research (A) "Mechanism of conception in terms of embryo-maternal interaction" (1999-2001)

Grant-in-Aid for Scientific Research, Japan Society for the Promotion of Science: Scientific Research (B) "Risk factors associated with progression and recurrence of endometriosis" (2000-2002)

Grant-in-Aid for Scientific Research, Ministry of Health and Welfare: "Status of endometriosis in Japan in terms of reproductive health" (1998)

Grant-in-Aid for Scientific Research, Ministry of Health, Labor and Welfare: "Strategy for reproductive health-keeping of women with menstrual disorders" (1999-2000)

Grant-in-Aid for Scientific Research, Ministry of Health, Labor and Welfare: "Status of reproductive health of women with reproductive disorders in the society" (2001-2002)

Select Publications (most recent 50 papers)

1. Hiroi H, Momoeda M, Yamauchi N, Abe Y, Yoshikawa H, Tsutsumi O and Taketani Y. An earlier menopause as clinical manifestation of granulosa-cell tumor: a case report. J Obstet Gynaecol Res 26, 9-12, 2000.
2. Hyodo H, Ishikawa Y, Tsuneyama H, Kashiwase K, Toyoda C, Uchikawa M, Akaza T, Fujii T, Kozuma S, Taketani Y and Juji T. New RhD(IVb) identified in Japanese. Vox Sang 79, 116-7, 2000.
3. Hyodo H, Ishikawa Y, Kashiwase K, Ogawa A, Watanabe Y, Tsuneyama H, Toyoda C, Uchikawa M, Akaza T, Fujii T, Kozuma S, Taketani Y and Juji T. Polymorphisms of RhD(Va) and a new RhD(Va)-like variant found in Japanese individuals. Vox Sang 78, 122-5, 2000.
4. Kamei Y, Takeda Y, Teramoto K, Tsutsumi O, Taketani Y and Watanabe K. Human NB-2 of the contactin subgroup molecules: chromosomal localization of the gene (CNTN5) and distinct expression pattern from other subgroup members. Genomics 69, 113-9, 2000.
5. Koga K, Osuga Y, Tsutsumi O, Okagaki R, Momoeda M, Yano T, Fujiwara T, Takai Y, Kugu K, Morita Y and Taketani Y. Increased concentrations of soluble tumour necrosis factor receptor (sTNFR) I and II in peritoneal fluid from women with endometriosis. Mol Hum Reprod 6, 929-33, 2000.
6. Koga K, Osuga Y, Tsutsumi O, Momoeda M, Suenaga A, Kugu K, Fujiwara T, Takai Y, Yano T and Taketani Y. Evidence for the presence of angiogenin in human follicular fluid and the up-regulation of its production by human chorionic gonadotropin and hypoxia. J Clin Endocrinol Metab 85, 3352-5, 2000.
7. Kuroda K, Kamei Y, Kozuma S, Kikuchi A, Fujii T, Unno N, Baba K and Taketani Y. Cephalopagus conjoined twins. Ultrasound Obstet Gynecol 16, 293, 2000.
8. Kuroda K, Kamei Y, Kozuma S, Kikuchi A, Fujii T, Unno N, Baba K and Taketani Y. Prenatal evaluation of cephalopagus conjoined twins by means of three-dimensional ultrasound at 13 weeks of pregnancy. Ultrasound Obstet Gynecol 16, 264-6, 2000.
9. Matsumi H, Yano T, Osuga Y, Kugu K, Tang X, Xu JP, Yano N, Kurashima Y, Ogura T, Tsutsumi O, Koji T, Esumi H and Taketani Y. Regulation of nitric oxide synthase to promote cytostasis in ovarian follicular development. Biol Reprod 63, 141-6, 2000.
10. Matsumoto K, Yoshikawa H, Nakagawa S, Tang X, Yasugi T, Kawana K, Sekiya S, Hirai Y, Kukimoto I, Kanda T and Taketani Y. Enhanced oncogenicity of human papillomavirus type 16 (HPV16) variants in Japanese population. Cancer Lett 156, 159-65, 2000.
11. Matsumoto K, Kawana K, Yoshikawa H, Taketani Y, Yoshiike K and Kanda T. DNA vaccination of mice with plasmid expressing human papillomavirus 6 major capsid protein L1 elicits type-specific antibodies neutralizing pseudovirions constructed in vitro. J Med Virol 60, 200-4, 2000.
12. Miki A, Fujii T, Ishikawa Y, Hamai Y, Yamashita T, Tadokoro K, Kozuma S, Juji T and Taketani Y. Immunotherapy prevents recurrent abortion without influencing natural killer receptor status. Am J Reprod Immunol 43, 98-106, 2000.
13. Nakagawa S, Yoshikawa H, Yasugi T, Kimura M, Kawana K, Matsumoto K, Yamada M, Onda T and Taketani Y. Ubiquitous presence of E6 and E7 transcripts in human papillomavirus-positive cervical carcinomas regardless of its type. J Med Virol 62, 251-8, 2000.
14. Osuga Y, Koga K, Tsutsumi O, Igarashi T, Okagaki R, Takai Y, Matsumi H, Hiroi H, Fujiwara T, Momoeda M, Yano T and Taketani Y. Stem cell factor (SCF) concentrations in peritoneal fluid of women with or without endometriosis. Am J Reprod Immunol 44, 231-5, 2000.
15. Wang Y, Yano T, Kikuchi A, Yano N, Matsumi H, Ando K, Kasai Y, Watanabe M, Okagaki R, Osuga Y and Taketani Y. Comparison of the effects of add-back therapy with various natural oestrogens on bone metabolism in rats administered a long-acting gonadotrophin-releasing hormone agonist. J Endocrinol 165, 467-73, 2000.
16. Yano T, Radulovic S, Osuga Y, Kugu K, Yoshikawa H, Taketani Y and Schally AV. Inhibition of human epithelial ovarian cancer cell growth in vitro by somatostatin analog RC-160. Oncology 59 Suppl 1, 45-9, 2000.
17. Yoshida S, Unno N, Kagawa H, Shinozuka N, Kozuma S and Taketani Y. Prenatal detection of a high-risk group for intrauterine growth restriction

based on sonographic fetal biometry. Int J Gynaecol Obstet 68, 225-32, 2000.
18. Yoshikawa H, Jimbo H, Okada S, Matsumoto K, Onda T, Yasugi T and Taketani Y. Prevalence of endometriosis in ovarian cancer. Gynecol Obstet Invest 50 Suppl 1, 11-7, 2000.
19. Hiroi H, Kugu K, Hoshino H, Kozuma S and Taketani Y. Hyperemesis gravidarum associated with thyrotoxicosis and a past history of an eating disorder. Arch Gynecol Obstet 265, 228-30, 2001.
20. Hiroi H, Yasugi T, Matsumoto K, Fujii T, Watanabe T, Yoshikawa H and Taketani Y. Mucinous adenocarcinoma arising in a neovagina using the sigmoid colon thirty years after operation: a case report. J Surg Oncol 77, 61-4, 2001.
21. Kanai T, Fujii T, Keicho N, Tokunaga K, Yamashita T, Hyodo H, Miki A, Unno N, Kozuma S and Taketani Y. Polymorphism of human leukocyte antigen-E gene in the Japanese population with or without recurrent abortion. Am J Reprod Immunol 45, 168-73, 2001.
22. Kanai T, Fujii T, Unno N, Yamashita T, Hyodo H, Miki A, Hamai Y, Kozuma S and Taketani Y. Human leukocyte antigen-G-expressing cells differently modulate the release of cytokines from mononuclear cells present in the decidua versus peripheral blood. Am J Reprod Immunol 45, 94-9, 2001.
23. Kanai T, Fujii T, Kozuma S, Yamashita T, Miki A, Kikuchi A and Taketani Y. Soluble HLA-G influences the release of cytokines from allogeneic peripheral blood mononuclear cells in culture. Mol Hum Reprod 7, 195-200, 2001.
24. Kawana K, Kawana Y, Yoshikawa H, Taketani Y, Yoshiike K and Kanda T. Nasal immunization of mice with peptide having a cross-neutralization epitope on minor capsid protein L2 of human papillomavirus type 16 elicit systemic and mucosal antibodies. Vaccine 19, 1496-502, 2001.
25. Kawana Y, Kawana K, Yoshikawa H, Taketani Y, Yoshiike K and Kanda T. Human papillomavirus type 16 minor capsid protein l2 N-terminal region containing a common neutralization epitope binds to the cell surface and enters the cytoplasm. J Virol 75, 2331-6, 2001.
26. Koga K, Osuga Y, Tsutsumi O, Yano T, Yoshino O, Takai Y, Matsumi H, Hiroi H, Kugu K, Momoeda M, Fujiwara T and Taketani Y. Demonstration of angiogenin in human endometrium and its enhanced expression in endometrial tissues in the secretory phase and the decidua. J Clin Endocrinol Metab 86, 5609-14, 2001.
27. Kugu K, Momoeda M, Sharma SS, Osuga Y, Fujiwara T, Okagaki R, Fukushima H, Yano T, Tsutsumi O and Taketani Y. Is an elevation in basal follicle-stimulating hormone levels in unexplained infertility predictive of fecundity regardless of age: Endocr J 48, 711-5, 2001.
28. Marumo G, Kozuma S, Ohyu J, Hamai Y, Machida Y, Kobayashi K, Ryo E, Unno N, Fujii T, Baba K, Okai T, Takashima S and Taketani Y. Generation of periventricular leukomalacia by repeated umbilical cord occlusion in near-term fetal sheep and its possible pathogenetical mechanisms. Biol Neonate 79, 39-45, 2001.
29. Minaguchi T, Yoshikawa H, Oda K, Ishino T, Yasugi T, Onda T, Nakagawa S, Matsumoto K, Kawana K and Taketani Y. PTEN mutation located only outside exons 5, 6, and 7 is an independent predictor of favorable survival in endometrial carcinomas. Clin Cancer Res 7, 2636-42, 2001.
30. Osuga Y, Koga K, Tsutsumi O, Yano T, Kugu K, Momoeda M, Okagaki R, Suenaga A, Fujiwara T, Fujimoto A, Matsumi H, Hiroi H and Taketani Y. Evidence for the presence of keratinocyte growth factor (KGF) in human ovarian follicles. Endocr J 48, 161-6, 2001.
31. Ryo E, Shiotsu H, Takai Y, Tsutsumi O, Okai T, Taketani Y and Takeuchi Y. Effects of pulsed ultrasound on development and glucose uptake of preimplantation mouse embryos. Ultrasound Med Biol 27, 999-1002, 2001.
32. Ryo E, Yorinaga Y, Nagasaka T, Yoshikawa H and Taketani Y. Tumor cell spillage to the vaginal cavity and vaginal stump during the surgery of endometrial carcinoma. Acta Obstet Gynecol Scand 80, 364-7, 2001.
33. Tsuchiya F, Ikeda K, Tsutsumi O, Hiroi H, Momoeda M, Taketani Y, Muramatsu M and Inoue S. Molecular cloning and characterization of mouse EBAG9, homolog of a human cancer associated surface antigen: expression and regulation by estrogen. Biochem Biophys Res Commun 284, 2-10, 2001.
34. Uemura H, Unno N, Osuga Y, Momoeda M, Ando K, Marumo G, Kikuchi A, Fujii T, Kozuma S and Taketani Y. A movable gestational sac in association with a myometrial defect. Ultrasound Obstet Gynecol 18, 675-7, 2001.
35. Xin CY, Matsumoto K, Yoshikawa H, Yasugi T, Onda T, Nakagawa S, Yamada M, Nozawa S, Sekiya S, Hirai Y, Shiromizu K, Fujii T and Taketani Y. Analysis of E6 variants of human papillomavirus type 33, 52 and 58 in Japanese women with cervical intraepithelial neoplasia/cervical cancer in relation to their oncogenic potential. Cancer Lett 170, 19-24, 2001.
36. Yoshida SH, Unno N, Kagawa H, Shinozuka N, Kozuma S and Taketani Y. Sonographic determination of fetal size from 20 weeks of gestation onward correlates with birth weight. J Obstet Gynaecol Res 27, 205-11, 2001.
37. Yoshino O, Osuga Y, Koga K, Tsutsumi O, Yano T, Fujii T, Kugu K, Momoeda M, Fujiwara T, Tomita K and Taketani Y. Evidence for the expression of interleukin (IL)-18, IL-18 receptor and IL-18 binding protein in the human endometrium. Mol Hum Reprod 7, 649-54, 2001.
38. Fujimoto A, Osuga Y, Yano T, Kusumi M, Kurosawa T, Fujii T and Taketani Y. Ovarian hyperstimulation syndrome complicated by peritonitis due to perforated appendicitis. Hum Reprod 17, 966-7, 2002.

39. Hashimoto K, Kato K, Imamura K, Kishimoto A, Yoshikawa H, Taketani Y and Esumi H. 5-amino-4-imidazolecarboxamide riboside confers strong tolerance to glucose starvation in a 5'-AMP-activated protein kinase-dependent fashion. Biochem Biophys Res Commun 290, 263-7, 2002.
40. Hasumi Y, Mizukami H, Urabe M, Kohno T, Takeuchi K, Kume A, Momoeda M, Yoshikawa H, Tsuruo T, Shibuya M, Taketani Y and Ozawa K. Soluble FLT-1 expression suppresses carcinomatous ascites in nude mice bearing ovarian cancer. Cancer Res 62, 2019-23, 2002.
41. Hiroi H, Osuga Y, Tarumoto Y, Shimokama T, Yano T, Yokota H and Taketani Y. A case of estrogen-producing Brenner tumor with a stromal component as a potential source for estrogen. Oncology 63, 201-4, 2002.
42. Horie K, Tomida A, Sugimoto Y, Yasugi T, Yoshikawa H, Taketani Y and Tsuruo T. SUMO-1 conjugation to intact DNA topoisomerase I amplifies cleavable complex formation induced by camptothecin. Oncogene 21, 7913-22, 2002.
43. Kawana K, Yasugi T, Kanda T, Kawana Y, Hirai Y, Yoshikawa H and Taketani Y. Neutralizing antibodies against oncogenic human papillomavirus as a possible determinant of the fate of low-grade cervical intraepithelial neoplasia. Biochem Biophys Res Commun 296, 102-5, 2002.
44. Matsumoto K, Yoshikawa H, Yasugi T, Onda T, Nakagawa S, Yamada M, Kawana K, Minaguchi T, Oda K, Hasumi Y and Taketani Y. Distinct lymphatic spread of endometrial carcinoma in comparison with cervical and ovarian carcinomas. Cancer Lett 180, 83-9, 2002.
45. Momoeda M, Taketani Y, Terakawa N, Hoshiai H, Tanaka K, Tsutsumi O, Osuga Y, Maruyama M, Harada T, Obata K and Hayashi K. Is endometriosis really associated with pain? Gynecol Obstet Invest 54 Suppl 1, 18-23, 2002.
46. Okada S, Tsuda H, Takarabe T, Yoshikawa H, Taketani Y and Hirohashi S. Allelotype Analysis of Common Epithelial Ovarian Cancers with Special Reference to Comparison between Clear Cell Adenocarcinoma with Other Histological Types. Jpn J Cancer Res 93, 798-806, 2002.
47. Osuga Y, Yano T, Kugu K, Koga K, Fukuoka K, Matsumi H, Wada O, Kikuchi A, Tsutsumi O and Taketani Y. Effects of gonadotropin-releasing hormone analog treatment on skin condition. Gynecol Endocrinol 16, 57-61, 2002.
48. Tang X, Yano T, Osuga Y, Matsumi H, Yano N, Xu J, Wada O, Koga K, Kugu K, Tsutsumi O, Schally AV and Taketani Y. Cellular mechanisms of growth inhibition of human epithelial ovarian cancer cell line by LH-releasing hormone antagonist Cetrorelix. J Clin Endocrinol Metab 87, 3721-7, 2002.
49. Xu J, Osuga Y, Yano T, Morita Y, Tang X, Fujiwara T, Takai Y, Matsumi H, Koga K, Taketani Y and Tsutsumi O. Bisphenol A induces apoptosis and G2-to-M arrest of ovarian granulosa cells. Biochem Biophys Res Commun 292, 456-62, 2002.
50. Zhang SQ, Kozuma S, Tanaka M, Ling D, Kitano Y, Fujii T, Baba K and Taketani Y. Studies on fetal forelimb movements by using a wrist actigraph in sheep. Psychiatry Clin Neurosci 56, 283-4, 2002.

Department of Gynecologic Surgery

Outline and Research Objectives

Our department was established for development of effective and safe gynecologic surgery on the basis of knowledge in reproductive medicine and gynecologic oncology.

Faculties and Students

Professor and Chair:	Osamu Tsutsumi, MD, PhD (from 2001)
Associate Professor:	Tetsu Yano
Lecturer:	Osamu Nishii
	Tomoyuki Fujii

Associate: 2
Postdoctoral Fellow: 2
Graduate Student:.....2
Research Student: 5
Secretary: 2

Past Research and Major Accomplishments

Professor Tsutsumi has been very actively working on both clinical and basic research in our department even before becoming Professor in 2001. In the clinical field, he conducted endoscopic surgery as the first person in gynecology. As for the basic research, many achievements were left so far in the embryogenesis, the genetics and the reproductive endocrinology.

Current Research

For the benign gynecological disorders, we have been constantly trying to minimize surgical invasion to patients as much as possible. With both of well-equipped instruments and well-trained expertise, more than 90% of surgeries for benign gynecological disorders are operated endoscopically, which make a total of 300 cases per year. On the other hand, various projects concerning treatment of gynecological malignancies and sexually transmitted viral infections are on-going. To improve the prognosis of gynecological malignancy, we are conducting the studies, including 1) Prognostic significance of pelvic and paraaortic lumphnode metastasis in the uterine cervical cancer, 2) application of chemotherapy (BLM + VCR + MMC + CDDP) for advanced or recurrent cervical cancer, 3) incidence and distribution of PLN and PALN metastasis in endometrial cancer, 4) relationship between the presence of estrogen and progesterone receptor and clinical course in endometrial cancer, 5) development of optimal surgical procedure for advanced ovarian cancer, 6) impacts of aggressive debulking (including bowel resection) on the prognosis of advanced ovarian cancer, 7) analysis of long term prognosis of ovarian cancer patients treated with paclitaxel containing chemotherapy, 8) analysis of adverse effects of CDDP-based chemotherapy, focused on nephrotoxicity and neurotoxicity, 9) effect of intermittent consolidation chemotherapy for advanced ovarian cancer, 10) evaluation of sensitivity and specificity of serum CA125 level assay and ultrasonographic follow-up for diagnosis of recurrent ovarian cancer, 11) trans-arterial chemotherapy for parenchymal liver metastasis of ovarian cancer, 12) estimation of effects of a combination chemotherapy (hydroxyurea + etoposide + DTIC) for uterine sarcomas, 13) cohort study of low-grade CIN.

In basic research section, the studies are on going on the effect of endocrine disrupters on the reproductive system, embryogenesis and oncogenesis.

Future Prospects

As well as proceeding the studies mentioned above, we are starting the project on developing vaccine against HPVs, using neutralizing epitope of HPV-16 capsid proteins L1 and L2 (L1/L2 capsids).

Research Grants

1. Grant-in-Aid for Core Research for Evolutional Science and Technology, Japan Science and Thechnology Corporation: "Effect of endocrine disrupters on reproductive functions " (1998-2003)
2. Grant-in-Aid for Scientific Research, Japan Society for the Promotion of Science: Scientific Research (B) "Effect of endocrine disrupters on reproductive functions" (1999-2001)
3. Grant-in-Aid for Scientific Research, Japan Society for the Promotion of Science: Scientific Research (B) "Effect of endocrine disrupters on reproductive functions" (2002-2004)
4. Grant-in-Aid for Scientific Research, Ministry of Health, Labor and Welfare: "Effect of endocrine disrupters on reproductive health" (1998-2000)

5. Grant-in-Aid for Scientific Research, Ministry of Health, Labor and Welfare: "Effect of endocrine disrupters on reproductive health" (2001-2002)

Select Publications

1. Tsutsumi O, Kurachi H and Oka T. A physiological role of epidermal growth factor in male reproductive function. Science 233, 975-7, 1986.
2. Tsutsumi O, Kubota Y and Oka T. Effect of sialoadenectomy, treatment with epidermal growth factor (EGF) antiserum and replacement of EGF on the epidermis in mice. J Endocrinol 113, 193-7, 1987.
3. Tsutsumi O and Oka T. Epidermal growth factor deficiency during pregnancy causes abortion in mice. Am J Obstet Gynecol 156, 241-4, 1987.
4. Tsutsumi O, Tsutsumi A and Oka T. Importance of epidermal growth factor in implantation and growth of mouse mammary tumor in female nude mice. Cancer Res 47, 4651-3, 1987.
5. Tsutsumi O, Tsutsumi A and Oka T. A possible physiological role of milk epidermal growth factor in neonatal eyelid opening. Am J Physiol 252, R376-9, 1987.
6. Tsutsumi O, Tsutsumi A and Oka T. Epidermal growth factor-like, corneal wound healing substance in mouse tears. J Clin Invest 81, 1067-71, 1988.
7. Tsutsumi O, Yano T, Satoh K, Mizuno M and Kato T. Studies of hexokinase activity in human and mouse oocyte. Am J Obstet Gynecol 162, 1301-4, 1990.
8. Tsutsumi O, Satoh K, Taketani Y and Kato T. Determination of enzyme activities of energy metabolism in the maturing rat oocyte. Mol Reprod Dev 33, 333-7, 1992.
9. Sadatsuki M, Tsutsumi O, Yamada R, Muramatsu M and Taketani Y. Local regulatory effects of activin A and follistatin on meiotic maturation of rat oocytes. Biochem Biophys Res Commun 196, 388-95, 1993.
10. Sadatsuki M, Tsutsumi O, Sakai R, Eto Y, Hayashi N and Taketani Y. Presence and possible function of activin-like substance in human follicular fluid. Hum Reprod 8, 1392-5, 1993.
11. Tsutsumi O, Iida T, Hakuno N, Sadatsuki M, Okai T, Taketani Y, Nagafuchi S and Nakahori Y. Y chromosome analysis and laparoscopic surgery in XY pure gonadal dysgenesis: a case report and a review of literature. Asia Oceania J Obstet Gynaecol 19, 95-9, 1993.
12. Tsutsumi O, Taketani Y and Oka T. The uterine growth-promoting action of epidermal growth factor and its function in the fertility of mice. J Endocrinol 138, 437-44, 1993.
13. Tsutsumi O, Taketani Y and Oka T. Evidence for the involvement of epidermal growth factor in fertility decline in aging female mice. Horm Res 39 Suppl 1, 32-6, 1993.
14. Ayabe T, Tsutsumi O and Taketani Y. Hexokinase activity in mouse embryos developed in vivo and in vitro. Hum Reprod 9, 347-51, 1994.
15. Morita Y, Tsutsumi O and Taketani Y. In vitro treatment of embryos with epidermal growth factor improves viability and increases the implantation rate of blastocysts transferred to recipient mice. Am J Obstet Gynecol 171, 406-9, 1994.
16. Tsutsumi O, Iida T, Taketani Y, Sugase M, Nakahori Y and Nakagome Y. Intact sex determining region Y (SRY) in a patient with XY pure gonadal dysgenesis and a twin brother. Endocr J 41, 281-5, 1994.
17. Tsutsumi O, Yano T and Taketani Y. Phosphofructokinase activity as a measure of maturation of rat oocytes developed in vivo and in vitro. Horm Res 41 Suppl 1, 63-7, 1994.
18. Morita Y, Tsutsumi O and Taketani Y. Successful treatment of catamenial pneumothorax with danazol. Int J Gynaecol Obstet 51, 263-4, 1995.
19. Tsutsumi O, Iida T and Taketani Y. Laparoscopic surgery and DNA analysis in patients with XY pure gonadal dysgenesis. J Obstet Gynaecol 21, 67-74, 1995.
20. Morita Y, Tsutsumi O, Kuramochi K, Momoeda M, Yoshikawa H and Taketani Y. Successful laparoscopic management of primary abdominal pregnancy. Hum Reprod 11, 2546-7, 1996.
21. Takai Y, Ogawara M, Tomono Y, Moritoh C, Imajoh-Ohmi S, Tsutsumi O, Taketani Y and Inagaki M. Mitosis-specific phosphorylation of vimentin by protein kinase C coupled with reorganization of intracellular membranes. J Cell Biol 133, 141-9, 1996.
22. Tsutsumi O, Iida T, Nakahori Y and Taketani Y. Analysis of the testis-determining gene SRY in patients with XY gonadal dysgenesis. Horm Res 46 Suppl 1, 6-10, 1996.
23. Tsutsumi O and Yoshimura Y. Sex differentiation and ovarian function. An overview. Horm Res 46 Suppl 1, 1-5, 1996.
24. Kawana K, Yoshikawa H, Yokota H, Onda T, Nakagawa K, Tsutsumi O and Taketani Y. Successful treatment of brain metastases from ovarian cancer using gamma-knife radiosurgery. Gynecol Oncol 65, 357-9, 1997.
25. Morita Y, Tsutsumi O and Taketani Y. Successful hormonal treatment of pulmonary parenchymal endometriosis. Int J Gynaecol Obstet 59, 61-3, 1997.
26. Morita Y, Tsutsumi O, Momoeda M and Taketani Y. Cornual pregnancy successfully treated laparoscopically with fibrin glue hemostasis. Obstet Gynecol 90, 685-7, 1997.
27. Sadatsuki M, Kaneko M and Tsutsumi O. Expectant management and methotrexate treatment of persistent ectopic pregnancy following laparoscopic salpingectomy. Int J Gynaecol Obstet 59, 49-51, 1997.
28. Tsutsumi O, Ando K and Momoeda M. Ruptured isthmal pregnancy following laparoscopic salpingostomy in the ipsilateral tube. Int J Gynaecol Obstet 57, 187-9, 1997.
29. Uechi H, Tsutsumi O, Morita Y and Taketani Y. Cryopreservation of mouse embryos affects later embryonic development possibly through reduced

expression of the glucose transporter GLUT1. Mol Reprod Dev 48, 496-500, 1997.
30. Takai Y, Tsutsumi O, Harada I, Fujii T, Kashima T, Kobayashi K, Toda T and Taketani Y. Prenatal diagnosis of Fukuyama-type congenital muscular dystrophy by microsatellite analysis. Hum Reprod 13, 320-3, 1998.
31. Tsutsumi O, Uechi H, Sone H, Yonemoto J, Takai Y, Momoeda M, Tohyama C, Hashimoto S, Morita M and Taketani Y. Presence of dioxins in human follicular fluid: their possible stage-specific action on the development of preimplantation mouse embryos. Biochem Biophys Res Commun 250, 498-501, 1998.
32. Igarashi T, Osuga U, Tsutsumi O, Momoeda M, Ando K, Matsumi H, Takai Y, Okagaki R, Hiroi H, Fujiwara O, Yano T and Taketani Y. Expression of Ah receptor and dioxin-related genes in human uterine endometrium in women with or without endometriosis. Endocr J 46, 765-72, 1999.
33. Okagaki R, Osuga Y, Momoeda M, Tsutsumi O and Taketani Y. Laparoscopic findings after ultrasound-guided transvaginal ethanol sclerotherapy for ovarian endometrial cyst. Hum Reprod 14, 270, 1999.
34. Takai Y, Tsutsumi O, Momoeda M, Osuga Y, Sadatsuki M, Kaibara M and Taketani Y. Non-functioning pituitary tumour after long-term treatment with gonadotrophin-releasing hormone agonists in a patient with vaginal agenesis who underwent neovaginoplasty and cauterization of endometriosis under laparoscopy. Hum Reprod 14, 2661-4, 1999.
35. Uechi H, Tsutsumi O, Morita Y, Takai Y and Taketani Y. Comparison of the effects of controlled-rate cryopreservation and vitrification on 2-cell mouse embryos and their subsequent development. Hum Reprod 14, 2827-32, 1999.
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Osuga Y, Koga K, Tsutsumi O, Yano T, Maruyama M, Kugu K, Momoeda M and
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Department of Pediatrics / Developmental Pediatrics

Outline and Research Objectives

Department of Pediatrics was founded in 1889 and continued its activity for 113 years. This is the oldest Pediatrics and has been the leader of Pediatrics in Japan. Many pediatricians received the training in our department and went to all over and out of Japan and worked as a leader of pediatrician in a lot of Japanese Medical School in the University, central and local hospitals and clinics.

The health problems of children and youth have changed historically in Japan. In the late 19th century, one of five children died as infectious diseases such as dysentery, pneumonia, diphtheria, and whooping cough. Now, few children die due to the diseases. The leading causes of death for children are perinatal problems for babies, injuries, congenital anomalies, malignant neoplasms, and congenital heart diseases. Many of these diseases have genetic background in their pathogenesis. Thus, the research objectives have greatly changed. Now, they are to clarify the molecular pathogenesis of these difficult diseases and to find safe and effective therapies for them and to find the way to promote the body and heart health of children in our Pediatrics.

Pediatrics covers all the issues in children and youth. Thus, our department studies almost all the issues about children and youth. Now, we have six active study groups such as Nephrology, Hematology and Oncology, Cardiology, Immunology and Allergy, Endocrinology and Metabolism, and Neurology. The main subjects of the research are 1) Identification of the molecular pathogenesis of renal tubular disorders, 2) Clarification and characterization of the genes which cause leukemia and neuroblastoma, 3) Role of hemodynamic factors on pulmonary hypertension complicated with congenital heart diseases, 4) Epidemiological survey and nationwide registry of primary immunodeficiency diseases and the efficacy of immunotherapy for cancer using peripheral dendritic cells, 5) Molecular and functional analysis of the genes for inherited endocrine and metabolic diseases, and 6) Pathogenesis of peroxisome biogenesis disorders. The details of the research projects are described bellow.

We have been the local registration center for children's cancer in Kantou-district. This helps and promotes the basic research in the fields of Hematology and Oncology in our Pediatrics.

Faculties and Students

Professor and Chair	Takashi Igarashi, M.D., Ph.D. (2000-)
Associate Professors	Tsutomu Iwata, M.D., Ph.D.
Lecturers	Yasuhide Hayashi, M.D., Ph.D.
	Masaru Takamizawa, M.D., Ph.D.
	Hitoshi Kato, M.D., Ph.D.
	Takashi Sekine, M.D., Ph.D.
	Yoichi Sakakihara, M.D., Ph.D.

Associates 15
Postdoctoral Fellow 4
Graduate student 18
Research student.....3
Secretary 3

Past Research and Major Accomplishments

Nephrology

1) Molecular pathogenesis of Dent's disease, proximal renal tubular acidosis and renal hypouricemia: feedback from bench to clinics.
2) The mechanisms of post-diarrheal hemolytic uremic syndrome (HUS).
3) Molecular identification of the proximal tubular transporters that excrete drugs from the kidney.

Hematology and Oncology

1) Identification of *HOXD11, HOXA13* and *HOXC11* genes as partner genes of *NUP98* in t (2;11)-, t (7;11)- and t (11;12)- acute myeloid leukemias.
2) Molecular analysis of tumor suppressor genes in neuroblastoma.

Cardiology

1) Role of hemodynamic factors on pulmonary hypertension complicated with congenital heart diseases.
2) Development of coronary artery from cardiac neural crest cells.
3) Effect of epoprostenol on severe port pulmonary hypertension complicated with biliary atresia.
4) Historical review of Kawasaki disease: When Kawasaki disease started in Japan?

Immunology and Allergy

1) Epidemiological survey and nationwide registry of primary immunodeficiency diseases.
2) The efficacy of immunotherapy for cancer using peripheral dendritic cells.
3) The effective and safe simultaneous administration of several vaccines in a short period of time before liver transplantation and their administration under immunosuppressive conditions after transplantation.
4) Prospective study of atopic status in infants of the cohort in Tokyo, Japan.
5) Epidemiology of bronchial asthma among children in rural and urban area in Bangladesh.

Endocrinology and Metabolism

1) Molecular and functional analysis of the genes for several inherited endocrine and metabolic diseases including the glutamate dehydrogenase gene in congenital hyperinsulinism hyperammonemia syndrome, glucose-6-phophatase gene in glycogen storage disease type 1a, CREB-binding protein in Rubinstein-Taybi syndrome, hepatocyte nuclear factor-1b in maturity-onset diabetes of the young type 5.

Neurology

1) Pathogenesis of peroxisome biogenesis disorders: Altered lipid metabolism in peroxisome-defective cells.
2) The genetic analysis of Japanese patients with spinal muscular atrophy.
3) The analysis of pathophysiology of epileptic syndrome and higher brain function in
children by magnetoencephalography.
4) Development of communication tool for patients with spinal muscular atrophy.

Current Research

Nephrology

1) Molecular and functional analysis of various ion transporters such as Cl channels, $Na^+/HCO3^-$ cotransporter, URAT1, barttin, and H^+-ATPase.
2) Molecular and functional analysis of LMX1B in nail patella syndrome and hepatocyte nuclear factor-1 β in MODY5.
3) The mechanisms of post-diarrheal HUS.

Hematology and Oncology

1) Identification of *HOXD11*, *HOXA13* and *HOXC11* genes as partner genes of *NUP98* in t (2;11)-, t (7;11)- and t (11;12)- acute myeloid leukemias.
2) Molecular analysis of tumor suppressor genes in neuroblastoma.

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1) Epidemiological survey and nationwide registry of primary immunodeficiency diseases.
2) The efficacy of immunotherapy for cancer using peripheral dendritic cells.
3) Prospective study of atopic status in infants of the cohort in Tokyo, Japan.
   Epidemiology of bronchial asthma among children in rural and urban area in Bangladesh.
5) Analysis of the function of basophils in allergic diseases.

Endocrinology and Metabolism

1) Molecular and functional analysis of the genes for several inherited endocrine and metabolic diseases including the glutamate dehydrogenase gene in congenital hyperinsulinism hyperammonemia syndrome, glucose-6-phophatase gene in glycogen storage disease type 1a, CREB-binding protein in Rubinstein-Taybi syndrome, hepatocyte nuclear factor-1b in maturity-onset diabetes of the young type 5.

Neurology

1) Pathogenesis of peroxisome biogenesis disorders-Altered lipid metabolism in peroxisome-defective cells.
2) The analysis of pathophysiology of epileptic syndrome and higher brain function in children by magnetoencephalography.
3) Development of communication tool for patients with spinal muscular atrophy.

Future Prospects

Nephrology

1) Molecular and functional analysis of various renal transporter disorders.
2) Identification of the genes for minimal change nephrotic syndrome.

Hematology and Oncology

1) Identification and characterization of *HOXD11*, *HOXA13* and *HOXC11* genes as partner genes of *NUP98* in t (2;11)-, t (7;11)- and t (11;12)- acute myeloid leukemias.
2) Molecular analysis of tumor suppressor genes in neuroblastoma.

Cardiology

1) Role of hemodynamic factors on pulmonary hypertension complicated with congenital heart diseases.
2) Development of coronary artery from cardiac neural crest cells.

Immunology and Allergy

1) Epidemiological survey and nationwide registry of primary immunodeficiency diseases.
2) The efficacy of immunotherapy for cancer using peripheral dendritic cells.
3) Prospective study of atopic status in infants of the cohort in Tokyo, Japan.
4) Epidemiology of bronchial asthma among children in rural and urban area in Bangladesh.
5) Analysis of the function of basophils in allergic diseases.

Endocrinology and Metabolism

1) Mutational and functional analysis of the genes for several inherited endocrine and metabolic diseases.

Neurology

1) Pathogenesis of peroxisome biogenesis disorders-Altered lipid metabolism in peroxisome-defective cells.
2) The analysis of higher brain function by magnetoencephalography.
3) Development of communication tool for patients with spinal muscular atrophy.

Research Grants (5 selections)

1) Igarashi T: Early diagnosis, management and treatment of intractable kidney and urinary tract diseases (Kodomokatei-H13-011). Ministry of Health, Labor and Welfare, 16,000,000 yen in 2001-2002.
2) Iwata T: The association between Urbanization and Childhood Asthma in Bangladesh.Nissan Science Foundation, 4,500,000 yen in 2000-2001, 3,600,000 yen in 2002-2003.
3) Hayashi Y: Analysis of molecular mechanism of cancer formation due to translocation gene by using genome information and expression profile (B-2-14370242). Ministry of Education Science, 8,800,000 yen in 2002-2004.
4) Hayashi Y: Gene analysis and diagnosis of intractable childhood leukemia and secondary leukemia and their application to the clinics. Ministry of Health, Labor and Welfare, 7,400,000 yen in 1996-2002.
5) Kato H: Role of hemodynamic factors on pulmonary hypertension complicated with congenital heart diseases (No. 09470177). Ministry of Health, Labor and Welfare, 5,300,000 yen in 1999-2001.

Select Publications

Nephrology

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Kawakami H, Endou H, Igarashi T, Goto A, Fujita T, Araie M, Seki G: Molecular basis of ocular abnormalities associated with proximal renal tubular acidosis. J Clin Invest 108: 107-115, 2001
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10. Chandler WL, Jelacic S, Boster D, Ciol M, Watkins S, Igarashi T, Tarr PI: Prothrombotic coagulation abnormalities preceding the hemolytic uremic syndrome. New Eng J Med 246: 23-32, 2002
11. Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Cha SH, Hosoyamada M, Takeda M, Sekine T, Igarashi T, Matsuo H, Kikuchi Y, Oda T, Ichida K, Hosoya T, Shimokata K, Niwa T, Kanai Y, Endou H: Molecular identification of a renal/urate/anion exchanger that regulates blood urate levels. Nature 417: 447-452, 2002

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leukemia. Genes Chromosomes & Cancer 31: 187-190, 2001
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36. Taketani T, Taki T, Ono R, Kobayashi Y, Ida K, Hayashi Y: The t (7;11)(p15;p15) in acute myeloid leukemia results in fusion of the NUP98 gene with a HOXA cluster gene, HOXA13, but not HOXA9. Genes Chromosomes & Cancer 34:437-443, 2002
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Cardiology

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Immunology and Allergy

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Endocrinology and Metabolism

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Neurology

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49. Tatsumi K, Saito M, Lin B, Iwamori M, Ichiseki H, Shimozawa N, Kamoshita S, Igarashi T, Sakakihara Y: Enhanced expression of a-series gangliosides in fibroblasts of patients with peroxisome biogenesis disorders. Biochim Biophys Acta 1535:285-293, 2001
50. Saito M, Fukushima Y, Tatsumi K, Bei L, Fujiki Y, Iwamori M, Igarashi T: Molecular cloning of Chinese hamster ceremide glucosyltransferase and its enhanced expression in peroxisome-defective mutant Z65 cells. Arch Biochem Biophys 403:171-178, 2002

Department of Pediatric Surgery / Department of Pediatric Oncology

Outline and Research Objectives

The history of Department of Pediatric Surgery is not long in University of Tokyo. It first started as a clinical department of University of Tokyo Hospital in 1971. In 1989 it became a department in The Faculty of Medicine and then transferred to The Graduate School of Medicine as a part of the change of the system. So the duration of research in our department is not long. Also we have only few staff in our department. However, we have continued research very intensively by collaboration with other departments in The Graduate School of Medicine, University of Tokyo, and other institutes in Japan and abroad.

Our main themes of research are in three areas, namely transplantation medicine, developmental biology of congenital anomalies and fetal surgery, and immunology of intestine.

Department of Pediatric Oncology was separated from Department of Pediatric Surgery when the system changed, and Graduate School of Medicine became the major. Before that, studies concerning pediatric oncology was done in the Department of Pediatric Surgery and also in the Department of Pediatrics. Now as a system, Department of Pediatrics is separated from the Department of Pediatric Oncology, the group of pediatric oncology in the Department of Pediatrics actually works with the Department of Pediatric Oncology, and constitutes a part of the department.

Pediatric malignancies are very special and consist only a very small part of all the malignancies considering the number of patients. However, because of their peculiarities, they have some privileges and advantages. For example, about the theory of oncogenesis, famous "two-hit theory" by Knudson was first proposed for pediatric malignancies, retinoblastoma and nephroblastoma. It is because that the mechanism of oncogenesis in these tumors is very simple compared to that of adult malignancies. Also the "multi-disciplinary treatment" of malignant diseases first successfully introduced to malignant solid tumors in infancy and children. So the study of pediatric oncology is very important and it has possibility of break-through in the study of oncology general. Now we mainly study oncogenes related to pediatric malignancies especially neuroblastoma, and immuno-therapy of cancer using dendritic cells.

Faculties and Students

Professor and Chair	Kohei Hashizume, M.D,,Ph.D.. (since 1997)
Lecturer	Yutaka Kanamori, M.D.,Ph.D.. (Yasuhide Hayashi, M.D.,Ph.D.)
Associates	3
Graduate Students	4
Secretary	2

Past Research and Major Accomplishments

In the area of transplantation medicine, we started clinical living-related liver transplantation with the Department of Artifitial Organ and Transplantation and have operated about 100 pediatric cases. Associate Professor Kawarasaki in our department who was in charge in liver transplantation moved to Jichi Medical School in 2001. So we stopped clinical liver transplantation in pediatric cases. But we continue research in this area now. We studied immunological tolerance using rat heart transplantation model, and found that donor specific transfusion induce immunological tolerance. Then we analyzed rat serum after donor specific transfusion using liquid chromatography. We found three kinds of proteins that have a function of immunosuppression. Especially one of those 3 protein, MAY-1 is a completely new protein with 234 amino acid and has a possibility of usage as a immunosuppression drug in clinical transplantation.

We studied small bowel transplantation using a model of small bowel transplantation with a free graft of newborn intestine into the recipient's omentum. In this model we showed good neovascularization and histologically mature intestine after the transplantation. We also showed the near normal motility and absorption in this transplanted intestine. In short-boweled rats, transplantation of newborn intestine

could restore the weight loss and could save the lives of these short-boweled rats. Also cryopreserved newborn intestine could function as good as fresh intestine after transplantation.

We also studied warm ischemia-reperfusion injury of the liver in rat model. We showed that pretreatment of the liver with cyclosporine reduce damage to the liver, but pretreatment with FTY720 rather prolong damage to the liver. So pretreatment with immuno-suppressive drugs of the liver does not universally beneficial for the prevention of warm ischemia-reperfusion injury.

In the area of developmental biology of congenital anomalies and fetal surgery, we very intensively studied congenital diaphragmatic hernia (CDH) using rat model induced by a drug nitrofen. CDH is one of the most difficult to treat congenital anomalies with high mortality. Until recently its experimental study was done using only sheep model that is made by fetal surgery. The problem is that the fetal surgery can be done only in late phase of pregnancy, many features of this model is quite different from that of human CDH. We noticed rat CDH induced by administration of nitrofen to pregnant rat. The CDH by this method develop at very early stage of fetal development and very similar to human CDH. First we showed clearly that hypoplasia of the lungs develop by CDH, and spreading of sufactant phospholipids in the alveolar cells to the lumen of alveoli is strongly impaired in fetuses with CDH. Then we studied the effects of fetal surgery to lung hypoplasia in CDH. We developed experimental model of tracheal ligation in rat CDH model. Using this model, we showed that tracheal ligation can overcome the hypoplasia of the lungs induced by CDH. By ligation of the trachea the lungs grow very rapidly, and the weight, contents of protein and DNA of the lungs, and histological structure normalize. By this experiment we clearly showed that tracheal ligation can overcome the hypoplasia of the lungs in CDH, and that this simple fetal surgery can same the lives of babies with CDH and severe hypoplasia of the lungs whom it is very difficult to treat after birth.

We also developed another new model of congenital anomaly in a species of amphibian, Cynopus pyrrhogaster. We succeeded to produce split cord malformation in Cynopus embryos experimentally incising a part of neural plate and notochord. With this procedure, fistulae developed between endoderm and ectoderm, and in some cases endodermal or neural cysts developed. This experiment shed light to the cause of split notochord syndrome and also duplication of intestine.

In the area of immunology of intestine, Kanamori first described novel lympoid tissues, cryptopatch in murine intestinal mucosa in 1996. Then we studied human intestinal mucosa for the existence of lymphoid tissues corresponding to the cryptopatch in mouse. We could not show the existence of such lymphoid tissues in human. So we turned to study the functions of already known lymphoid tissues in human if they have functions corresponding to cryptopatch in mouse and compensate the absence of that. Using surgical specimens of jejunum of infants, we looked for lymphoid tissues in the mucosa of the jejunum, and examined the distribution of these tissues. We found Peyer's patches and isolated lymphoid follicles. Peyer's patches distributed in antimesenteric area, but isolated lymphoid follicles distributed irregularly all through the surface of the mucosa, and in these isolated lymphoid follicles CD19 positive and CD3 positive lympoid cells are distributed.

We introduced new synbiotics therapy to various intestinal conditions in children, namely short bowel syndrome, inflammatory bowel diseases, and pseudo-Hirschsprung disease. We administered two types of probiotics (Bifidobacterium brevs and Lactobacillus casei) together with prebiotic (galactooligosaccarides) to these patients. After the introduction of this therapy, the patients' clinical conditions dramatically improved. Feces became more solid and less foul-smelling, the patients got weight, abnormal dilatation of the intestine improved, and frequency of bacterial translocation decreased. We also showed change of bacterial flora of feces. Those two types of probiotics became the main flora, and the number of pathogenic bacteria dramatically decreased.

In the area of pediatric oncology, we started our study of pediatric oncology in the field of histochemistry. We studied expression of multi-drug resistance related protein, P-glycoprotein in neuroblastoma cells. Surprisingly, it was shown that high expression of P-glycoprotein was related to better prognosis of patients. It looks paradoxical, but we also found in normal adrenal medulla cells, P-glycoprotein is expressed. So high expression of P-glycoprotein in neuroblastoma means rather well-differentiation of these tumors, and consequently better prognosisi. Our result was confirmed later by other publications.

Recently we are concentrated in the study of oncogene in pediatric malignancies, especially neuroblastoma and Wilms tumor. It is well known that neuroblastomas whose cells show chromosome 1p deletion have poor prognosis. We intensively looked for probable oncogene in this region, but it has not yet discovered. There was one great side product of this project. In this region we found kinesin superfamily motor protein KIF1B, and it was shown loss-of-function mutation in the motor domain of the KIF1B gene causes Charcot-Marie-Tooth disease type 2A. We studied expression, LOH, and mutation of p73 gene that is mapped to 1p36. We found aberrant expression of p73 is significantly higher in advanced-stages neuroblastoma, but no homozygous deletion of p73 was

found in any of the sample. So we conclude p73 is less involved in the development but involved in the progression of neuroblastoma. We also studied other genes mapped in other chromosomes because other chromosome anomalies other than 1p deletion are related to prognosis of neuroblastoma. For example, 17q gain is known to relate to poor prognosis. We studied survivin mapped to 17q25, which is a member of inhibitor of apoptosis proteins (IAPs). We found high expression of survivin is a strong prognostic indicator for the advanced stage neuroblastomas, and there is a possibility that it is one of the candidate genes for the 17q gain.

In the study of Wilms tumor, we found a novel WT1 gene mutation in a patient with Wilms tumor, male hermaphroditism, but without renal disease. The mutation was at intron 7 in tumor cells and also germ line cells. This mutation is thought to produce truncated WT1 protein, and it is related to the genitourinary anomalies and genesis of Wilms tumor in this patients. Also the clinical course of this patient was rather atypical for Wilms tumor in general, and we think this peculiar mutation should influence the course of the disease.

Other than neuroblastoma and Wilms tumor, we studied hepatoblastoma. We examined mutation of beta-catenin in the tumors of 68 cases of hepatoblastoma. We found mutation of beta-catenin in 44 (65%) tumors. In these 44, 9 was point mutation, 35 was deletion mutation. We also studied the expression of beta-catenin by histochemistry. We found beta-catenin is accumulated in the nuclei of tumor cells, and in these cases with beta-catenin accumulation, cyclin D1 was also accumulated in the nuclei. We conclude that in hepatoblastoma because of frequent mutation of beta-catenin gene, beta-catenin protein accumulates in the nuclei and cause activation of cyclin D1, that results growth or progression of the tumor. We also found beta-catenin accumulation in the nuclei of two cases of hepatic adenoma. In one of these 2 cases, mutation of beta-catenin gene was found. This is the first report of beta-catenin mutation in the case of hepatic adenoma, and we think it shed light to the genesis of hepatic adenoma and its relation to hepatoblastoma.

Current Research

In the area of transplantation medicine, our main themes are prevention of ischemia-reperfusion injury in liver transplantation, and development of safer method in transplantation of small bowel. In the former theme, we developed partioal liver transplantation model in rat, and studying the effect of gene introduction to the graft. In the preliminary study, we got promising effect of gene introduction. In tranplantation of small intestine, we have succeeded in the transplantation of cryopreserved newborn intestine, but found cryopreservation had no effect on antigenicity of the graft. So we are studying methods to reduce the antigenicity of the intestinal graft to improve the survival of intestinal transplantation.

In the area of developmental biology of congenital anomalies and fetal surgery, we are doing experimental fetal surgery of tracheal obstruction using lambs. We developed new laryngoscope specially designed for the obstruction of trachea of fetal lambs using balloon. We have successfully introduced balloon into fetal trachea, and have shown growth of the lungs after the introduction of balloon.

In the area of immunology of intestine, we are studying the cells found in isolated lymphoid follicles in the mucosa of infants, their characters, development, and migration. We are considering of using probiotics in wider varieties of diseases, for example patients in PICU who receive rather intensive antibiotics therapy and are prone to develop bacterial translocation and sepsis.

In Pediatric Oncology Department, we continue the search of tumor suppressor gene of neuroblastoma suspected to reside in chromosome 1p. We have established cell line of Wilms tumor with WT1 mutation. This cell line has morphological features of stromal cell and epithelial cell. Using this cell line, we are considering to do a study concerning the factors that determine the differentiation of the tumor. Wilms tumor shows a very wide variety of histology. In some tumors, histology is almost universally epithelial, but in other tumors, they show stroma-dominant histology with only small part of epithelium. Because the histological type relate to the prognosis of the tumor, we can know the factors related to prognosis, if we can find out factors that determine the histological features of the tumor.

Concerning the therapy of malignant tumors in children, we are doing a research of immunotherapy using dendritic cells. Immunotherapy using dendritic cells is not studied fully in malignant tumors in children. However, it is well known that neuroblastoma cells show strong tumor-specific antigen, and spontaneous regression of neuroblastoma is well documented. So we think immunotherapy of neuroblastoma is promising. We found using OK-432, dendritic cells can be activated, and CTL can be induced. We want to test this method using target of neuroblastoma cells.

Compared to neuroblastoma and Wilms tumor, genetic and molecular study of hepatoblastoma is retarded. It is necessary to examine genes related to genesis and progression of hepatoblastoma. To examine many kind of genes, gene chip is very effective method, and we are collaborating with Research Center for Advanced Science and Technology of University of Tokyo. Using this method and compar-

ing gene expression profiles of hepatoblastoma, normal liver, and cirrhotic liver, we have found some genes that specifically expressed in hepatoblastoma.

Future Prospects

One very important aspect of study in our department is establishment of new area of medicine "fetology". To know and to treat patients with various congenital anomalies, it is mandatory to know fetal development of normal baby and babies with congenital anomalies. Development of imaging methods in these ten years is enormous. However, we need not only information of structures of fetuses, but also functions of various organs during fetal life. With the development of new technology which will make it possible, we can know the physiology of fetus and the effects of fetal conditions to the health after birth in children and adults.

In this 20 years, prognosis of pediatric malignancies in general has improved dramatically. However there are small fraction of patients whose tumors are very resistant to standard treatment, and are apt to recur after a short period of remission. These tumors probably has some genetic characteristics, and if we can find out some of these characteristics, we can improve the method of therapy and also can improve the prognosis of these patients.

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Department of Geriatric Medicine / Department of Aging Research

Outline and Research Objectives

The Department of Geriatrics was established in1962, as the first geriatric department in Japan.

Since elderly patients usually have multiple organ disorders, we have to take care of the patients as whole from multiple points of view. In addition, in the elderly patients, symptoms and signs, responses to the treatment are sometimes quite different from the young. We have to have a broad knowledge on the physiological and metabolic changes with aging when we treat the elderly patients. Quality of life of the patients is another point of view which should be emphasized.

Our sub-specialty includes respirology, cardiology, neurology, hematology, bone metabolism, besides the general geriatric internal medicine. We are trying to elucidate the pathophysiology of aging process and elderly patients from viewpoints of basic aging science using molecular biology technique and clinical aspects using the recent advancement of technology and geriatric assessment.

There are 19 plus additional beds about 6 in the clinical ward, which are under the supervision of the residents and assistant staff members. An assistant staff member with more than 10 years experience teams up with the resident on a man-to-man basis, giving instruction as to actual clinical decision making and procedures. The final decision making is performed during the weekly Professor's rounds.

We have also developed new geriatric scale such as vitality index. This is a unique index for assessment of energy and vitality in frail elderly patients. Comprehensive geriatric assessment and critical pass applied for the treatment and care of the patients. Based on these comprehensive approaches, both staffs of medical social service and welfare division of Tokyo University Hospital and we develop the new system which bridge between in-patients and out-patients in terms of maintaining a constant level of quality of life of patients and caregivers.

Specialized services are provided to out-patients on a daily in all areas internal medicine. Approximately 300 new and a total of 16,000 patients visit the out-patients clinic in a year.

Faculties and Students

Professor and Chair	Yasuyoshi Ouchi,M.D. (1995~)
Lecturer	Yoshio Namba,M.D.
	Takahide Nagase,M.D.
	Satoshi Inoue,M.D.
	Koichi Kozaki, M.D.
Associate	6
Postdoctoral Fellow	4
Graduate Student	8
Research Student	5
Secretary	6

Past Research and Major Accomplishments

Lung diseases including pneumonia are major causes of death in the elderly. In respiratory diseases, there are several inflammatory disorders to which no pharmaceutical agents are currently effective. For example, adult respiratory distress syndrome (ARDS) is an acute lung injury and the mortality rate for ARDS ranges from 40-70% despite of intensive care using currently available drugs. Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal disease, while current medical intervention for IPF is only oxygen therapy except for lung transplantation. However, their mechanisms still remain to be elucidated. Therefore, we have aimed to elucidate the pathophysiological and molecular mechanisms underlying inflammatory diseases. Our recent studies have shown that various mediators including cytokines, eicosanoids or adhesion molecules are involved in the development of inflammatory lung disorders. Especially, platelet-activating factor (PAF) and metabolites of arachidonic acid, i.e., eicosanoids, are lipid mediators that have various biological effects. PAF is a proinflammatory phospholipid mediator that exerts its action via activation of G-protein-coupled PAF

receptor (PAFR). A key enzyme for the production of these inflammatory mediators including eicosanoids and PAF is cytosolic phospholipase A2 (cPLA2). To perform this study, we used mutant mice, i.e., PAFR transgenic mice, PAFR gene-disrupted mice, and cPLA2 gene-disrupted mice, in collaboration with Department of Biochemistry. Our observations suggest that both PAF and cPLA2 are involved in the pathogenesis of acute lung injury and pulmonary fibrosis. The inhibition of these pathways might provide a novel therapeutic approach to ARDS and IPF. We have also examined the host-defense system, especially antimicrobial peptides including defensins. Recently, we have discovered a novel mouse beta-defensin, mBD-6, predominantly expressed in skeletal muscle. In humans and mice, we have also identified multiple novel epididymis-specific beta-defensin isoforms. These finding suggest novel physiological roles of this peptide family.

Cardiovascular research laboratory has been performing research of atherosclerosis. It is generally accepted that premenopausal women are protected from atherosclerotic diseases because female hormone, especially estrogen, appears to have a beneficial effect on vascular wall. We have identified that vascular smooth muscle cells (VSMC) expressestrogen receptor (ER) and these cells respond to estrogen from the evidence that estrogen inhibits endothelin-1 production and c-fos gene expression in rat aorta and estrogen inhibits migration and proliferation of vascular smooth muscle cells. We also found estrogen exerts beneficial effect in vivo by showing that estrogen inhibits intimal thickening of rat femoral artery induced by cuff-placement around the artery. With respect to endothelial cells (EC), another major component constituting the vascular wall, we found that estrogen attenuates endothelin-1 production in bovine endothelial cells via estrogen receptor and that estrogen prevents oxidative stress-induced endothelial cell apoptosis in rats.

Besides estrogen, we have revealed that red wine polyphenols (RWPs) have inhibitory roles in VSMC function. RWPs inhibit VSMC proliferation, which is mediated by cyclin A downregulation. RWPs also inhibit VSMC migration via two distinct signaling pathways, phosphatidylinositol-3' kinase and p38 mitogen-activated protein kinase. We also showed potential involvement of various vasoactive substances, calcitonin gene-related peptide, parathyroid hormone-related protein, vasopressin, and activin-A, in the pathogenesis of atherosclerosis.

From the clinical perspective, our laboratory has a useful technique to evaluate vascular function, flow-mediated vasodilatation (FMD). With this approach, we have shown that endothelium-dependent vasodilatation of the brachial artery is increased in the follicular and luteal phase of women's menstrual cycle when serum estradiol level is high, indicating that endogenous estradiol is involved in menstrual cycle-related vasodilatation. We also found that FMD is impaired in obese men with visceral fat accumulation, FMD negatively correlates with intima-media thickness in the carotid artery in men, long-term reduced-dose hormone replacement therapy improves FMD and intima-media thickness in the carotid artery in postmenopausal women.

Currently, most of the research activities in neurological laboratory focus on the molecular aspects of Alzheimer's disease(AD). The main research topics are elucidating the molecular mechanism underlying the accumulation of amyloid b-protein, determining the implications of apolipoprotein E (apoE ε4) genotype and various risk factors in AD.

Endocrine/Metabolism Research Laboratory focuses on the clinical and basic research concerning endocrine and metabolic diseases. We are particularly interested in the pathophysiological mechanisms in osteoporosis and hormone-dependent cancers. Regarding osteoporosis, we have shown that genetic factors are very important to develop the disease by analyzing polymorphisms of the genes relating bone metabolism. On the other hand, we recently have revealed that an estrogen responsive RING finger protein Efp takes a critical role in estrogen-dependent growth control of breast tumor, by proteolysis of a cell-cycle checkpoint 14-3-3 sigma (Nature 2002, 417, 871). This finding may provide a new tool for diagnosis and treatment of breast tumor, especially of tumor that is resistant to anti-estrogenic drugs.

We have also studied disuse syndrome as well as the program of prevention and treatment of that. Now we are investigating many aspects of elderly patients by using newly developed geriatric scale.

Current Research

To further investigate the pathophysiological and molecular mechanisms underlying inflammatory diseases, we continue to study the roles of various mediators including cytokines, eicosanoids, adhesion molecules, and CGRP family in the development of inflammatory lung disorders. Especially, CGRP family peptides including CGRP and adrenomedullin are neuropeptides that have various biological actions such as responses to sensory stimuli, cardiovascular regulation and vasodilation. Based on their physiological roles, it is assumed that CGRP family might be involved in the pathogenesis of inflammatory diseases including bronchial asthma. Currently, in collaboration with Department of Cardiovascular Medicine, we are studying the pathophysiological role of CGRP family using mutant mice deficient in either CGRP or

adrenomedullin.

High incidence of respiratory infection including pneumonia is a major characteristic of geriatric disease, while little is known about its mechanism. We currently hypothesize that ageing process might affect the expression pattern of defensins, leading to the susceptibility to infection in the elderly. To address this question, we are studying the ageing effects on the expression pattern of defensins using mice. In addition, to better understand the pathophysiological roles of defensins, we are now developing the mutant mice deficient in defensins.

We are currently pursuing the differential role of estrogen receptors, ER α and β, in VSMC function and in other cell types utilizing adenoviral overexpression system, because we have previously shown that estrogen has anti-proliferative and anti-migratory effects in VSMC (Atherosclerosis. 1997). We are also trying to overexpress each ER subtype in the aorta of laboratory animals to identify the differential role of ER in estrogen's action. We are studying the role of selective estrogen receptor modulator such as raloxifene to explore the usefulness of this new estrogen-modifying drug.

Our laboratory has been investigating vascular calcification, one of the hallmarks of vascular aging. We have thus far found that VSMC calcify when cultured in the presence of high inorganic phosphate, the phenomenon augmented by the addition of vitamin D3, dexamethasone and advanced glycation end products, attenuated by bisphosphonate and HMG CoA reductase inhibitor. We are currently studying the mechanism how VSMC calcification is regulated.

It is well known that flow-mediated vasodilatation (FMD) is under much influence by nitric oxide (NO). Because it has been shown that an endogenous inhibitor of NO synthase, asymmetric dimetylarginine (ADMA), and its hydrolyzing enzyme, NG,NG-dimethylarginine dimethylaminohydrolase (DDAH), are circulating in human blood, we are interested in the role of ADMA and DDAH in such pathophysiologic conditions as pre- and post-female hormone replacement therapy and pre- and post-treatment of sleep apnea syndrome using nasal continuous positive airway pressure.

The ε4 allele of apoE is a major risk factor for both sporadic and late-onset familial AD. The apoE receptor family consists of cell-surface receptors that recognize extracellular ligands and internalize them for degradation by lysosomes. In order to gain insight about these receptors in the CNS, we raised a rabbit polyclonal antibody and examined immunohistochemically human brain tissue. The immunoreactivity was found in senile plaque in AD. These results may suggest a role of apoE receptor in amyloid formation.

As estrogen is one of the key factors that can determine the stages and prognosis of osteoporosis and hormone-dependent cancers, we are particularly studying the molecular mechanism of estrogen in its target organs. Biochemical and genetic approaches are utilized for the project, including analysis using osteoblasts and tumor cell lines, characterization of animal models targeting estrogen receptors and estrogen-responsive genes, genetic analysis using clinical samples from patients.

Future Prospects

Major causes of death in the elderly include respiratory diseases including pneumonia, especially aspiration pneumonia. Furthermore, there are fatal inflammatory disorders such as ARDS and IPF, to which no useful drugs are currently available. We expect that the inhibition of PAF and cPLA2 pathways might provide a novel therapeutic approach to ARDS and IPF, leading to the development of a revolutionary medicine.

Genetic features including single nucleotide polymorphism (SNP) are potentially associated with the etiology of asthma. The current study may suggest that CGRP family genes could be targets for SNP research. High incidence of respiratory infection including pneumonia in the elderly might be explained by the mechanism that ageing process might alter the expression pattern of defensins, leading to the immunosupression and the susceptibility to infection. We expect that our ongoing study related to defensins could make a contribution to the innate-immunity researches. Furthermore, novel roles of defensins might potentially provide a novel therapeutic approach to infectious diseases.

Because the aging process and age-related diseases are closely associated with vascular aging, to prevent atherosclerosis is a way to improve physical activity in the elderly. Our laboratory keeps pursuing the mechanism of atherosclerosis, especially how hormone and its receptor regulate vascular function. We will keep performing research as to how sex hormones or their related biological materials modulate vascular function in vitro and in vivo. We will also try to elucidate the mechanism how we can reduce vascular calcification, because vascular calcification appears tightly linked with vascular aging, which is one of our interests.

We are studying the genetic and environmental risk factors and prevalence, and incidence of Alzheimer's disease among the elderly in Japan.

Because estrogen is one of the key factors that can determine the stages and prognosis of osteoporosis, hormone-dependent cancers, and age-related changes of females, we are pursuing prevention and new treatment of osteoporosis and cancer. It may be contribute

to maintain the constant level of physical and social activity in elderly peoples. Furthermore, our basic research focuses on novel findings of new molecular targets for drug development concerning osteoporosis and hormone-dependent cancers.

Based on these clinical and basic science data, we are pursuing prevention of a variety of age-related diseases and geriatric syndrome. We also propose standards for facilitation of care across the health service continuum, care of the nursing home resident, and palliative and hospice care.

Research Grants

Yasuyoshi Ouchi

1. Grant-in Aid (No.13557062) for Scientific Research from the Minstry of Education, Science and Culture of Japan. Elucidation of the differential role of estrogen receptor a and b in vascular lesion formation. 1999-2001 (three year research foundation grant B2).
2. Funds for Comprehensive Research on Aging and Health, Japan Foundation for Aging and Health. Hormone replacement therapy for elderly women. Yasuyoshi Ouchi 1998-2000 (three year grant, H10-tyojyu-007).

Nagase Takahide

1. Grant-in Aid(No. 12470134) for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan. The study of molecular mechanisms underlying ARDS using genetically-engineered mice to develop a novel treatment (three year research foundation grant B).
2. Health Science Research Grant-in Aid for Comprehensive Research on Aging and Health from the Ministry of Health, Labour and Welfare of Japan. The study of pathophysiological mechanisms underlying inflammatory/intractable lung diseases in the elderly: a strategic development of novel therapeutic approaches (H14-).

Yoshio Namba

1. Health Science Research Grant-in Aid for Brain Science from the Ministry of Health and Welfare of Japan. Genetic and environmental risk factors for Alzheimer's disease (three year grant, H10-H12).

Select Publications

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