Department of Cardiothoracic Surgery

Outline and Research Objectives

Our department specializes in all areas of cardiothoracic surgery including congenital and acquired cardiac diseases, thoracic and abdominal aortic diseases, and benign and malignant diseases of respiratory and mediastinal organs, except for diseases of the esophagus and mammary glands. The Department of Cardiothoracic Surgery, University of Tokyo, was established in December 15, 1964 as the first department of this field in the Japanese national universities. Since then it has played an internationally leading role and contributed to development of the field. Professors and Chairs in the history of the department are as follows; Seiji Kimoto (1964.12.15 ~ 1968.3.31), Masahiro Saigusa (1968.4.1 ~ 1981.3.31), Ken-ichi Asano (1981.4.1 ~ 1986.3.31), Akira Furuse (1986.4.1 ~ 1997.3.31) and Shinichi Takamoto (1997.6.1 ~). The cardiothoracic department of the University of Tokyo has created highly active research programs in the every field of cardiothoracic surgery. Recently, most of the basic research activities are focused in the fields of brain and spinal cord protection during aortic surgery, homo- and xeno-transplantation of the heart, lung, heart valves and trachea, and surgical oncology of the pulmonary and thymic neoplasms. Although, there are many other active research projects such as stent-graft repair for thoracic aortic aneurysm, minimally invasive cardiac surgery, and intraoperative real-time 3-D echocardiography.

Faculties and Students

Professor and Chair	Shinichi Takamoto,M.D. (1997-)
Associate Professors	Yutaka Kotsuka, M.D
	Jun Nakajima, M.D.
Lecturer	Arata Murakami, M.D. and
	Toshiya Ohtsuka, M.D.

Associate.....8
Graduate Students.....10
Research Students.....1

Past Research and Major Accomplishments

Dr. Takamoto invented a new method of brain protection during surgery of a distal arch aneurysm under deep hypothermia (Fig 1). The new method is a kind of retrograde cerebral perfusion, which simplify the retrograde perfusion system for patients of distal aortic arch aneurysmon. This new method has been accepted as a standard procedure of a distal arch replacement in all over the world. The method has been applied to many patients, and it was clarified that the method provides a prolongation of safety limits of circulatory arrest and a beneficial effect in prevention of brain embolism.

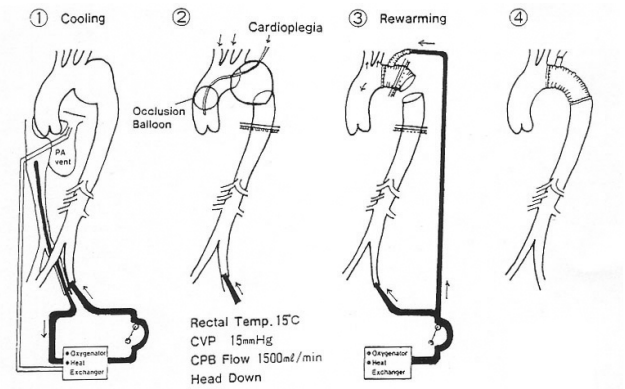


Fig 1

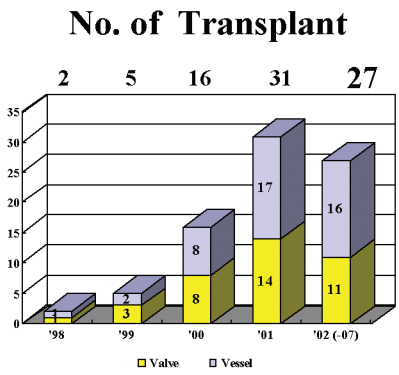


Fig 2

Allograft tissue has sevral advantages in that anti-infection, softness, and less compliance mismatching. Cell viability of the tissue can be maintained for more than hundred years if properly preserved under the liquid nitrogen. We started basic study on homografts tissue transplantation including the cardiac valve, aorta and trachea 8 years ago. We founded the Universty of Tokyo Tissue Bank (UTTB) in 1999, where human cardiac valves, vessels and tracheas

obtained from non-brain dead donors are cryopreserved. Cardiac valves are used for the patients of infective endocarditis, congenital heart disease. Vessels are used for artificial graft infection, liver transplant recipients. The number of donor and usage of these allogaft tissus are increasing every year, and more and more patients are being saved with these allograft tissues (Fig 2).

As for clinical activities, surgical cases are remarkably increasing as shown in the table below.

Table 1: Patients who underwent surgery in the department

	1997	1998	1999	2000	2001
Cardiovascular	152	157	179	225	272
General Thoracic	178	202	170	197	185
Total	330	359	349	422	457

Current Research

Thirteen staff members including professors and lecturers all participate not only in surgeries but also patient care on both in-patient and out-patient bases. They are all engaged in research activities for clinical and experimental subjects. As the subjects of cardiothoracic surgical fields are so close one another, we do not have sectioned research groups within our department. Instead, we make a project team for each research subject with most appropriate staff members and residents. Every associate takes part in at least one to several project teams. Main subjects of current research includes brain and spine protection during aortic surgery, homo- and xeno-transplantation of the heart, lung, heart valves and and trachea, surgical oncology of the pulmonary and thymic neoplasms, stent-graft repair for thoracic aortic aneurysm, minimally invasive cardiac surgery, and intraoperative 3-D echocardiography.

Spinal cord protection: Paraplegia remains one of the most serious complications after thoracoabdominal aortic aneurysm repair. In order to prevent paraplegia, it is important to identify and preserve critical segmental arteries. We developed new method to identify critical segmental artery. The ultrasonographic evaluation of the hemodynamics of intercostal arteries was the key to identify critical segmental artery (Fig 3).

Cryopreserved allotransplantation: Cryopreserved allogeneic heart valves and vessels have come to be widely utilized in cardiothoracic surgery because of their excellent durability. We have studied the allogenicity of the cryopreserved tissues using cell cultures of the airway epithelium, vascular endothelium, and fibroblasts. We have investigated whether cryopreserved tracheal allotransplantation is applicable. Experimental cryopreserved tracheal allotransplantation was performed in primates, which have a closer anatomical and immunological relation with humans than other animals, to confirm the possible clinical feasibility of cryopreserved tracheal allotransplantation. Immunogenicity was attenuated by cryopreservation, and cryopreserved tracheal allografts were incorporated in all animals (Fig 4).

Stent-graft repair: We developed ultrathin-wall vascular grafts with a wall thickness of 42 to 137 μm for endovascular surgery. We studied the physical properties of the ultrathin-wall grafts in in vitro experiments. We conclude that the newly developed ultrathin-wall grafts are suitable for endovascular surgery (Table 2).

After animal experiments, we applied the grafts to clinical patients with good results. We also developed auto-swelling vascular grafts, using ultrathin-wall Dacron vascular grafts and superabsorbent polymer. These grafts were designed to prevent endoleak following stent-graft repair of aortic aneurysm. Stent-grafts covered with auto-swelling grafts are expected to have beneficial effects in preventing endoleak.

Minimally invasive cardiac surgery: We have been using minimally invasive techniques in various procedures of thoracic and cardiac surgery. We have employed video-assisted thoracoscopic surgery (VATS) for pulmonary or mediastinal surgery since 1992. We have made retrospective studies on feasibility and surgical outcome of VATS for diagnosis and treatment of lung neoplasms. We have concluded that VATS for diagnosing pulmonary indeterminate nodules and

fig3

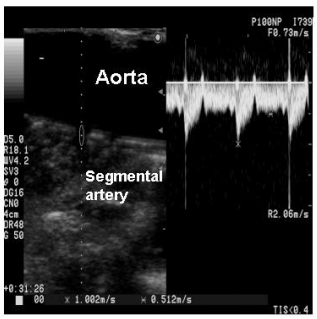


Fig.1: Segmental arteries are clearly identified with a 5MHz epiaortic scanning probe. The flow velocities of segmental arteries are measured with pulsed Doppler ultrasonography

fig4

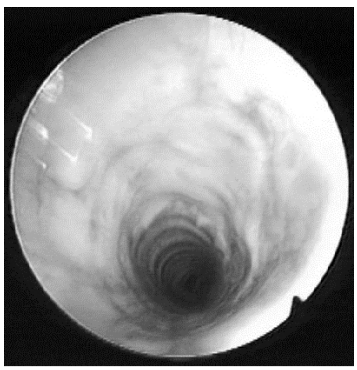
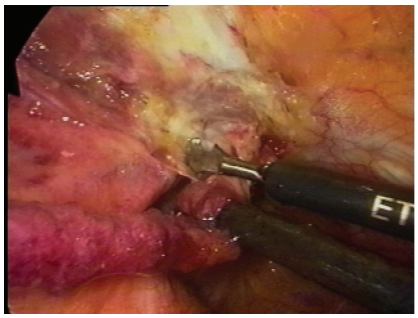


Table 2

Wall thickness (μm)	137	117	95	85	75	64	50	42
Transverse Microscopic Porosity (μm)	0	0	0	0	0	11.3±13.6	57.4±25.0	75.9±18.8
Longitudinal Microscopic Porosity (μm)	0	0	0	0	0	36.9±7.8	39.0±7.9	132.3± 7.8
Planimetric Porosity (μm2)	0	0	0	0	0	416±494	2,238±1193	>10,000
Longitudinal Tensile Strength (Kg)	22.5±2.0	19.4±1.2	15.3±0.8	14.1±1.8	13.1±0.9	9.5±0.9	7.4±0.5	–
Water Permeability (ml/min/cm2)	330±17	220±20	250±36	180±17	380±53	1,700±361	2,960±443	3,840±668

fig5

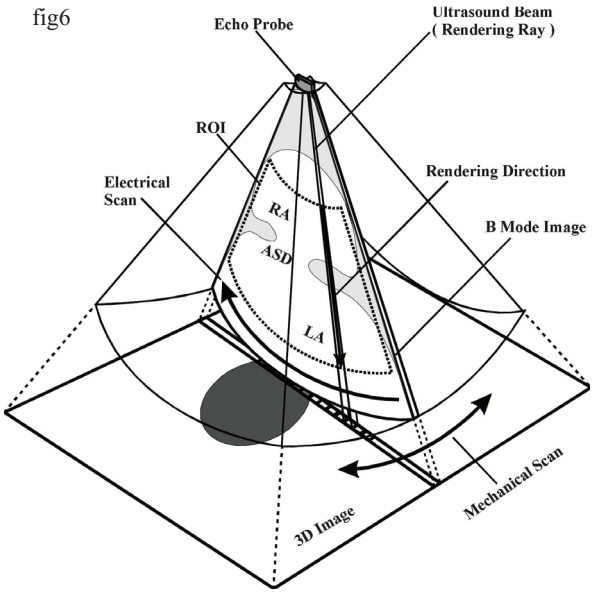


VATS for pulmonary metastasectomy are justified as a standard therapeutics. Off-pump coronary artery bypass is achieved without hemodynamic assistance by cardiopulmonary bypass, and it has been applied to increasing number of patients with multi-vessel ischemic heart disease. A single bypass from the internal mammary artery (IMA) to the left anterior descending coronary artery has been accomplished via a mini-thoracotomy approach. Valvular disease or atrial septal defect have been repaired via a limited sternotomy using a special retractor and port-accessible heart-lung machine. Video-endoscopy has been positively used for minimally invasive approach. Thoracoscopy has been used for mobilization of ITA graft (Fig 5), and cardioscopy has been used in valvular repair, correction of intra-cardiac anomaly, and left-atrial cryo-ablation.

Real-time 3-D echocardiography: We have developed real-time three-dimensional echocardiography (RT3DE) and applied it to monitoring heart operations, especially ASD closure, as a means of assisting treatment (Fig 6). In the animal experiment, ASD was successfully closed by RT3DE monitoring, and examination of the excised heart showed that all sutures were located, and the reliability of the images obtained by RT3DE was confirmed.

Surgical oncology of the thymic neoplasms: To classify the thymic epithelial neoplasms, the maturation stage of T-lineage lymphoid cells infiltrating thymic neoplasms (TIL) was examined by flow-

fig6



cytometry to associate it with the degree of tumor malignancy. $CD4^{+}CD8^{+}$ or $CD10^{+}$ T-lineage cells were the most reliable markers of the benignancy of thymic epithelial tumors. CD4 / CD8 single positive cells or CD20-positive cells were characteristic in thymic carcinoma. Flow-cytometry on the maturity of lymphoid cells infiltrating thymic epithelial tumors was feasible for determining their degree of malignancy. Recently we have investigated T-cell receptor (TCR) gene rearrangement of the TIL. We have observed the appearance of clonal bands in TCR-beta and gamma, suggesting that partial gene rearrangement occurred in the TIL.

Future Prospects

Cardiac Transplantation is established treatment in the world. However, this treatment has not been well developed in Japan due to domestic reasons. We are now preparing clinical cardiac transplantation. We are going to develop basic and clinical research on cardiac transplantation as well as clinical application.

Research Grants

1. Grant-in Aid for Scientific Research from the Japanese Ministry of Education, Science, Sports and Culture (A)(1): Studies on management of heart transplant recipients and maintenance of donor organs. 1998-2000
2. Grant-in-Aid for Publication of Scientific Research Results: Japan Adult Cardiovascular Surgery Database. 2002
3. Grant-in-Aid for University and Society Collaboration: Establishment of Tissue Banking System on the basis of regional linkage. 2000-2002
4. Grant-in Aid for Scientific Research from the Japanese Ministry of Education, Science, Sports and Culture (B)(2): Basic and clinical study on percutaneous endovascular surgery with ultrathin-wall vascular grafts. 1997-1998
5. Grant-in Aid for Scientific Research from the Japanese Ministry of Education, Science, Sports and Culture (B)(2): Development of auto-swelling vascular grafts using super-absorbent polymer. 1999-2001

Select Publications

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10. Kotsuka Y, Tanaka O, Takamoto S, Furuse A. Intravalvular implantation technique for aortic valve replacement in aortitis syndrome. Ann Thorac Surg 67, 89-92, 1999.
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22. Kubota H, Takamoto S, Kotsuka Y, & Furuse A: Successful treatment of massive pulmonary tumor embolism from renal cell carcinoma. Ann Thorac Surg 69, 972-3, 2000.
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34. Ohtsuka T, Takamoto S, Ono M, Motomura N. Aortic root replacement and coronary Interposition using a cryopreserved allograft and its branch. Eur J Cardiothorac Surg 20, 631-2, 2001.
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Department of Gastrointestinal Surgery / Department of Surgical Metabolism and Nutrition and Endocrine Surgery

Outline and Research Objectives

Since 2001, the former Third Department of Surgery, which was located in a branch hospital of the University of Tokyo, has been divided into two departments, the Department of Gastrointestinal Surgery and the Department of Surgical Metabolism and Nutrition and Endocrine Surgery, in line with the integration of the main and branch hospitals the elevation to a department in the graduate school of medicine at our university. Our research activities in both departments have been well organized and ultimately successful by maintaining a close connection.

The main research activities of the department of Gastrointestinal Surgery are focused on diagnosis and therapy for gastrointestinal diseases and clinical and basic research for gastrointestinal carcinogenesis. A historical and outstanding achievement of the department of Gastrointestinal Surgery is the successful innovation of the "Gastrocamera" a half century ago. Thereafter, we have been active in the diagnosis and treatment of gastric cancer and established the feasibility of extended gastrectomy with intraoperative chemotherapy for advanced cancer, and limited lymph node dissection for early gastric cancer. With a view to further development of research for gastrointestinal carcinogenesis, we established the Japanese Society for Gastroenterological Carcinogenesis in 1989, and have been studying the underlying mechanisms of development, progression and prevention of digestive cancer.

The department of Surgical Metabolism and Nutrition and Endocrine Surgery has been studying one of the most fundamental issues in surgery, i.e., "surgical stress," which indicates postoperative physiological and endocrinological internal reaction, and nutritional support for the postoperative patients. Our department is a pioneer in this area in Japan, and we established the Japanese Society for Surgical Metabolism and Nutrition in 1965. In addition, we have been studying endocrine issues, i.e., surgical therapy for breast, thyroid and parathyroid diseases.

Faculties and Students

Professor and Chairman	Michio Kaminishi, MD., Ph.D. (since 1997)
Associate Professor	Ken-ichi Mafune, MD., Ph.D. (Yoshikazu Mimura, M.D., Ph.D. from Division of Surgical Operation Center)
Lecturer	Shouji Shimoyama, MD., Ph.D. Toshihisa Ogawa, MD., Ph.D., Mitsue Saito MD., Ph.D.,

Associate.....12
Postdoctor Fellow.....8
Graduate Student.....9
Secretary.....4

Past Research and Major Accomplishments

In research on gastrointestinal carcinogenesis, we have established experimental models of gastric carcinogenesis and looked closely at the important roles of repetition of injury and regeneration of gastric mucosa. In particular, we demonstrated that infection of *Helicobacter pylori* acts not only in promotion but also in co-initiation of gastric carcinogeneis. This was the first report in the world to show the direct relationship between H.p. infection and gastric carcinogenesis using experimental models. Furthermore, we verified that duodenogastric reflux and denervation of the gastric mucosa enhance gastric mucosal injury, resulting in development of gastric remnant cancer.

Based on these results, we have adopted new operations for gastric cancer and obtained better results in terms of postoperative QOL and outcome. Our detailed histopathological analysis of colon carcinogenesis revealed de novo carcinogenesis other than adenoma-carcinoma sequence, leading to the current hypothesis of the dysplasia-carcinoma sequence.

In research on surgical metabolism and nutrition, we clearly showed the importance of nutritional support under condition of postoperative hypoxia and endotoxemia. Fatty acids reduced the morbidity and mortality due to panperitonitis, and glutamine attenuated acute lung injury after the organism was challenges with endotoxin. Research on the metabolism of phosphate, calcium and sodium is one of the most important means to clarify the mechanism of the postoperative physiological reaction. We demonstrated the close relationship between these metabolites and catecholamine after surgical stresses such as hypoxia, endotoxiemia and ischemic reperfusion injury. These studies aim to reduce the intra- and post-operative stresses that would be risky for patients.

Current Research

The main focus of our current research in the field of Gastrointestinal Surgery is the tailor-made treatment of cancer based on its stage and characteristics. We try to establish the optimal limited surgery for early cancer by application of sentinel node navigation system and molecular analysis of lymph node micrometastasis. For advanced cancer, multimodal therapy combined with extended surgery and perioperative chemotherapy is required. In regard to chemotherapy, a new strategy using apoptosis-related and/or cell differentiation-related agents is likely to achieve better prognosis in advanced cases.

Current research topics in the department of Gastrointestinal Surgery are the followings.

1) Carcinogenesis of gastrointestinal cancer

- Roles of *Helicobacter pylori* infection in gastric carcinogenesis
- Roles of Trefoil Peptides in gastric metaplasia
- Clinical and experimental studies on Barrett esophagus

2) Molecular mechanisms of gastrointestinal cancer

- Effects of hypoxia and nutritional deprivation on cancer development and progression
- Roles of PPARr in gastric carcinogenesis and treatment of gastric cancer by PPARr ligands
- Angiogenic factors in gastrointestinal cancer
- Telomerase activity in gastrointestinal tumors
- Lymph node micrometastasis of gastric cancer

3) Minimally invasive treatment of upper GI cancers

- Indication and results of laparoscopic surgery
- Sentinel node navigation surgery for early gastric cancer
- Evaluation of results of PPG and jejunal interposition after gastrectomy in terms of postoperative QOL

4) Multimodal treatment for esophageal and gastric cancers

- Neoadjuvant or definitive chemoradiation therapy for esophageal cancer
- Apoptosis induced by TRAIL
- Prediction of gastric cancer recurrence by molecular analysis of samples of peritoneal washes
- Mechanisms of adverse effects of chemotherapy for gastrointestinal cancer on the intestinal mucosa and its preventive therapy

5) Gastrointestinal motility

- Mechanism of peppermint oil solution on relaxation of digestive tract
- Role of cytokine and COX-2 in gastrointestinal motility
- Effects of intra- and extra-abdominal environments on gastrointestinal motility
- Gastric motility after gastrectomy

The main focus of our current research in the field of Surgical Metabolism and Nutrition is "adaptive response to surgical stresses". In particular, "cross tolerance among different stresses" is a very challenging and important phenomenon to be elucidated, and the clinical application of findings will lead to reduction of morbidity and mortality due to severe surgical stresses and endotoxin shock. On the other hand, there is a definite difference in adaptive response to surgical stress between genders. We have clearly demonstrated the gender difference in cytokine secretion after endotoxin challenge.

In the field of Endocrine Surgery, we have introduced minimally invasive surgery for breast cancer and thyroid tumors through the application of laparoscopic procedures. In terms of differential diagnosis of thyroid tumors, we established a method for the immunohistochemical detection of telomerase reverese ranscriptase (hTERT) by in situ hybridization, providing a good marker for distinction between follicular adenoma and follicular cancer.

Current research topics in the department of Surgical Metabolism and Nutrition and Endocrine Surgery are the followings

1) Surgical metabolism and nutrition

- Mechanisms of cross tolerance among different stresses (endotoxin-hypoxia/ hypoxia-endotoxin) after surgery
- Role of catecholamines in adaptation to surgical stress such as endotoxemia
- Bacterial translocation after major surgery and anti-cancer chemotherapy
- Gender difference is a modulation factor for post-operative morbidity
- Parathyroid function after surgical stress
- Ischemic preconditioning and its underlying mechanism (NO, HSP, metalothionein)

2) Endocrine surgery

- Cytology of breast and thyroid tumors by in situ hybridization of telomerase reverse transcriptase (hTERT)
- Effects of preoperative endocrine therapy of breast cancer
- Detection of breast cancer cell in the drainage vein from the breast by using RT-PCR
- Molecular analysis of heterogeneity in breast and thyroid cancers
- Development of QOL questionnaire for breast cancer patients

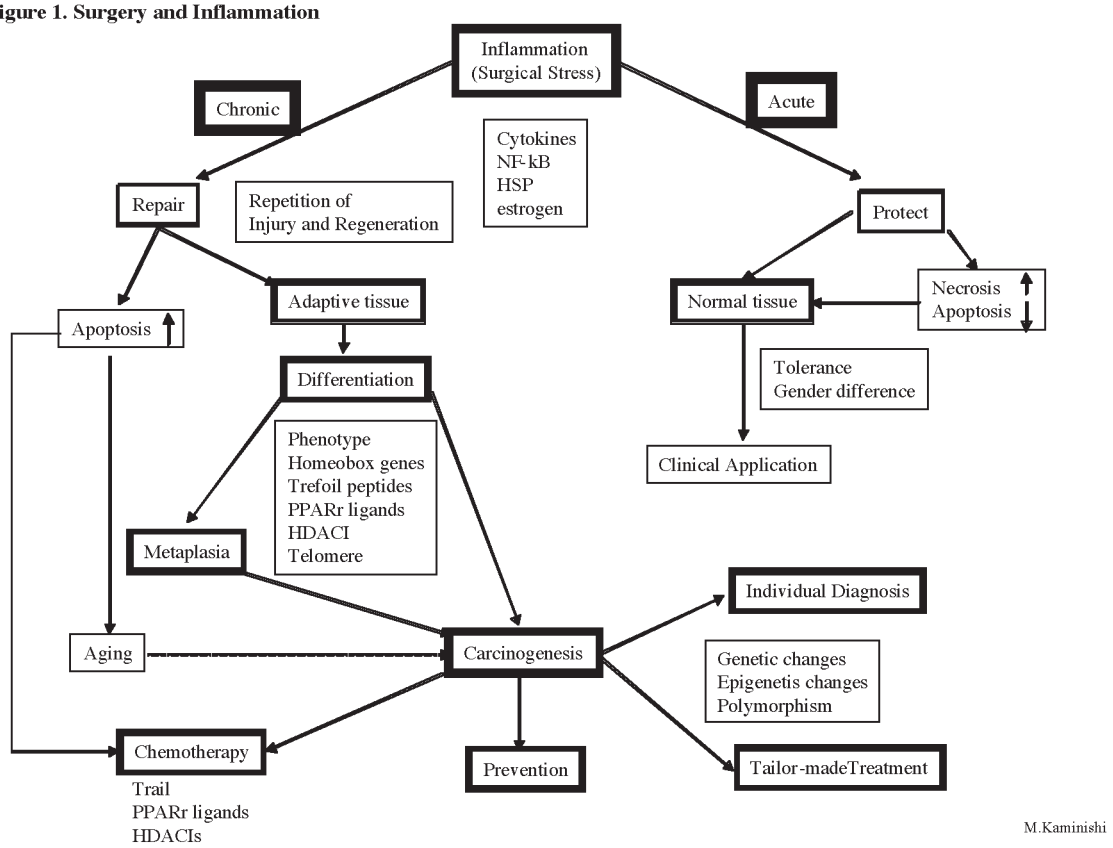
Future Prospects (Figure 1)

Our main theme in basic and clinical research is "Surgery and Inflammation". There are 2 phases of inflammation, acute and chronic. Under acute inflammation or acute stress, injured tissue recovers to normal promptly after subsidence of the acute causes. In that case, the organ represses apoptosis and maintains or restores the normal tissue. Many factors such as cytokines, NO, NF-κB, and HSP play important roles in development and progression of the inflammatory process. Conversely, these molecular factors play a key role in the attenuation of morbidity through across tolerance mechanism. Clinical application of therapy based on cross tolerance leads to a better prognosis for morbid patients after severe surgical stress.

Under chronic inflammation, for, example, In cases of chronic gastritis, however repetition of injury and subsequent regeneration is observed regardless of the causes. The accelerated regeneration of the gastric mucosa induces a newly developed tissue that is adapted for chronic injury by balancing cell proliferation and apoptosis. This phenomenon is widely recognized as metaplasia and all metaplastic change in the human organ is considered to be a result of adaptive reaction. Furthermore, the metaplastic cells and/or the cells departing from the adaptive process have potential for malignant transformation.

The relation between chronic inflammation and carcinogenesis is commonly observed not only in the stomach, but also in the esophagus, colon, liver and other tissues. Examples include reflux esophagitis and Barrett's cancer, ulcerative colitis and colitic cancer, viral hepatitis and hepatoma. Some key factors such

Figure 1. Surgery and Inflammation



as NF-kB, COX, NO, PPARr, HSP, and trefoil peptides play important roles in the process of chronic inflammation. In addition, those factors are also expressed in breast and thyroid tumors.

The development of molecular biology-based diagnosis for cancers and the tailor-made treatment for cancer patients depending on the properties of each cancer and each patient's genetic background, are urgent issues. Further analysis of the relevant factors may contribute to advances in diagnosis, treatment and prevention of not only gastrointestinal cancers but also breast and thyroid cancers. In particular, PPARr, trefoil peptide and histone deacetylase inhibitors (HDAIs) modulate not only cell proliferation but also cell differentiation. We are trying to develop a new strategy of molecular targeting therapy for gastrointestinal, breast and thyroid cancers by application of these cell-differentiating factors.

Research Grants

- Clonal analysis of isolated intestinal metaplastic glands of stomach using X linked polymorphism
- Quantitative detection of micrometastases in the lymph nodes of gastric cancer patients with real-time RT-PCR
- Histopathological change and expression of genes and proteins in chief cells through gastric carcinogenesis in rodent models
- Sublethal endotoxin administration evokes superresistance to systemic hypoxia.
- Telomeres and telomerase activity in digestive and endocrine organs: Clinical application to the diagnosis and therapy.

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Department of Hepato-Biliary-Pancreatic Surgery / Department of Artificial Organ and Transplantation

Outline and Research Objectives

In September 1893, Professor Sankichi Satoh founded "the Second Department of Surgery, University of Tokyo". He was a pioneer of visceral surgery in Japan and he also founded the Japanese Society of Surgery in 1899. His pupils, professor Waichiroh Okada, professor Keizo Doi, professor Hisashi Ishihara founded departments of otorhinolaryngology, dermatology, and dental surgery, respectively at Unversity of Tokyo Hospital.

In May 1952, professor Seiji Kimoto became the 5th chairman of our department. He was a pioneer of cardiovascular surgery in Japan, and founded the department of thoracic surgery in 1964. In the same year, he also performed the first case of kidney transplantation in Japan.

In July 1971, professor Shigeru Hatano, the 6th chairman, founded the department of Pediatric Surgery.

In April 1994, I (professor Masatoshi Makuuchi) became the 10th chairman. I started living donor liver transplantation on January 31st, 1996 and has done 191 cases by the end of September 2002. As the result of the shift to the Graduate School of Medicine, the three Departments of Surgery were transformed to one Department and 6 divisions in April 1998. Our second Department of Surgery took charge of "Hepato-Biliary-Pancreatic Surgery Division, andArtificial Organ and Transplantation Division".

Our current main research objectives are surgical treatment of hepato-biliary-pancreatic cancer, liver transplantation, and development of artificial liver.

Faculties and Students

Professor and Chairman	Masatoshi Makuuchi, MD, PhD (1994-)
Associate Professors	Norihiro Kokudo, MD
	Yasuhiko Sugawara, MD
Lecturer	Hiroshi Imamura, MD
Associate	11
Postdoctal Fellow	5
Graduate student	9
Research student	2
Secretary	4

Past Research and Major Accomplishments

Between late 1970's and early 1980's, I have developed the application of ultrasound to the various treatment modalities of hepatobiliary diseases. First, I have developed the percutaneous transhepatic cholangiography (PTC) and the percutaneous transhepatic biliary drainage (PTBD) method under ultrasound guidance. With these methods, intrahepatic biliary tract was punctured selectively and drainaged directly by real-time guidance. Ultrasound-guided PTC and PTBD methods are simple and easy to perform and now are widely used over the world. I also investigated precisely the anatomy and its variation of the intrahepatic portal branches for the first time by the ultrasound examination. Before this work, information on its anatomy was obtained mainly by the study of the cadaveric liver which was somewhat mal understood or by the angiographic studies which by itself does not allow a precise evaluation on each patients. I then developed an intraoperative ultrasound probe and it was facilitated liver surgery for the first time in the world. By its usage, the positional relationship between the tumor and intrahepatic vasculobiliary structure can be understood during the hepatic parechymal transection. This is particularly important in liver resection in cirrhotic liver because the examination of the tumor by bimanual palpation is difficult in such cases. Further, I developed the method to resect anatomically the Couinaud's segment by the aid of ultrasound and so-called staining technique of the intrahepatic portal branch. This small but anatomical resection is now accepted as a standard procedure for the patients with hepatocellular carcinoma de facto and called also as 'Makuuchi's

procedure'. Based on the findings of the liver anatomy, I have developed and performed, besides the above described anatomical resection, central bisectorectomy or right paramedian sectorectomy. This can be considered a remarkable advance in the era when solely the right or left hepatcetomy was performed as anatomical hepatc resections.

Development and application of intermittent hemihepatic or total inflow occlusion technique is also a fruit of my effort in this period. In 1980's, total inflow occlusion was sporadically carried out over the world. But it was used always as a continuous manner and maximum length of the occlusion was considered 60 minutes. Moreover, it was almost a central dogma that the cirrhotic liver could not tolerate the inflow ischemia. Since intermittent ischemia was a recycle of ischemia/reperfusion injury it was believed to be worse than continuous ischemia. In these circumstances, I, for the first time, proved the inflow occlusion can be applied to cirrhotic liver and intermittent inflow occlusion can be applied safely and better than continuous occlusion technique.

The development of various operative procedures preserving the thick short hepatic vein as a drainage vein of right lateral sector and scarifying the right hepatic vein is the achievement of this period. In addition, I first demonstrated the right hepatic vein can be safely divided and ligated extrahepatically if the inferior vena cava ligament was divided and cut prior to the dissection. These vein and ligament are now called as 'Makuuchi's vein' and 'Makuuchi's ligament' worldwide.

Extended right hemihepatectomy is often necessary in the surgical treatment of hilar cholangiocarcinoma. Such a procedure may lead to the increased risk of postoperative liver insufficiency. I have developed and applied the preoperative portal vein embolization (PVE) to induce the atrophy of the liver to be resected and thus induce the compensatory hypertrophy of the liver part to be preserved after the resection. In 1982, I performed the first case of PVE in the world. This method is simple to apply and now is widely applied all over the world.

By virtue of the development of these procedures and improvement in the technical skill, the operative mortality of liver resection in my institute is almost zero including that for the cirrhotic liver and for the hilar cholangiocarcinoma compromized with obstructive jaundice.

In June 1990, I started living donor liver transplantation (LDLT). Based on my own experience of LDLT, I have proposed a formula that allows the calculation of the ideal liver volume to the recipient or the donor used the preoperative decision of what kind of donor hepatectomy should be performed. This formula is now called as 'Makuchi's formula'. In 1993, I performed successfully for the first time in the world the adult-to-adult LDLT using left hemiliver. Following this success, I have carried out adult-to-adult LDLT including emergency transplantation for patients with fulminant hepatic failure. The number of patients undergoing LDLT until now exceeds 200 cases with less than 10 % overall mortality. Recent my contribution to this field is the establishment of the feasibility of the right lateral sector graft and the establishment of the criteria for reconstruction of the middle hepatic venous tributaries in case of right hemiliver graft.

Current Research

I have established a safe and effective hepatic resection techniques based on the liver anatomy and challenged repeated hepatic resections for recurrent liver tumors including hepatocellular carcinoma (HCC) and metastatic tumors. As one of the top institutes of hepato-biliary surgery in the world, we have achieved no mortality and minimum morbidity hepatic resection in recent series of patients, and we have encouraged surgeons worldwide. The accumulated clinical data will reveal the long-term results that demonstrate the advantages of surgical treatment for liver tumors. The molecular biological investigations of liver tumors will elucidate the biological behaviors and prognostic factors of these malignant diseases. However, there are a number of patients with HCC who are not candidates for hepatic resection because of the limited liver functional mass. Since Milan group reported promising results of orthopic liver transplantation for HCC in selected cases, I have started living donor liver transplantation (LDLT) for recurrent HCC. As one of the treatment options for HCC, LDLT will be commonly performed in Japan. The indications for cadaveric liver transplantation for HCC have been limited because of donor shortage. I am trying to expand the indications of LDLT for HCC beyond the Milan criteria. The long-term results may clarify the indications for LDLT for HCC.

Strong and co-workers reported the first successful transplantation from a living donor (LDLT). LDLT is mainly conducted in an attempt to alleviate the shortage of donor organs and to decrease mortality among children awaiting transplants. I started the LDLT program in 1990 when I was in Shinshu University. The indications of LDLT expanded to the adults and I performed the first successful case in 1994. After I moved to University of Tokyo, I started the program in 1996. Until September 2002, I accumulated 191 cases. The mortality rate of the patients is less than 10%, which is much superior to the world standard.

The major limitation for LDLT for adults is the adequacy of the graft size. To overcome this problem, I devised the left liver plus caudate lobe graft with its

venous reconstruction. The caudate lobe can provide about a 7% increase in graft weight, which contributed the less frequent cholestasis after the operation. The right liver graft is now most commonly used graft in LDLT for adults. The right liver graft is usually harvested without the trunk of the middle hepatic vein. However, this type of grafts can cause severe congestion of the right paramedian sector because middle hepatic vein often drains the considerable part of this sector. Middle hepatic vein drainage into the recipient's venous system can be reconstructed using vein grafts. This provides a functioning liver mass comparable to an extended right liver graft. I firstly proposed reconstruction criteria.

Right liver harvesting from living donors is sometimes dangerous when the volume ratio of right liver is large. Some donors have larger right lateral sector compared with left liver. I firstly performed LDLT suing this type of graft.

List of On-going Research Projects

1) Hepato-pancreato-biliary surgery

Extended hemihepatectomy for hilar bile duct carcinoma
Development of ultrasonic diossector equipped with electrocautery
Liver resection of liver metastases from GIST
Long-term evaluation of two-staged pancreaticoduodenectomy
Intraoperative ultrasound-guided direct pancreatography
Liver hypertrophy after hepatopancreatoduodenectomy
Resection of S4inf during hepaticojejunostomy
Reconstruction of superior mesenteric vein using cryopreserved homograft vein
Repeated hepatic resection for colorectal metastases
Risk factors for biliary leakage after liver resection
Arterial buffer response in cirrhotic patients
Evaluation of hepatic functional reserve using GSA scintigraphy
Resection of IVC wall and/or root of hepatic vein in colorectal metastasis
Effect of cimetidine on the postoperative recurrence in HCC patients
Disruption of pRb-p16^{INK4} pathway: a common event in ampullary carcinogenesis
Qualitative and quantitative analysis of des-gamma-carboxy prothrombin (DCP) in cancerous and non-cancerous liver tissue of patients with HCC
Protein induced by Vitamin K absence or antagonist II absence (PIVKA-II) in cancerous and non-cancerous liver tissue of patients with HCC
Serum anandamide levels in infection

2) Transplantation

Diagnostic criteria for fungal infection in post-transplant patients
Quality of life in donors for LDLT
Argorythms for the timing of liver biopsy after LDLT
Effect of hANP in post-transplant oliguria
Serological marker for early detection of carinii pneumonia
Reconstrucrion of venous tributaries in right liver graft (long-term outcome)
Re-evaluation of the Milan's criteria for the indication of cadeveric liver
transplantation to patients with hepatocellular carcinoma
Donor inflow occlusion technique in living donor liver transplantation
Liver regeneration in donors
Development of anti-septic biliary drainage tube for LDLT

3) Artificial Organ

Artificial liver for xeno-cross circulation and clinical application
Artificial liver and transgenic pig for clinical application
Development of artificial erythrocyte for liver support system
Reconstruction of liver tissue using bone marrow transplantation

Future Prospects

Beyond the technical challenges are various medical issues that perhaps need to be given greater attention in the future. LDLT has come to address a health concern of epidemiologic dimension in Japan, namely hepatitis B and C and consequently occurred hepatocellular carcinoma. Recurrent disease after liver transplantation remains a major threat and efforts aimed at prevention and cure have to continue.

Issues related to immunosuppression have to be tackled and induction or facilitation of graft tolerance, which may not be as elusive in LDLT, is yet to be achieved. Management of infection in the immunosuppressed transplant patient is a peculiar challenge that transplant specialists must face in the near future.

Research project of artificial liver device is almost close to clinical use for the bridge to liver transplantation for the patients with liver failure. Recent advance of research about the regeneration medicine has demonstrated the possibility of hepatocyte differenti-

ation from bone marrow or embryonic stem cells. For the treatment of fulminant liver failure, the human hepatocytes cultured and expanded from bone marrow will be used in the future.

Research Grants

1999-2001 Improvement of surgical treatment for biliary cancer.
Grant for the prevention of cancer, the ministry of health and labor
4,800,000 yen

1999-2001 Artificial liver for xeno-cross circulation and clinical application
Grant from the ministry of education and science (A)(2)
35,800,000yen

2000-2001 Clinical improvement and development of organ transplantation
Grant for the human genome and regeneration, the ministry of health and labor
4,500,000 yen

2000-2001 Research on intractable liver disease
Grant for intractable diseases, the ministry of health and labor
1,000,000 yen

2001-2002 Artificial liver and transgenic pig for clinical application
Grant for advanced medicine (A), the ministry of health and labor
196,840,000 yen

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Department of Urology

Outline and Research Objectives

Originally, our department had been attached to Department of Dermatology since 1890, later in 1926, the current department of urology was founded. Initially, urology dealt with urinary tract infection, especially gonorrheal urethritis. Subsequently, its scope has been expanded dramatically and now is covering the diseases of the adrenal gland, the kidney, the urinary tract and the male genital system by means of surgical and non-surgical procedures. Its subspecialty includes pediatric urology, neurourology, female urology, renal transplantation, vascular surgery, endocrine surgery and geriatric urology. For this reason, urology in these days is beyond a section of surgery.

During these progresses, we have been taking national and international leadership in developing and applying the new or minimally invasive treatment modalities. They are exemplified by endoscopic management of the diseases in the upper urinary tract, extracorporeal shock wave lithotripsy (ESWL), laser therapies for prostatic hypertrophy and laparoscopic adrenalectomy or nephrectomy substituting open procedures. Nowadays we are expanding the frontier by introducing less invasive surgeries or more sophisticated treatment modalities to urology. This expansion is supported by incorporating updated cellular and molecular biology to clinical medicine.

Faculties and Students

Professor and Chair	Tadaichi Kitamura, M. D., Ph. D. (1998-)
Associate Professors	Yukio Homma, M. D., Ph. D., Nobutaka Ohta, M. D., Ph. D.
Lecturers	Takumi Takeuchi, M. D., Ph. D., Satoru Takahashi, M. D., Ph. D. Kyoichi Tomita, M. D., Ph. D., Makoto Suzuki, M. D., Ph. D.

Associate.....12
Graduate student.....11
Research student.....3
Secretary.....5

Past Research and Major Accomplishments

1) Clinical accomplishment

We have been applying endoscopic procedures to clinical practice as less invasive treatment modalities. For example, we are the pioneers of pyeolureteroscopy, by which the upper urinary tract diseases are endoscopically managed.

We have developed new prognostic predictors such as fluorescence in-situ hybridization analysis of exfoliated urothelial cells for bladder cancer recurrence. We examined accuracy of diagnostic procedures for voiding dysfunctions and detected anatomical and electrophysiological abnormalities of the striated urethral sphincter in stress urinary incontinent women.

As the new treatment modalities, dendritic cell immunotherapy was successfully performed in patients with metastatic renal cell carcinoma. Magnetic stimulation of the sacral roots was developed to improve urinary incontinence.

2) Basic research

In oncology field, we found that hepatocyte growth factor, IL4, Fas ligand or caspase-1 enhanced the invasiveness of renal cell carcinoma, and that anti-apoptotic Bcl-2 proto-oncogene expression increased resistance of human prostatic cancer cells to various apoptotic stimuli. For bladder cancer we detected frequent agreement of genetic alternations (loss of heterozygosity at 10 microsatellite loci and methylation of $p16^{INK4}$ CpG-island) in cancerous mucosa and "normal" bladder mucosa, suggesting morphologically normal epithelium possesses genetic or epigenetic aberrations common with cancer.

In nephrology we produced a knockout mouse model of autosomal dominant polycystic kidney disease (ADPKD) with a targeted deletion of *Pkd1*. Homozygote embryos developed hydrops, cardiac conotruncal defects and renal cystogenesis partly through the E-cadherin-b-catenin-c–MYC pathway and tyrosine phosphorylation of EGFR and Gab1. Maternally-administered pioglitazone, a thiazolidinedione compound, improved survival of knockout embryos, the degree of renal cystogenesis and endothelial dysfunction, suggesting thiazolidine-

diones as a new therapeutic for ADPKD.

Other basic investigations include transplantation research to improve graft survival by expressing IL4 or Fas ligand in the graft, and pharmacologic researches to examine adrenoceptor expression in the prostate or to apply adrenomedullin, a vasorelaxant peptide, to erectile dysfunction and nephron sparing surgery.

3) Investigation in urinary virology

Over these 15 years, we have been investigating the mode of infection in urinary polyomavirus JC virus (JCV) that causes progressive multifocal leukoencephalopathy in immuno-compromized patients. It has long been known since 1970's that JCV is ubiquitous in the human population and infects children asymptomatically. However, other characteristics of JCV had not been elucidated further. From our long-run study for about 15 years, many facts have been elucidated. JCV persists and replicates in renal tissue throughout life and is shed frequently into urine after late adolescent and the excretion rate exceeds 60% after around age 50.

The main mode of transmission of JCV is from parents to children through long term cohabitation. During the course of study, we have identified 3 major types of JCV, types A, B and C, according to their DNA sequence variance. A distinct relationship was demonstrated between JCV genotypes and human races. Type A is predominant in Caucasian and type B predominates in Asian, while most Africans have type C, which is verified by phylogenetic tree analysis. Recently Japanese-Americans have shown to reserve their original or Japanese type of JC virus, which supports the hypothesis that JCV is transmitted mostly within the family through long-term cohabitation. As of the end of September in 2002, many urine samples have been collected from across the world more than 50 different countries. In a result, JCV can be classified into at least 12 JCV genotypes that occupy unique domains in the world. Each of 12 JCV genotypes has a special association with distinct human population. Those results have been published in 20 papers of PNAS, J of Virology, Virology, J of Infectious Diseases, and so on.

Current Research

We are more and more concentrating on prostate cancer as the target disease. The expression level of estrogen receptor and its responsive genes are analyzed to further understand molecular mechanisms of responsiveness of prostate cancer cells to estrogens. The expression level of these molecules in human specimens is investigated for predictability of clinical progression of the prostate cancer. Cadherin and its variant forms are also investigated for its predictability of invasion and metastasis of the prostate cancer, urinary bladder cancer and renal pelvic cancer. Genetic variant of metabolic activation of estramustine phosphate is analyzed for individual patients with hormone refractory prostate cancer to minimize adverse events associated with the agent. Laparoscopic surgery has been established for adrenalectomy, and now being used for prostatectomy, nephrectomy and nephroureterectomy. Treatment for advanced cancer is a challenge in oncology. A new combination chemotherapy regime including paclitaxel and cis-platinum is attempted for metastatic prostate and bladder cancers. Tissue oxidative stress, which is measured by the ratio of reduced-to-total coenzyme Q contents, is now investigated in relation to carcinogenesis, invasion and metastasis of prostate cancer in rats.

Apart form prostate cancer we are developing instruments to measure symptoms and quality of life to assess the efficacy of treatment for voiding dysfunction. As an innovative treatment modality for benign prostatic hyperplasia, high-intensity-focused ultrasound that evaporates prostatic tissue is being applied to reduce the urethral obstruction. Alpha-adrenoceptor is known to mediate tonus of bladder outlet. Knock out mice of the receptors are being investigated for their voiding habits and physiological characteristics of the prostate and bladder. We are exploring genetic abnormality in recurrent stone formers with special interest in genes related to sodium dicarboxylate cotransporter, which transports citrate in renal tubules. For virology we are now examining the offspring of mixed marriages to address the issue of whether JCV has a paternal or maternal bias to its transmission to children. JC virus genotypes in *AINU* people and Antarctic people are analyzed to obtain further information on migration of human-beings in the history..

Future Prospect

Of clinical relevance, improving skills for endoscopic surgeries, especially for laparoscopic procedures are mandatory.

In the field of basic research, tailor-made medicine for advanced prostate cancer will be mainly pursued hereafter, as well as elucidating the pathogenesis of urological malignancies. Besides oncology, clinical and basic research will be performed in the fields of neurogenic bladder, female urology, geriatric urology, urolithiasis, erectile dysfunction and urinary virology.

Research Grants

1. Grant source Grant-in-Aid for Scientific Research (A) from the Ministry of Education, Science, Sports and

Culture, Japan Research title Application of gene therapy in urologic oncology Principle investigator Tadaichi Kitamura Fund amount 28,800,000 Yen Term 1999-2002

2. Grant source Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Science, Sports and Culture, Japan Research title Prevention of prostate carcinogenesis by suppressing tissue oxidative stress Principle investigator Yukio Homma Fund amount 3,200,000 Yen Term 2001-2004
3. Grant source Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Science, Sports and Culture, Japan Research title Functional role of adrenoceptor subtype in lower urinary tract obstruction in knockout mice Principle investigator Nobutaka Ohta Fund amount 14,700,000 Yen Term 2001-2002
4. Grant source Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Science, Sports and Culture, Japan Research title Estrogen receptors and estrogen receptor responsive genes in prostate cancer and benign hyperplasia Principle investigator Satoru Takahashi Fund amount 4,000,000 Yen Term 2002-2003
5. Grant source Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Science, Sports and Culture, Japan Research title Role of cadherins in invasion and metastasis of prostate cancer Principle investigator Kyoichi Tomita Fund amount 3,600,000 Yen Term 2001-2002

Select Publications

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Department of Surgical Oncology

Outline and Research Objectives

The Department of Surgical Oncology was taken over from the First Department of Surgery, which was established in 1893. Dr. Tetsuichiro Muto, who was the ninth Professor of the First Department of Surgery, was appointed as the first Professor of the Department of Surgical Oncology in 1997 based on the introduction of a new system for postgraduate education. Dr. Hirokazu Nagawa was appointed as the second Professor of this department in 1999.

The main research objective in this department is to augment quality of life in patients with malignant disorders by applying knowledge of radiology, molecular biology, cell biology and immunology to clinical setting as well as surgical techniques.

The Department of Surgical Oncology provides comprehensive evaluation, diagnosis, treatment and management for adult patients with both general and oncologic surgical problems, in the ambulatory as well as inpatient setting. Additionally, surgical specialities in the department include the treatment of benign and malignant disorders of the breast and management of malignancies of the gastrointestinal tract (esophageal, gastric, and colorectal). The department is also well known for its innovative therapy for inflammatory bowel disease. Department specialists have expertise in biological cancer immunotherapy, chemotherapy for a variety of malignancies, and radiotherapy for rectal cancer. The department was responsible for 309 inpatients and 18,845 outpatients in the 2000 fiscal year, and 402 inpatients and 16,663 outpatients in the 2001 fiscal year.

Faculties and Students

Professor and Chair	Hirokazu NAGAWA, M.D., Ph.D. (1999-)
Associate Professors	Toshiaki WATANABE, M.D., Ph.D.
Lecturer	Joji KITAYAMA, M.D., Ph.D.
Associate	9
Postdoctoral Fellow	5
Graduate Students	16
Research Students	7
Secretaries	5

Past Research and Major Accomplishments

1. Preoperative radiotherapy for lower rectal cancer

Preoperative radiation therapy for advanced rectal cancer has been reported to reduce local recurrence in studies in Western countries, but its effectiveness has not yet found wide acceptance in Japan. The reason for this seems to be that although the local recurrence rate is lower in the irradiated group than that in the non-irradiated group in studies in Western countries, the rate shows values around 10% (7.8% to 12.4 %), which is almost equal to or somewhat higher than the rate after surgical treatment alone in Japan. This might be due to the difference between Western countries and Japan in terms of surgical procedure in that the importance of regional lymphadenectomy including lateral node dissection has been emphasized for advanced lower rectal cancer in Japan. Thus, extended lymphadenectomy including lateral node dissection (EXT-L) contributes to a low incidence of local recurrence of lower rectal cancer. However, EXT-L is frequently associated with impairment of sexual and urinary functions. We therefore compared the effectiveness of preoperative radiotherapy with that of EXT-L in a prospective, randomized, controlled study as well as a retrospective analysis. Our studies have suggested that lateral node dissection is not necessary in terms of curability for patients with advanced carcinoma of the lower rectum who undergo preoperative radiotherapy (**reprint numbers 1 and 2**).

Thus, preoperative radiotherapy reduces the rate of local recurrence and improves the chance of survival in patients with resectable, advanced rectal carcinoma. However, because not all tumors respond similarly to radiation, sorting out suitable patients is required to irradiate tumors rationally. Therefore, we investigated the predicting values of radiosensitivity in human rectal carcinoma. Specifically, p53, p21/WAF1 and Ku protein expressions in preradiation

biopsy specimens from patients with primary rectal carcinoma were analyzed immunohistochemically. The proteins of p53 and p21 are those related to cell cycle and apoptosis pathways, and Ku protein is related to the repair of damaged DNA. Our studies have indicated that immunohistochemistry detection of p53, p21 and Ku expressions may be useful parameters for selecting patients with rectal carcinoma for preoperative radiotherapy **(reprint numbers 3 and 4)**.

2. Appropriate application of chemotherapy to patients with colon carcinoma

A combined administration of 5-fluorouracil (5-FU) and leucovorin is regarded as a standard chemotherapy for patients with colon carcinoma. Not all tumors, however, respond similarly to the regimen of chemotherapy. Therefore, we investigated the predicting values of chemosensitivity in patients with colon carcinoma from viewpoints of metabolism and apoptotic effects of 5-FU on the tumors. Specifically, we investigated the effects of thymidylate synthase (TS) and dihydropyrimidine dehydrogenase (DPD) from metabolic aspects and Bcl-2 family from apoptotic aspects on the colon carcinoma. Our studies have indicated that TS is a prognostic factor for colon carcinoma, and that 5-FU adjuvant chemotherapy is appropriate for colon carcinoma with high expression of TS and low expression of DPD **(reprint number 5)**. Our studies have also suggested that the ratio of Bcl-X_L (apoptosis inhibitor) to Bax (apoptosis inducer) is related to chemosensitivity to 5-FU **(reprint number 6)**.

3. Analysis of cell functions from the viewpoint of anti-tumor immunity

Immunotherapy using dendritic cells (DCs) is a modality for cancer patients. We have analyzed characteristics of DCs for the purpose of applying effective DCs to clinical setting. We have demonstrated for the first time the direct activation of human natural killer (NK) cells by DC-NK cell interaction in vitro, suggesting that DCs may have a central role linking the innate and adaptive immune responses. Moreover, in stimulating NK cell function, peripheral blood DCs appear to have a different potential from monocyte-derived DCs. Furthermore, the function of dendritic cells (DCs), antigen-presenting cells that can initiate and regulate cellular and humoral responses, is highly influenced by their level of maturation. Immature DCs may be harmful in anti-tumor immunotherapy, because they can induce immunotolerance rather than immunostimulation. With respect to this issue, we have demonstrated that DC culture in an anti-CD40 monoclonal antibody-immobilized plate in medium supplemented with interferon-gamma has a positive impact on DC maturation and may be optimal for eliciting an antigen-specific T-cell response without the need for CD4+ T-helper epitopes **(reprint number 7)**.

Another candidate of effector cells on the anti-tumor immunity is a subset of natural killer (NK) cells in the liver, which are enhanced by alpha-glycosylceramides. Alpha-glycosylceramides induce antitumor immunity in various murine cancer models. Our observations have strongly suggested the potential usefulness of alpha-glycosylceramides for immunotherapy of liver cancer in humans based on their ability to activate CD3-CD56+ NK cells in the liver **(reprint number 8)**.

4. Experimental analysis of hematogenous and lymphatic metastasis on gastrointestinal cancers

We have made efforts to elucidate the mechanism of hematogenous and lymphatic metastasis on gastrointestinal cancers using a flow adhesion system. With respect to hematogenous metastasis, cultured colon cancer cells bound to laminin (LM), but not to fibronectin or vitronectin under the physiological shear condition. Most of the tethered cells did not roll, but arrested immediately and spread within 10-30 min on LM under the continuous presence of shear flow. Our data have suggested that LM can mediate from tethering to spreading of colon cancer cells under the blood flow and plays an essential role in hematogenous metastasis. Our studies have also suggested that E-selectin alone can mediate colon cancer cell lodgment and subsequent metastasis without the contribution of integrin molecules and that the different distribution of E-selectin ligands may affect the adhesion behavior of colon cancer cells in flow conditions **(reprint number 9)**.

With respect to lymphatic metastasis, our studies have indicated high affinity between cancer cells and lymphatic endothelial cells (LEC), and suggested that lymph node metastasis arises from cancer cells adherent to LEC, which can be augmented by an inflammatory stimulus.

5. Projects on upper gastrointestinal tract

Although our study is mainly focused on colorectal cancer, we have also investigated and achieved gastric and esophageal cancers in terms of scientific research as well as surgical techniques. Recently, we identified X-chromosome-linked inhibitor of apoptosis protein (XIAP) and the gene was designated as hRFI, standing for human Ring Finger homologous to IAP type. Northern blot analysis showed that in 70% (14 out of 20) of esophageal cancer patients, expression of hRFI in cancerous regions was two or more times higher than in the corresponding normal tissues **(reprint number 10)**. The other major accomplishment in this field is listed as follows.

1. p21 Waf1/Cip1 expression is a prognostic marker in curatively resected esophageal squamous cell carcinoma, but not p27Kip1, p53, or Rb
2. Local resection with lymphadenectomy for early gastric cancer
3. Quantative analysis of the cyclin expression in human esophageal cancer cell lines
4. Extended lymph node dissection for gastric cancer cases with N2 lymph node metastasis
5. Microvascular anastomosis for additional blood flow in reconstruction after intrathoracic esophageal carcinoma surgery
6. Prognostic significance of non-gastric malignancy after treatment of early gastric cancer

The relationship of macroscopic shape of superficial esophageal carcinoma to depth of invasion and regional lymph node metastasis.

Current Research

The clinical and academic interests of our department are the upper and lower gastrointestinal tract. We have begun to apply the techniques used in molecular and cellular biology to our research based on the past research and major accomplishment mentioned above. The following are the major themes under research.

1. Cancer therapy targeting to the tumor vessels
2. Immunotherapy with dendritic cells
3. Modulated chemotherapy in association with gene therapy
4. Genetic analysis of colorectal cancer and adenoma
5. Carcinogenesis in superficial early colorectal cancer
6. Prognostic factor of early colorectal cancer
7. Genetic alterations in synchronous and metachronous multiple colorectal cancers
8. Microsatellite instability and a risk of developing multiple colorectal cancers
9. Surveillance program following colectomy for colorectal cancer
10. The mechanism of liver metastasis of colorectal cancer
11. Genetic alterations in ulcerative colitis
12. Association study of candidate genes in ulcerative colitis
13. Carcinogenesis in ulcerative colitis
14. Cancer surveillance in ulcerative colitis
15. Association study of candidate genes in Crohn's disease
16. Angiogenesis inhibition in peritoneal metastasis of gastric cancer

Future Prospects

Research projects described in the past research and the current research are continuously pursued in our department. More specifically, we are interested in cancer therapy targeting angiogenesis resulting from tumor development, immunotherapy with dendritic cells and effective chemotherapy for patients with cancer. We are also interested in investigating what mechanism is involved in metastasis, and how the metastasis is inhibited or suppressed in cancer patients.

It is considered that the need for appropriate clinical and psychological care for outpatients is increasing due to the rising number of patients with intractable malignant diseases. The number of major operations for elderly patients is also increasing. Taking all these trends into account, we need to make greater endeavors in our clinical practice and research in order to meet the demands of today's society.

Research Grant

1. Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, 1997-2001, ¥112,800, 000
2. Grant-in-Aid for Scientific Research from the Ministry of Health, Labor and Welfare of Japan, 1997-2001, ¥45,500,000
3. Grant-in-Aid for Scientific Research from the Ministry of Public Management, Home Affairs, Posts and Telecommunications of Japan, 1997-2001, ¥140,600,000

Select Publications (50 papers)

Colorectum

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Chemotherapy

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Immunology

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Metastasis

28. Nakayama H, Kitayama J, Nagawa H. Rat gastric adenocarcinoma cell line BV9 avidly adheres to lymphat-

ic endothelium under lymphatic flow condition. J Exp Clin Cancer Res 21, 289-94, 2002.
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Molecular biology

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Stomach and esophagus

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45. Seto Y, Nagawa H, Muto T. Results of extended lymph node dissection for gastric cancer cases with N2 lymph node metastasis. Int Surg 82, 257-261, 1997.
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47. Nagawa H, Seto Y, Muto T. Recent advances in gastric cancer. Digestion 58(Suppl 1), 62-64, 1997.
48. Nagawa H, Seto Y, Nakatsuka T, Kaizaki S, Muto T. Microvascular anastomosis for additional blood flow in reconstruction after intrathoracic esophageal carcinoma surgery. Am J Surg 173, 131-133, 1997.
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50. Seto Y, Nagawa H, Muto T. Impact of lymph node metastasis on survival in early gastric cancer. World J Surg 21, 186-190, 1997.

Department of Dermatology

Outline and Research Objectives

Department of Dermatology has been chaired by Kunihiko Tamaki M.D.Ph.D. since 1994. The Department of Dermatology celebrated its 100th anniversary in 1990. Originally it was founded as the Department of Dermatology and Urology, which also encompassed venereology. In 1946 the Department of Dermatology was separated from that of Urology. Department of Dermatology had its branch department in Branch Hospital for about 50 years until these two departments joined last year. A professor, two associate professors, four lecturers and nine associates take part in in-patient and out-patient cares as well as research and teaching activities. We usually have around 10 residents and 8 students of doctoral PhD. course. Thirty doctors who basically belong to our department are currently out in affiliated hospitals mainly engaged in clinical works there. Additionally there are four staff members abroad in the US and involved in advanced research activities in cell biology and molecular biology as postdoctoral fellow.

We have specialized out-patient clinic in which some of doctors who are in affiliated hospitals also participate and each specialized service reflects its own research field in a disease oriented manner.

Of course these specialized groups performing their clinical and reseach activities are not exclusive, and there are increasing communications in our department as well as with other departments. Specialized out-patient clinic include the following; atopic dermatitis, psoriasis, collagen diseases including systemic sclerosis, SLE and dermatomyositis, skin surgery and laser surgery including malignant melanoma, squamous cell carcinoma and basal cell carcinoma, and infection especially fungal infection. These clinical groups are divided into three main research groups;

Immunology and allergology group, 2) collagen disease group and 3) skin surgery group. Immunology and allergology group engaged in atopic dermatitis and psoriasis clinic and focuses on Langerhans cell and keratinocyte biology research including cytokine and chemokine. Collagen group engaged in collagen disease clinic and focuses mechanisms TGF-β and collagen. Skin surgery group engaged in skin surgery and laser surgery clinic and focuses of tumor growth, metastasis, fibrosis and dermatoscopic clinical study. Research groups are maintained by associate professor or lecturer. These senior investigators have ten to fifteen year experience as dermatologist and more that seven year experience of research in Japan as well as in U.S.A. They have one to three associates and students of Ph.D. course to extend their research. Professors participate and understand the research activities in this department through conferences which are usually held once to twice a month by each research group.

Faculties and Students

Professor and Chairman	Kunihiko Tamaki M.D. Ph.D.(1994-)
Associate Professors	Kanako Kikuchi M.D. Ph.D.
	Akihiko Asahina M.D. Ph.D.
Lecturer	Mayumi Komine M.D. Ph.D.
	Hironobu Ihn M.D. Ph.D.
	Hidehisa Saeki M.D. Ph.D.
	Takahiro Watanabe M.D. Ph.D.

Associate 9
Graduate student 8
Secretary 3

Past Research and Major Accomplishments

1) Immunology and allergology group:

We established a method to purify murineLangerhans cells(LC), which comprise from one to three percentage of epidermal cells, over 95% purity in each experiment and conducted a series of experiments. We found that murine LC produced IL-12 which is a key cytokine for Th1 induction and that IL-12 production was inhibited by GM-CSF and enhanced by TGF-b1. Furthermore we found prion-related protein was expressed in LC as well as ker-

atinocytes. Prion-related protein is maintained on LC after culture suggesting its participation of LC in peripheral inoculation of prion disease. With regards to atopic dermatitis (AD) we found that lesional skin of NC/Nga mice, which exhibit AD like skin lesion, shows enhanced expression of Th2 chemokine TARC/CCL17 and MDC/ CCL22 and their receptor CCR4. We extended this to human AD and other skin diseases such as bullous pemphigoid, an autoimmune blistering disease and mycosis fungoides, cutaneous T cell lymphoma, all exhibit hypereosinophilia and high serum IgE and found that TARC, MDC and CCR4 are involved in these diseases.

2) Collagen disease group:

TGF-β has been implicated in the pathogenesis of fibrosis. In collaboration with skin surgery group we showed upregulated expression of TGF-β receptors in lesional skin of fibrosis such as systemic sclerosis and localized scleroderma and that upregulated expression of TGF-β receptors is implicated in fibrosis. Fibroblast proliferation is also important in fibrosis as well as wound healing. We demonstrated that fibroblast proliferation is mediated via extracellular signal related kinase (ERK)-dependent pathway. We also studied the expression of tissue inhibitor of metalloproteinases (TIMPs) and showed that TIMP2 was upregulated by IL-4 via p-38 mitogen-activated protein kinase dependent pathway. With regards to clinical research we investigated the prevalence and clinical significance of various autoantibodies in collagen diseases. We also studied the levels of various cytokines and adhesion molecules and their significance.

3) Skin surgery group:

We investigated progressive and metastatic factors in malignant melanoma and other skin tumors. We found dysregulated expression of TGF-β and its receptor in basal cell carcinoma and also found that pattern of basal cell keratin 14 expression is a possible marker for tumor progression in Bowen's disease. We also reported TIMP-1 and TIMP-2 differently regulate the growth of human melanoma cell lines. With regards to clinical research we established criteria for the diagnosis of pigmented plantar nevi which is useful to differentiate pigmented nevi from early acral lentiginous melanoma. We also proposed criteria to differentiate Hutchingson's sign seen in malignant melanoma from subungual nevus.

Current Research

1) Immunology and allergology group:

Using the TGF-β primed LC we are trying to induce Th1 instead of Th2. We succeeded in inducing Th1 in vitro and trying to induce Th1 in vivo. We continue to characterize murine LC and found LC express Toll-like receptor (TLR)-2 3 4 and 9. We are trying to induce Th1 using these receptors. From the results of mouse and human study we are trying to establish K14-TARC transgenic mice to further characterize the significance of TARC expression in the epidermis. With regards to clinical research we are analyzing gene polymorphism of AD and proriasis such as Eotaxin, TARC, IL-13 and IL-12. We are also investigating the CTACK/CCL27 expression of AD and psoriasis. We are analyzing the human peripheral blood dendritic cells (DC) for the expression of cutaneous lymphocyte associated antigen (CLA), fucosyltransferase VII, CCR4 and CCR10, and their function.

2) Collagen disease group:

We are studying the interaction of transcription factors Sp 1, Smad 3 and p300/CBP and the significance of these transcriptional factors in TGF-β induced collagen gene upregulation. PKC is important in collagen accumulation, thus we are studying the regulation of collagen deposition by PKC especially PKC a and PKCd The regulation of TGF-β receptors by various cytokines such as EGF and TNF-α are now being studied. We found overexpression of aVb5 and Vb3 integrin on fibroblasts from fibrotic tissue. The function of this is under investigation using stable transfectants of integrins. We also are studying the regulation of tenasin gene expression by IL-13, PDGF and TGF-β.

3) Skin surgery group:

We are now trying to establish the significance of sentinel lymph mode biopsy in the clinic and trying to find the metastatic factors in malignant melanoma. We are analyzing chemokine and chemokine receptor expression of primary and metastatic melanoma. We also are studying the effect of narrow band UVB on human melanocytes in order to understand the enhanced pigmentation seen in patients receiving narrow band UVB therapy.

Future Prospects

Immunology and allergology group: We will continue the murine LC study to further clarify the characteristics of LC and their participation in skin diseases. We will also study the possibility to use LC for therapy as well as DC from human peripheral blood. We will try to find novel gene products using purified LC and analyze their function. We will establish other transgenic mice such as K-14- CTACK to further analyze the participation of chemokine in skin diseases. With regards to clinical research we will further examine other cytokine and chemokine in skin dis-

eases such as AD and psoriasis and try to use their antagonist for therapy.

Collagen disease group: To further analyze the molecular mechanisms of TGF-β induced collagen gene expression, the cross talk of PI3 kinase and Smad pathway will be determined. Significance of integrin expression in fibrosis will be determined. The mechanisms of EGF and FK506 on the expression of collagen gene expression will be studied in conjunction with the therapeutic approach.

Skin surgery group: DC therapy for malignant tumors using DC from peripheral blood and skin resident LC will be investigated. We will also analyze chemokine / chemokine receptor expression in growth and metastasis of skin tumors.

Research Grants from

1. The Ministry of Education, Science and Culture (A,2002-2005)
   "Study on the dendritic cells and chemokine in the pathogenesis of skin diseases"
2. The Health Science Research Grants from the Ministry of Health, Welface and Labor (2002-)
   "Study to identify organ specific molecules in the pathogenesis of skin diseases"
3. The Health Science Research Grants from the Minictry of Health, Welface and Labor (2001-2002)
   "Basic Research for Atopic Dermatitis using Dendritic cells as a tool"
4. The Ministry of Education, Science and Culture (B. 1157063 1999-2000)
   "The study of skin specific T cells in the pathogenesis of skin diseases"
5. The Ministry of Education, Scince and culture (B,11470179,1999-2001)
   "The study to establish Langerhans cell cell line and its use for treatment"

Select Publications

1. Kakinuma T, Wakugawa M, Nakamura K, Hino H, Matsushima K, Tamaki K. High level of TARC (thymus and activation-regulated chemokine/CCL17) in blister fluid and sera of patients with bullous pemphigoid. *Br J Dermatol*, in press.
2. Sugaya M, Nakamura K, Watanabe T, Asahina A, Yasaka N, Koyama Y, et al: Expression of cellular prion-related protein by murine Langerhans cells and keratinocytes. *Journal of Dermatology Sci.* 28:126-134,2002
3. Hattori N, Komine M, Yano S, Kaneko T, Hanakawa Y, Hashimoto K, Tamaki K.: Interferon-g, a strong suppressor of cell proliferation, induces upregulation of karatin K6, one of the inflammatory- and proliferation-associated keratins. *J Invest Dermatol* 119: 403-10, 2002.
4. Kakinuma T, Nakamura K, Wakugawa M, Mitsui H, Tada Y, Saeki H, Torii H, Komine M, Asahina A, Tamaki K. Serum macrophage-derived chemokine (MDC) levels are closely related with the disease activity of atopic dermatitis. *Clin Exp Immunol*, 127: 270-3, 2002.
5. Ihn H, Yamane K, Asano Y, Kubo M, Tamaki K. IL-4 upregulates the tissue inhibitor of metalloproteinase-2 in dermal fibroblasts via the p38 mitogen-activated protein kinase-dependent pathway. *J Immunol* 168: 1895-902, 2002.
6. Tamaki K, Nakamura K: The role of lymphocyte in healthy and eczematous skin. *Curr Opinion Allergy Clin. Immunol* 1:455-60,2001
7. Kubo M, Ihn H, Yamane K, Asano Y, Jinnin M, Tamaki K: Differential expression of transforming growth factor-beta receptors in squamous cell carcinoma. *Br J Dermatol.* 145: 840-2, 2001
8. Kubo M, Ihn H, Kuwana M, Yamane K, Yazawa N, Tamaki K: Prevalence in myositis of antibodies recognizing anti-U3 RNA probably in a novel complex with 22/25 kD protein and not fibrillarin. *Clin Exp Immunol.* 126: 339-44, 2001
9. Yazawa N, Ihn H, Yamane K, Kubo M, Fujimoto M, Kikuchi K, Soma Y, Tamaki K: Elevated circulating soluble CD30 levels in patients with polymyositis/dermatomyositis. *Br J Dermatol.* 145: 676-8, 2001
10. Hoashi T. Kadono T. Kikuchi K. Etoh T. Tamaki K: Differential growth regulation in human melanoma cell lines by TIMP-1 and TIMP-2. *Biochem Biophys Res Commun.* 288: 371-9, 2001
11. Komine M. Okinaga M. Takeda F. Nashiro K. Kikuchi K. Murakami T. Soma Y. Tamaki K: Patterns of basal cell keratin 14 expression in Bowen's disease: a possible marker for tumour progression. *Br J Dermatol.* 145: 223-8, 2001
12. Wakugawa M. Nakamura K. Kakinuma T. Onai N. Matsushima K. Tamaki K: CC chemokine receptor 4 expression on peripheral blood CD4+ T cells reflects disease activity of atopic dermatitis. *J Invest Dermatol.* 117: 188-96, 2001
13. Tamaki K, Sugaya M, Tada Y, Uasaka N, Uehira M, Nishimoto H, Nakamura K: Epidermal and dermal gamma-delta T cells. *Chem Immunol 79:43-51,2001*
14. Asano Y. Ihn H. Yamane K. Yazawa N. Kubo M. Fujimoto M. Tamaki K: Clinical significance of surfactant protein D as a serum marker for evaluating pulmonary fibrosis in patients with systemic sclerosis. *Arthritis Rheum.* 44: 1363-9, 2001
15. Asahina A. Tada Y. Nakamura K. Tamaki K: Griseofulvin has a potential to modulate the expression of cell adhesion molecules on leukocytes and vascular endothelial cells. *Int Immunopharmacol.* 1: 75-83, 2001
16. Kubo M. Ihn H. Yamane K. Tamaki K: Up-regulated expression of transforming growth factor beta receptors in dermal fibroblasts in skin sections from patients with localized scleroderma. *Arthritis Rheum.* 44: 731-4, 2001
17. Tada Y. Asahina A. Nakamura K. Miyazono K. Tomura M. Fujiwara H. Tamaki K: Transforming

growth factor-beta up-regulates CD40-engaged IL-12 production of mouse Langerhans cells. *Eur J Immunol.* 31: 294-300, 2001
18. Kakinuma T. Nakamura K. Wakugawa M. Mitsui H. Tada Y. Saeki H. Torii H. Asahina A. Onai N. Matsushima K. Tamaki K: Thymus and activation-regulated chemokine in atopic dermatitis: Serum thymus and activation-regulated chemokine level is closely related with disease activity. *J Allergy Clin Immunol.* 107: 535-41, 2001
19. Yazawa N. Ihn H. Yamane K. Etoh T. Tamaki K: The successful treatment of prurigo pigmentosa with macrolide antibiotics. *Dermatology.* 202: 67-9, 2001
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21. Kawabata Y. Ohara K. Hino H. Tamaki K: Two kinds of Hutchinson's sign, benign and malignant. *J Am Acad Dermatol.* 44: 305-7, 2001
22. Wakugawa M. Hayashi K. Nakamura K. Tamaki K: Evaluation of mite allergen-induced Th1 and Th2 cytokine secretion of peripheral blood mononuclear cells from atopic dermatitis patients: association between IL-13 and mite-specific IgE levels. *J Dermatol Sci.* 25: 116-26, 2001
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25. Ihn H. Tamaki K: Increased phosphorylation of transcription factor Sp1 in scleroderma fibroblasts: association with increased expression of the type I collagen gene. *Arthritis Rheum.* 43: 2240-7, 2000
26. Ihn H. Tamaki K: Oncostatin M stimulates the growth of dermal fibroblasts via a mitogen-activated protein kinase-dependent pathway. *J Immunol.* 165: 2149-55, 2000
27. Wakugawa M. Nakamura K. Hino H. Toyama K. Hattori N. Okochi H. Yamada H. Hirai K. Tamaki K. Furue M: Elevated levels of eotaxin and interleukin-5 in blister fluid of bullous pemphigoid: correlation with tissue eosinophilia. *Br J Dermatol.* 143: 112-6, 2000
28. Nakamura K. Imakado S. Takizawa M. Adachi M. Sugaya M. Wakugawa M. Asahina A. Tamaki K: Exacerbation of pustulosis palmaris et plantaris after topical application of metals accompanied by elevated levels of leukotriene B4 in pustules. *J Am Acad Dermatol.* 42: 1021-5, 2000
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30. Tada Y. Asahina A. Nakamura K. Tomura M. Fujiwara H. Tamaki K: Granulocyte/macrophage colony-stimulating factor inhibits IL-12 production of mouse Langerhans cells. *J Immunol.* 164: 5113-9, 2000
31. Ihn H. Sato S. Fujimoto M. Igarashi A. Yazawa N. Kubo M. Kikuchi K. Takehara K. Tamaki K: Characterization of autoantibodies to endothelial cells in systemic sclerosis (SSc): association with pulmonary fibrosis. *Clin Exp Immunol.* 119: 203-9, 2000
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33. Yamane K. Ihn H. Kubo M. Yazawa N. Kikuchi K. Soma Y. Tamaki K: Increased serum levels of soluble vascular cell adhesion molecule 1 and E-selectin in patients with localized scleroderma. *J Am Acad Dermatol.* 42: 64-9, 2000
34. Salgado CG, Nakamura K, Sugaya, M, Tada Y, Asahina A, Fukada, S, Koyama Y, Irie S, Tamaki K. Differential effects of cytokines and immunosuppressive drugs on CD40, B7-1, and B7-2 expression on purified epidermal Langerhans cells. *J Invest Dermatol* 113: 1021-7, 1999.
35. Kanda N, Tamaki K. Ganglioside GD1b suppresses immunoglobulin production by human peripheral blood mononuclear cells. *Exp Hematol* 27: 1487-93, 1999.
36. Sugaya M, Nakamura K, Tamaki K. Interleukins 18 and 12 synergistically upregulate interferon-g production by murine dendritic epidermal T cells. *J Invest Dermatol* 113: 350-4, 1999.
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42. Kubo M, Kikuchi K, Nashiro K, Kakinuma T, Hayashi N, Nanko H, Tamaki K. Expression of fibrogenic cytokines in desmoplastic malignant melanoma. *Br J Dermatol* 139: 192-7, 1998.

43. Kanda N, Tamak K. Ganglioside CQ1b enhances Ig production by human PBMCs. *J Allergy Clin Immunol* 102: 813-20, 1998.
44. Kubo M, Kikuchi K, Fujimoto M, Tamaki K. Serum concentration of carboxyterminal propeptide of type 1 procollagen and tissue inhibitor of metaloproteinase 1 in patients with dermatomyositis. *Arch Dermatol Res* 290: 253-7, 1998.
45. Kawabata Y, Tamaki K. Distinctive dermatoscopic features of acral lentiginous melanoma in situ from plantar melanocytic nevi and their histopathologic correlation. *J Cutan Med Surg* 2: 199-204, 1998.
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47. Watanabe T, Tsuchida T, Ito Y, Kanda N, Ueda Y, Tamaki K. Annular erythema associated with lupus erythematosus / Sjogren's syndrome. *J Am Acad Dermatol* 36: 214-8, 1997.
48. Kanda N, Tsuchida T, Tamaki K. Testosterone suppresses anti-DNA antibody production in peripheral mononuclear cells from patients with systemic lupus erythematosus. Arthritis Rheum 40: 1703-11, 1997.
49. Kikuchi K, Kadono T, Furue M, Tamaki K. Tissue inhibitor of metalloproteinase-1 (TIMP-1) may be an autocrine growth factor in scleroderma fibroblasts. J Invest Dermatol 108: 281-4, 1997.
50. Furue M, Kato M, Nakamura K, Nashiro K, Kikuchi K, Okochi H, Miyazono K Tamaki K. Dysregulated expression of transforming growth factor β and its type I and II receptors in basal cell carcinoma. *Int J Cancer* 71: 505-9, 1997.

Department of Plastic and Reconstructive Surgery

Outline and Research Objectives

The Department of Plastic and Reconstructive Surgery was established in 1960 as the first independent clinical department in Japan. Clinical activities were initially focused on congenital anomalies and skin surgery. In the 1970's, however, surgical techniques such as microsurgery, craniofacial surgery, tissue expansion, etc. were developed, and our activities were significantly expanded so that could lead the world in the field of the free tissue transfers, head and neck cancer reconstruction, hand surgery, craniomaxillofacial surgery, etc. Recently, cosmetic surgery and aesthetic dermatology were also added to our clinical field, and now we have the greatest number of patients for cosmetic purposes among all universities in Japan. Current research objectives are tissue and cell engineering from somatic stem cells, hair regeneration, anti-aging effects of hormones on skin, embryonic development of congenital anomaly, and application of retinoids to skin and keloids.

Faculties and Students:

Professor and Chair	Kiyonori Harii, M.D. (1989-)
Associate Professors	Hirotaka Asato, M.D. (1998-)
Lecturer	Kotaro Yoshimura, M.D. (1998-)
Associates	4
Postdoctral Fellows	5
Graduate Students	4
Secretaries	2

Past Research and Major Accomplishments

Professor Harii has developed a number of surgical techniques in reconstructive microsurgery such as muscle transplantation for facial reanimation in facial-paralyzed patients, and microsurgical reconstruction of head and neck cancer patients. These activities were published in various international medical journals and textbooks. He accepted a number of trainees from countries all over the world, who studied and mastered microsurgery in our laboratory.

Current Research

We have several research projects, both basic and clinical. In basic research, molecular and cellular approaches to reveal the mechanism of congenital anomalies, such as cleft lips and palates, ear deformities, and craniofacial deformities, are ongoing. We are seeking genes which can cause those anomalies. In addition, influences of hormones, especially estrogen, on skin aging are being investigated. Genes, which can be upregulated or downregulated by estrogen in dermal fibroblasts, are being investigated by microarray technique. We are trying to determine the mechanism by which estrogen affects the chronological aging of skin. The third one is on hair regeneration. We harvest and culture dermal papilla cells from hair follicles, which can transform epidermal stem cells into hair follicles. We have tried to determine critical factors released by dermal papilla cells in order to apply to a practical treatment of alopecia. The last one is mesenchymal stem cells extraction from lipoaspirates. We are trying to transform the stem cells into adipocytes, chondrocytes, osteoblasts, dermal fibroblasts, and others for clinical use. The optimal protocols to culture and transform the stem cells have been investigated.

Clinically, we have attempted to establish a classification of pigmented skin lesions. Also, the mechanism of hyperpigmentation and rational therapies are currently being established. Clinical effects of a chemopreventional therapy for keloids using retinoids are now under estimation.

Future Prospects

Our research projects will be more focused on tissue and cell engineering using somatic (mesenchymal) stem cells in the future. Cosmetic augmentation of soft tissue such as breasts, cheek, and eyelids may be clinically available using adipose cells or tissues produced by mesenchymal stem cells extracted from lipoasipates. The stem cells could be applied to therapies of a wide variety of diseases such as hepatic dysfunction, arterial sclerosis, joint cartilage problems, myocardial infarction, leukemia, etc.

Research Grants

1) Kotaro Yoshimura, Grants-in aid for scientific research (B) 2002-2003, Molecular biological research on MMPs and TIMPs expression of human keloids.
2) Hirotaka Asato, Grants-in aid for scientific research (B) 2002-2003, Study on a specific skeletogenic potential of the cranial neural crest cells.
3) Kiyonori Harii, Grants-in aid for scientific research (A), 2000-2001, Evaluation of rejection at the transplantation of cultured cell and induction of local torelance without systemic immunosuppuression.
4) Kotaro Yoshimura, Grants-in aid for scientific research (B), 2000-2001, Molecular biological research on actions of retinoids on wound healing and pigmentation in skin.
5) Shinichi Wakita, Grants-in aid for scientific research (B), 1999-2000, Mesenchymal stem cells; actions in wound healing and application to tissue engineering.

Select Publications

1. Takushima A, Asato H, Harii K, Masashi S. Simultaneous harvest of intercostal nerves and elevation of rectus abdominis musculocutaneous flap for facial nerve cable grafting. Plast Reconstr Surg 110, 541-544, 2002.
2. Yoshimura K, Asato H, Jejurikar SS, Cederna PS, Urbanchek MG, Kuzon WM Jr. The effect of two episodes of denervation and reinnervation on skeletal muscle contractile function. Plast Reconstr Surg 109, 212-219, 2002.
3. Takushima A, Harii K, Asato H, Yamada A. Neurovascular free-muscle transfer to treat facial paralysis associated with hemifacial microsomia. Plast Reconstr Surg 109, 1219-1927, 2002.
4. Kimata Y, Uchiyama K, Sakuraba M, Ebihara S, Hayashi R, Haneda T, Onitsuka T, Asakage T, Nakatsuka T, Harii K. Velopharyngeal function after microsurgical reconstruction of lateral and superior oropharyngeal defects. Laryngoscope 112, 1037-1042, 2000.
5. Harii K., Asato H.: Facial reanimation. The Unfavorable Result in Plastic Surgery, 3rd Ed. (ed. by Goldwyn, R.M., Cohen, M.N.), Lippincott, Williams and Wilkins, Philadelphia, 2001
6. Kitano Y, Yoshimura K, Uchida G, Sato K, Harii K. Pretreatment with topical all-trans-retinoic acid is beneficial for wound healing in genetically diabetic mice. Arch Dermatol Res 293, 515-521, 2001.
7. Ichioka S, Nakatsuka T, Ohura N, Sato Y, Harii K. Clinical use of amrinone (a selective phosphodiesterase III inhibitor) in reconstructive surgery. Plast Reconstr Surg 108, 1931-1937, 2001.
8. Nagase T, Nakamura S, Harii K, Osumi N. Ectopically localized HNK-1 epitope perturbs migration of the midbrain neural crest cells in Pax6 mutant rat. Dev Growth Differ 43, 683-692, 2001.
9. Takushima A, Harii K, Asato H, Nakatsuka T, Kimata Y. Mandibular reconstruction using microvascular free flaps: a statistical analysis of 178 cases. Plast Reconstr Surg 108, 1555-1563, 2001.
10. Yoshimura K, Tsukamoto K, Okazaki M, Virador VM, Lei TC, Suzuki Y, Uchida G, Kitano Y, Harii K. Effects of all-trans retinoic acid on melanogenesis in pigmented skin equivalents and monolayer culture of melanocytes. J Dermatol Sci 27, S68-75, 2001.
11. Nakagawa M, Miyagoe-Suzuki Y, Ikezoe K, Miyata Y, Nonaka I, Harii K, Takeda S. Schwann cell myelination occurred without basal lamina formation in laminin alpha2 chain-null mutant (dy3K/dy3K) mice. Glia 35, 101-110, 2001.
12. Yoshimura K, Harii K, Masuda Y, Takahashi M, Aoyama T, Iga T. Usefulness of a narrow-band reflectance spectrophotometer in evaluating effects of depigmenting treatment. Aesthetic Plast Surg 25, 129-133, 2001.
13. Nagase T, Shimoda Y, Sanai Y, Nakamura S, Harii K, Osumi N.: Differential expression of two glucuronyltransferases synthesizing HNK-1 carbohydrate epitope in the sublineages of the rat myogenic progenitors. Mech Dev 98, 145-149, 2000,.
14. Kimata Y, Uchiyama K, Ebihara S, Saikawa M, Hayashi R, Haneda T, Ohyma W, Kishimoto S, Asai M, Nakatsuka T, Harii K.: Postoperative complications and functional results after total glossectomy with microvascular reconstruction. Plast Reconstr Surg 106, 1028-1035, 2000.
15. Kimata Y, Uchiyama K, Ebihara S, Sakuraba M, Iida H, Nakatsuka T, Harii K. Anterolateral thigh flap donor-site complications and morbidity. Plast Reconstr Surg 106, 584-589, 2000.
16. Ichioka S, Nakatsuka T, Ohura N, Sato Y, Harii K.: Topical application of amrinone (a selective phosphodiesterase III inhibitor) for relief of vasospasm. J Surg Res 93, 149-155, 2000.
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18. Yoshimura K, Harii K, Aoyama T, Iga T. Experience with a strong bleaching treatment for skin hyperpigmentation in Orientals. Plast Reconstr Surg 105, 1097-1108, 2000.
19. Yoshimura K, Ouchi K, Wakita S, Uda K, Harii K. Surgical correction of cryptotia with superiorly based superficial mastoid fascia and skin paddle. Plast Reconstr Surg 105, 836-841, 2000.
20. Kimata Y, Uchiyama K, Ebihara S, Kishimoto S, Asai M, Saikawa M, Ohyama W, Haneda T, Hayashi R, Onitsuka T, Nakatsuka T, Harii K. Comparison of innervated and noninnervated free flaps in oral reconstruction. Plast Reconstr Surg104, 1307-1313, 1999.
21. Shimoda Y, Tajima Y, Nagase T, Harii K, Osumi N, Sanai Y. Cloning and expression of a novel galactoside beta1, 3-glucuronyltransferase involved in the biosynthesis of HNK-1 epitope. J Biol Chem 274, 17115-17122, 1999.

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23. Nakatsuka T, Harii K, Takushima A, Yoshimura K, Ichioka S, Sugasawa M, Ichimura K, Seto Y, Nagawa H. Prefabricated free jejunal transfer: a new reconstructive technique for high pharyngeal defects. Plast Reconstr Surg103, 458-64, 1999.
24. Harii K. Asato H. Nakatsuka T. Ebihara S. Reconstructive plastic surgery in cancer treatment: surgery for quality of life. Jap Soc Clin Oncol 4, 193-201, 1999.
25. Yoshimura K, Harii K. A regenerative change during muscle adaptation to denervation in rats. J Surg Res 81, 139-146, 1999.
26. Gonda K, Okamoto H, Takuwa N, Yatomi Y, Okazaki H, Sakurai T, Kimura S, Sillard R, Harii K, Takuwa Y. The novel sphingosine 1-phosphate receptor AGR16 is coupled via pertussis toxin-sensitive and -insensitive G-proteins to multiple signalling pathways. Biochem J 337, 67-75, 1999.
27. Harii,K. : Free groin flap reconstruction of severe burn neck constructure. Grabb's encyclopedia of flaps second edition (eds. Strauch,B. et al.) vol.1, pp.478-480, Lippincott-Raven, Philadelphia, 1998.
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31. Hirabayashi S, Sugawara Y, Sakurai A, Harii K, Park S. Frontoorbital advancement by gradual distraction. Technical note. J Neurosurg 89, 1058-61, 1998.
32. Kimata Y, Uchiyama K, Ebihara S, Nakatsuka T, Harii K. Anatomic variations and technical problems of the anterolateral thigh flap: a report of 74 cases. Plast Reconstr Surg 102, 1517-1523, 1998.
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36. Yoshimura K, Kuzon WM, Harii K. Myosin heavy chain expression in skeletal muscle autografts under neural or aneural conditions. J Surg Res 75, 135-147, 1998.
37. Ueda K, Harii K, Asato H, Yamada A. Neurovascular free muscle transfer combined with cross-face nerve grafting for the treatment of facial paralysis in children. Plast Reconstr Surg 101, 1765-1773, 1998.
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42. Ueda K, Harii K, Yamada A. Free vascularized double muscle transplantation for the treatment of facial paralysis. Plast Reconstr Surg 95, 1288-1296, 1995.
43. Yamada A, Harii K, Ueda K, Asato H, Tanaka H. Versatility of a cross-leg free rectus abdominis flap for leg reconstruction under difficult and unfavorable conditions. Plast Reconstr Surg 95, 1253-1257, 1995.
44. Kimata Y, Uetake M, Tsukada S, Harii K. Follow-up study of patients treated for ingrown nails with the nail matrix phenolization method. Plast Reconstr Surg 95, 719-724, 1995.
45. Ueda K, Harii K, Yamada A. Electromyographic study of functional recovery of free vascularized muscles grafted to the face. Plast Reconstr Surg 95, 296-304, 1995.
46. Kawashima T, Yamada A, Ueda K, Asato H, Harii K. Tissue expansion in facial reconstruction. Plast Reconstr Surg 94, 944-950, 1994.
47. Ueda K, Harii K, Yamada A. Free neurovascular muscle transplantation for the treatment of facial paralysis using the hypoglossal nerve as a recipient motor source. Plast Reconstr Surg 94, 808-817, 1994.
48. Komuro Y, Takato T, Harii K, Yonehara Y. The histologic analysis of distraction osteogenesis of the mandible in rabbits. Plast Reconstr Surg 94, 152-159, 1994.
49. Ueda K, Harii K, Yamada A. Long-term follow-up of nerve conduction velocity in cross-face nerve grafting for the treatment of facial paralysis. Plast Reconstr Surg 93, 1146-1149, 1994.
50. Nakatsuka T, Harii K, Yamada A, Asato H, Ebihara S. Versatility of a free inferior rectus abdominis flap for head and neck reconstruction: analysis of 200 cases. Plast Reconstr Surg 93, 762-769, 1994.

Department of Oral and Maxillofacial Surgery

Outline and Research Objectives

Department of Oral and Maxillofacial Surgery, commenced by Dr. Hisashi Ishihara in 1900, is one of the oldest departments in Graduate School of Medicine, University of Tokyo. Professor Takato is the 7th professor in our department. The department has been the center of the clinical and basic research in oral and maxillofacial region in Japan. Congenital anomalies, jaw deformities, benign and malignant oral tumors, facial bone fractures, temporomandibular joint diseases, and dental treatment in systemic diseases are mainly treated and researched in our department. Multidisciplinary treatment teamed by plastic surgeons, oral surgeons, orthodontists, prothodontists, etc. is characteristic and has performed excellent results in clinical works. In research fields, we have mainly performed the experimental studies on the regenerative capacity of tissues, especially bone, periosteum, cartilage, perichondrium, vessels, nerve, skin, etc. At present, we are focusing on tissue engineering in research works especially in bone, cartilage, vessels. Professor Takato has established Division of Tissue Engineering in Tokyo University Hospital and our department has two endowment departments: Department of Cartilage and Bone Regeneration (Menicon Co.,Ltd.) and Department of Clinical Vascular Regeneration (Daiichi Pharmaceutical Co., Ltd.) in Tissue Engineering Division. These departments have 1 associate professor, 1staff, and 4 graduate students in each. These staff are focusing on translational research works in maxillofacial regions.

Research Objectives

1) Multidisciplinary treatment of facial deformities in patients with cleft lip and palate or other congenital maxillofacial anomalies
2) Multidisciplinary treatment of dentomaxillofacial deformities, fractures and temporomandibular diseases
3) Multidisciplinary treatment of malignant tumors in head and neck region
4) Reconstruction using bone and cartilage grafts in maxillofacial region
5) Clinical and research works on distraction osteogenesis in maxillofacial region
6) Basic research of bone metabolism
7) Basic research on osteogenic capacity of periosteum
8) Basic research on capacity of perichondrial regeneration
9) Basic research on growth plate
10) Tissue engineering on bone, cartilage, and vessels, etc

Faculties and Students

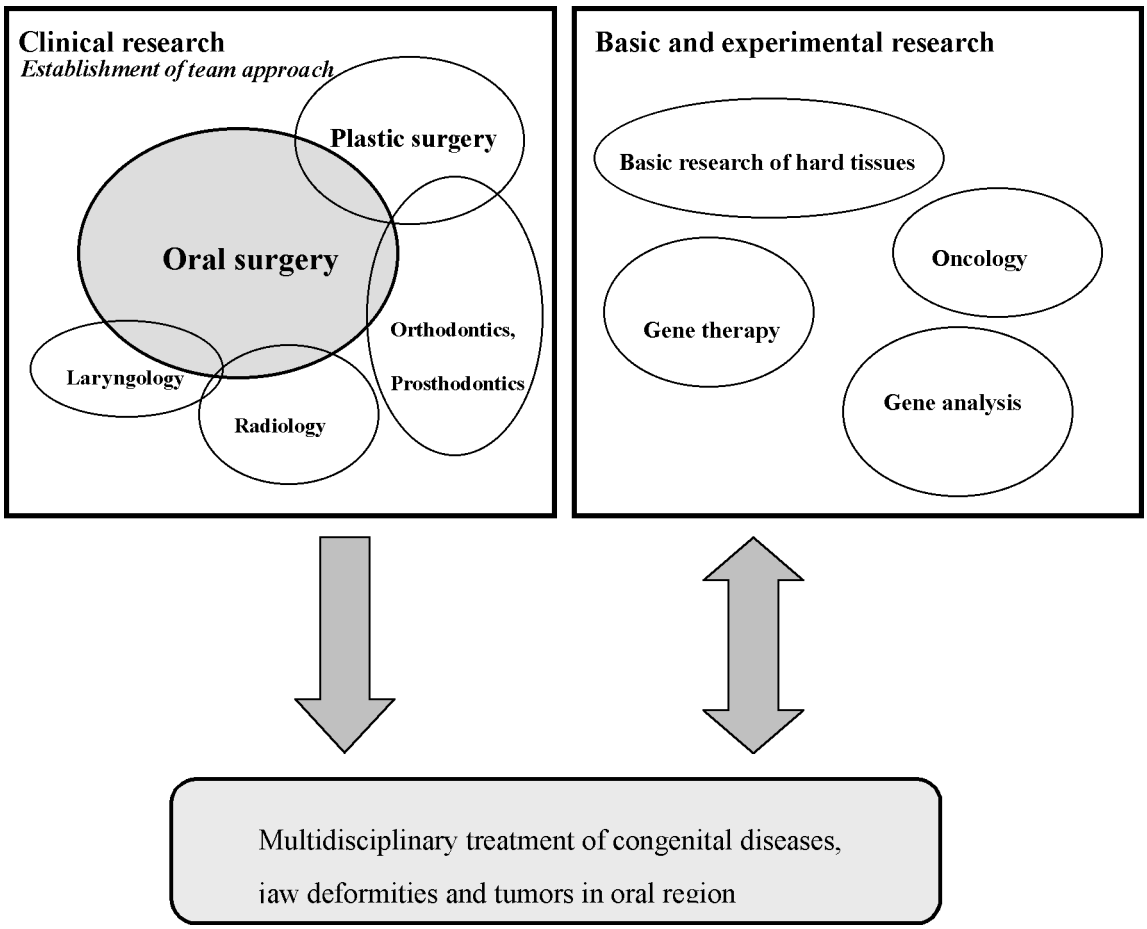
Professor and Chair	Tsuyoshi Takato, M.D., PhD. (since 1996)
Associate Professor	Takafumi Susami, D.D.S., PhD.
Lecturer	Yoshiyuki Mori, D.D.S., PhD.
	Tomoaki Eguchi, M.D., PhD.
	Tetsuya Yoda, D.D.S., PhD.
	Hisako Hikiji, D.D.S., PhD.

Associate 10
Clinical Stuff.....7
Resident 9
Graduate student 12
Research student.....1
Secretary 2

Past Research and Major Accomplishments

1. Clinical research:

1) Multidisciplinary treatment of facial deformities in patients with cleft lip and palate or other congenital maxillofacial anomalies
2) Multidisciplinary treatment of dentomaxillofacial deformities, fractures and temporomandibular diseases
3) Multidisciplinary treatment of malignant tumors in head and neck region

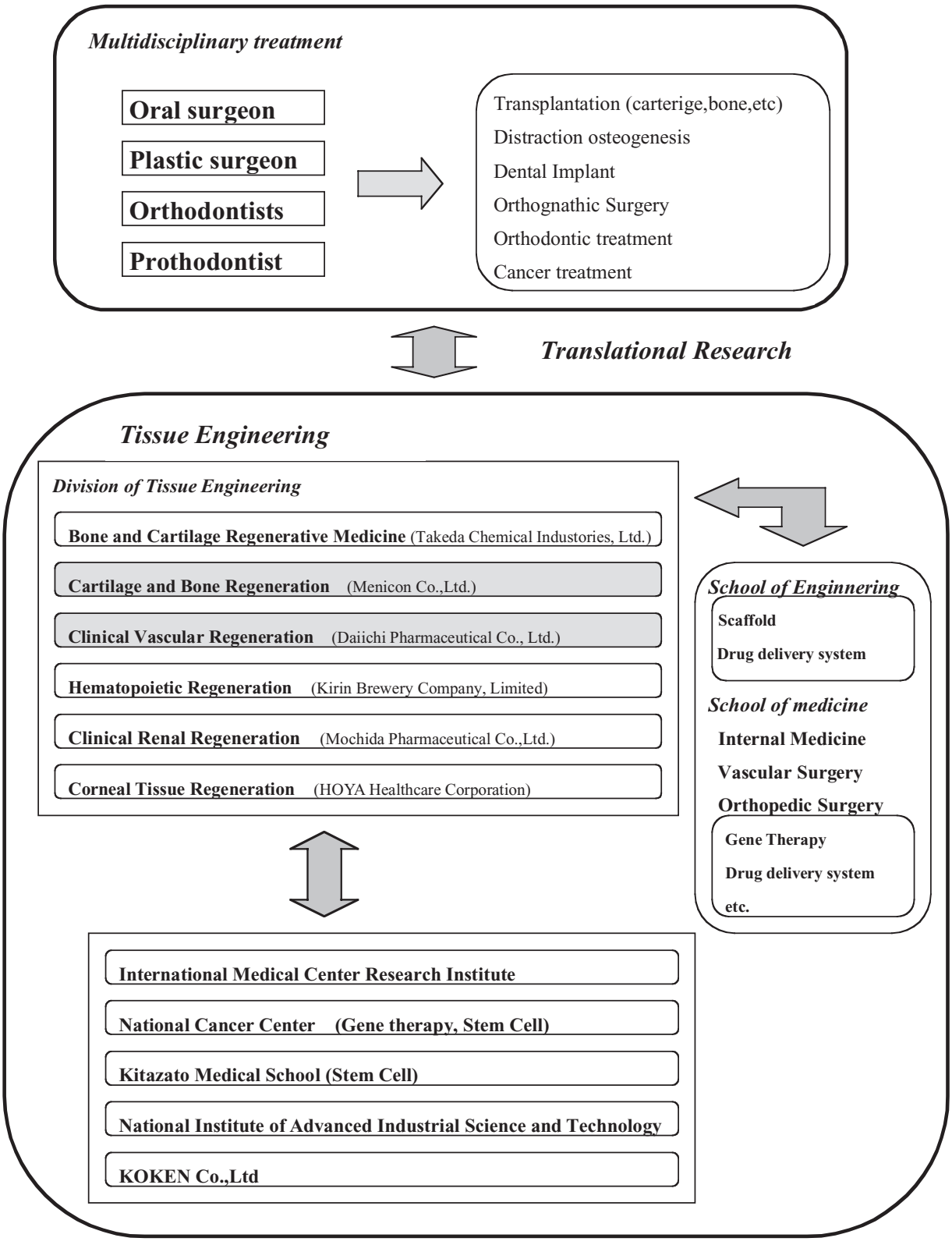


4) Facial bone lengthening by distraction osteogenesis
5) Correction of facial deformity in cleft lip and palate patients
6) Speech problems in cleft lip and palate patients
7) Facial growth in craniofacial anomalies
8) Evaluation of the treatment outcomes in patients with cleft lip and/or palate
9) Combined surgical-chemical-radiological treatment for malignant tumors
10) Development of dental implant
11) Surgical-orthodontic treatment of dentofacial deformities
12) Effects of arthrocentesis or therapeutic exercises for temporomandibular disorders
13) Effects of masticatory force on facial form
14) Non-surgical treatment system for facial bone fractures

2. Basic and experimental research:

1) Osteogenic capacity of periosteum
2) Capacity of perichondrial regeneration
3) Osteogenic capacity of growth plate
4) Development of various types of new skin flaps
5) Metabolism of poly ADP-ribose in DNA repair and cell differentiation
6) Gene analysis of congenital anomalies of oral and maxillofacial region
7) Effect of free radicals on bone metabolism
8) Intracellular calcium handling on osteoblasts
9) Differentiation mechanism of osteoblasts in terms of cell cycle molecule
10) Functional analysis on domains of P130Cas in actincytoskeleton organization, cell migration, and Src transformation
11) Osteochondrogenic differentiation of bone marrow derived mesenchymal stem cells by spheroid culture
12) Cloning of the 5'Upstream Region of the Rat p16 Gene and Its Role in Silencing
13) Studies on relationship between dystrophin associated protein and advanced heart failure
14) Mandibular lengthening by floating bone method
15) Periodontal tissue regeneration on dental implants
16) Characterization of skin derived multipotent stem cells, especially differentiation mechanism into neuronal cell
17) Bone and cartilage repair in dentomaxillofacial region using tissue engineering technique

Current Research



Future Prospects

Our department has been the center of the treatment and research in dentomaxillofacial diseases for the last century in Japan. For decade years, we established the system of the multidisciplinary treatment for diseases in dentaomaxillofacial region. We are now in the next step to develop the new treatment for deficiency of dentomaxillofacial region using tissue-engineering technique. For this purpose, Professor Takato established the Division of Tissue Engineering in Tokyo University Hospital in 2001. We have been researching the development of the materials, tissues and organs which are constructed with the tissue-engineering technique. Three-dimensional construction of cartilage and bone with neovascularization is our most important theme to investigate. These regenerated tissues would repair the deficiency of the dentomaxillofacial region without the harvest of grafted materials from the donor sites. To achieve this translational research, we are cooperating with several companies and Ministries.

Research Grants

The Ministry of Edition, Science, Culture and Technology
Research Grant B2 (1995-1996)
Research Grant B1 (1997-1998)
Research Grant B2 (1997-1998)
Research Grant B2 (1999－2001)
Grant for development of advanced medicine (2002-2004)

Select Publications

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Department of Orthopaedic Surgery

Outline and Research Objectives

Our department was established in 1906 as the first department of orthopaedic surgery in Japan. Since then our efforts have been dedicated to responding to the needs of patients for orthopaedic care and to related research. We have pioneered handicapped children's care, developed new and innovative surgical techniques, and invented arthroscopy which is now used worldwide.

Our department seeks to elucidate the molecular and genetic backgrounds of bone and cartilage disorders including osteoporosis, osteoarthritis, and joint destruction in rheumatoid arthritis. To achieve this, we utilize the newest methodologies, and with the knowledge gained, we are working to develop groundbreaking treatments for these conditions, such as bone and cartilage regeneration. At the same time we are attempting to establish a non-invasive analyzing system to evaluate the mechanical property of the skeletal system and a computer-guided operating system to put to use our findings of the last half decade.

Faculty and Students

Professor and Chair	Kozo Nakamura, M.D., Ph.D. (1998-)
Associate Professor	Hiromi Oda, M.D., Ph.D.
	Yoshio Takatori, M.D., Ph.D.
Lecturer	Isao Ohnishi, M.D., Ph.D.
	Atsushi Seichi, M.D., Ph.D.
	Takahiro Goto, M.D., Ph.D.
	Hiroshi Kawaguchi, M.D., Ph.D.
	Hiroshi Okazaki, M.D., Ph.D.

Associate 12
Postdoctoral Fellow 1
Graduate student 25
Secretary 3

Past Research and Major Accomplishments

1. Regulation of anabolic and catabolic bone metabolism by fibroblast growth factor-2 (FGF-2)

We have had achieved notable advances in laboratory and clinical research on cytokines / growth factors in bone. Perhaps our most important contribution has been in defining the actions of FGF-2 on bone. We have reported the anabolic action of FGF-2 on bone formation using several physiological and pathological animal models of both rodents and primates. Our efforts in this area have led to studies of clinical application of FGF-2 to fracture healing and osteoporosis. The involvement of FGF-2 on bone resorption has also been investigated and this may possibly be involved in the joint destruction by rheumatoid arthritis.

2. Molecular mechanism of age-related bone loss (A novel aging suppressor gene: *klotho*)

Reverse genetic analysis revealed that mice deficient in the *klotho* gene exhibited bone loss with low turnover which is characteristic of human osteoporosis with aging. Using a forward genetic approach, we found that two polymorphisms at the human *klotho* locus are correlated with bone density in postmenopausal women, especially in their older years and independent of race, suggesting that the *klotho* gene may be involved in bone loss with aging.

3. Involvement of insulin signaling in bone anabolic action

Through clinical studies we found that the severity of ossification of the posterior longitudinal ligament of the spine (OPLL) is associated with insulin secretory response due to impairment of the response to insulin in its target tissues. The importance of insulin signaling in the anabolic bone metabolism was confirmed by reverse genetic approach on knock-out mice of the insulin receptor substrates IRS-1 and IRS-2, which are essential intracellular signaling molecules of insulin. It was shown that IRS-1 maintains bone turnover while IRS-2 is needed to maintain the predominance of bone formation over bone resorption; the integration of these two signalings causes a potent bone anabolic action by insulin.

4. Molecular mechanism of osteoclast differentiation in rheumatoid arthritis (RA)

Recent studies have revealed that a TNF-α superfamily cytokine, receptor activator of nuclear factor-kB ligand (RANKL) plays a pivotal role in osteoclast differentiation and activation. We found that RANKL is

highly expressed in synovial fibroblasts obtained from RA patient synovial tissues, and critically implicated in the bone and joint destruction of RA.

5. Gene transfer to osteoclasts and gene therapy

We recently established a gene transduction system into mature osteoclasts using adenovirus vectors, and successfully regulated osteoclast function by introducing several genes that modulate the function and survival. Protooncogene product c-Src is a non-receptor type tyrosine kinase which is indispensable for osteoclast activation. The kinase activity of c-Src is regulated by another cytoplasmic tyrosine kinase Csk (C-terminal Src kinase). Introduction of *csk* gene into osteoclasts by the adenovirus vector completely disrupted the cytoskeletal organization of the cells, and strongly suppressed their bone-resorbing activity. Using the adenovirus vector-mediated gene transduction system, we also found that the Ras-ERK pathway is critical for the survival of osteoclasts.

6. Gene therapy of arthritic joint destruction using adenovirus vectors

Adenovirus vectors are effective not only *in vitro* but also *in vivo* gene delivery into osteoclasts. Local injection of Csk adenovirus reduced IL-1-induced bone destruction in calvarial bone. When injected into arthritic joints, adenovirus vectors efficiently transduce synovial fibroblasts as well as osteoclasts. Csk adenovirus inhibited proliferation of synovial fibroblasts and their proinflammatory cytokine production *in vitro*, and intraarticular injection of the virus significantly ameliorated joint destruction in adjuvant arthritis rats. These results demonstrate that the adenovirus vector system is a good therapeutic approach to arthritic bone destruction.

We also found that adenovirus vector-mediated *csk* gene transduction suppressed the tumor metastasis and constitutively active MEK1 gene recovered the paraplegia after spinal cord injury.

7. Regulation of bone homeostasis by RANKL and IFNs (*interferons*)

Investigation of the regulation of osteoclastogenesis by the immune system showed the critical involvement of IFNs in bone metabolism. Mice deficient in IFNGR1 (IFN-γ receptor) exhibited more severe bone damage accompanied by enhanced osteoclastogenesis when stimulated with lipopolysaccharide (LPS). Activated T cells strongly inhibited osteoclastogenesis via IFN-γ, and IFN-γ interfered with RANKL signaling by inhibiting expression of TRAF6 (TNF receptor associated factor 6). Thus, IFN-γ protects against T cell-mediated inflammatory bone loss. In contrast, mice deficient in IFNAR1 (IFN-α receptor, one of IFN-α/β receptor components) spontaneously develop marked osteopenia accompanied by enhanced osteoclastogenesis. RANKL induces IFN-β gene in osteoclast precursor cells and IFN-β inhibits the differentiation by interfering with the RANKL-induced expression of c-Fos, an essential transcription factor for osteoclastogenesis. Thus, IFN-β acts as a negative feedback regulator of RANKL-induced osteoclastogenesis in physiological bone remodeling. Thus, IFN-γ and IFN-β, both of which play pivotal roles in the immune system, also function in the negative regulation of RANKL signaling via distinct mechanisms.

Current Research

1. Reverse and forward genetic approach to the pathophysiology of osteoarthritis

Osteoarthritis, a major skeletal disorder, is considered a collective result of heterogeneous etiopathologic factors affecting cartilage. We actually identified two novel genes associated with chondrocyte differentiation and degradation: cystacin10 and cgk2. To further determine the molecular background of the disorder, we created an osteoarthritis model in mice by cutting ligaments in and around the knee joint. Several knock-out or transgenic mice were subjected to an operation to learn the involvement of the manipulated gene in the disorder. In addition, as a forward genetic approach, we are in the middle of the genome-wide association study on the human knee and hip osteoarthritis.

2. Gemone-wide association study of OPLL

Based on a reverse genetic study, we have found that nucleotide pyrophosphate (Npps) gene is related to the incidence and progression of OPLL. Since OPLL is a polygenic disease, we are conducting a genome-wide association study of the condition in which more than 100,000 single nucleotide polymorphisms (SNPs) will be evaluated for their association with susceptibility to and severity of OPLL. DNA samples are now being collected in a national project headed by the presenter.

3. Molecular mechanism of age-related bone loss (PPAR-γ)

Considering that osteoblasts and adipocytes share origins in bone marrow mesenchymal cells, and that human aging is associated with a reciprocal increase in adipocytes and a decrease in osteoblasts in bone marrow, PPAR-γ may be clinically involved in the pathophysiology of bone loss with aging as a suppressor of osteoblastogenesis. To identify the role of endogenous PPAR-γ *in vivo*, we examined the bone of PPAR-γ hetero knock-out mice, and found that bone mass in these mice increases with stimulation of

osteoblastogenesis from bone marrow progenitors without affecting mature osteoblasts or osteoclast-lineage cells. The forward genetic approach beginning with the screening of polymorphisms of the human PPAR-γ gene is now underway.

4. Cloning master gene(s) of osteoclast differentiation

In an attempt to identify gene(s) that regulate osteoclast differentiation, we are utilizing a molecular indexing technique, and have found several genes that regulate osteoclast-specific promoter activity. We are currently working on the function of the genes in osteoclasts.

5. Treating arthritic bone destruction by targeting RANKL/RANK pathways

As mentioned above, RANKL/RANK pathways are critically involved in pathological bone resorption, and therefore can be a good therapeutic target. The effect of osteoprotegerin (OPG), a natural inhibitor of RANKL, on pathological bone resorption is currently being examined. In a preliminary study, local injection of recombinant human OPG into arthritic joints effectively ameliorated the bone destruction in adjuvant arthritis rats.

We are also trying to establish a technology of RANKL vaccination therapy, in which modified RANKL is utilized to induce anti-RANKL self-antibody, which has neutralizing activity against self RANKL, and therefore has a therapeutic effect on bone destruction.

6. Molecular mechanism of osteoclast apoptosis

Osteoclasts are terminally differentiated non-proliferating cells with a very short life span. We are now trying to identify molecule(s) that induce osteoclast apoptosis, and have found that a pro-apoptotic Bcl-2 family member Bim plays an essential role. In our studies on the role of small GTP-binding proteins on osteoclast survival, Rac1 transduction was found to prolong the survival.

7. Gene therapy of arthritic bone resorption

We recently found that adenovirus vectors carrying dominant negative Ras gene ($AxRas^{DN}$) strongly suppressed the proliferation and proinflammatory cytokine production of synovial fibroblasts. We are currently investigating the effect of $AxRas^{DN}$ on arthritic bone destruction, and in a preliminary study, found that this virus could significantly suppress joint destruction in adjuvant arthritis rats.

8. Evaluation of mechanical properties of skeletal system

A system of analyzing mechanical properties of a skeletal system has been required to clinically evaluate the efficacy of osteoporosis treatment and to decide on a method or term of fracture treatment. We are developing a non-invasive analyzing system *in vivo* using CT based finite element analyses which can make it possible to predict fracture load and location, which is based on the maximum principal stress failure theory.

9. Investigation of adult neural progenitors as a new therapeutic tool for damaged spinal cord

Seeking a therapeutic tool useful in the treatment of the damaged spinal cord, we have investigated adult endogenous neural progenitors, including stem cells. Their widespread occurrence and proliferation in response to injury have been demonstrated. One of their regulatory mechanisms *in vivo*, Notch signaling, is suggested from their molecular property. Thus, genetic manipulations of endogenous progenitors *in situ* may enable the recruitment of their latent regenerative potential. Further advances of such strategies may make possible significant structural repair of the damaged spinal cord.

10. Development of a joint prosthesis with less loosening

We are developing a new type of hip joint prosthesis whose surface is covered with a synthetic material, methacryloyloxyethyl phoshorylcholine (MPC), resembling the human membrane phospholipid. We have confirmed that the prosthesis successfully decreases the friction index up to 1/5 of the conventional one. Due to the similarity of the material to living membrane, this may possibly elicit a less rejective response causing loosening. This prosthesis will improve the outcome of joint replacement surgery and lead to a new era in osteoarthritis treatment.

11. Navigation robot for minimally invasive surgery

Image-guided surgery is gradually spreading with the advancement of pre-surgical simulation using X-ray CT or MR images to achieve minimally invasive and safer surgical procedures. In cervical bone fixation surgery, highly accurate positioning accuracy is required during drilling to avoid injuring the spinal cord and major blood vessels. However, when using an image-guided navigation system, we encounter difficulties in obtaining accurate "registration" between the navigation results and a device such as a needle, screw or drill; these difficulties arise mainly either from a surgeon's tremor or complicated spatial orientation relations. To overcome these problems, we have developed the first prototype of a simple robot having two degrees-of-freedom (2-DOF), which controls the orientation of a device. The characteristics of

the robot, low DOF, restricted range of movement, and light weight, make it possible to use it in a clinical setting.

Future Prospects

1. Bone and cartilage regeneration

We plan to introduce a new type of bone and cartilage regeneration based not only on tissue engineering, but also on molecular and genetic biology. Endochondral bone development is characterized by a process in which a cartilage mold is replaced by bone. During this process, cartilage induces bone in the adjacent tissue. We have found that a subgroup of cartilage containing hypertrophic chondrocytes plays an essential role in this induction. In addition, these chondrocytes induce vascular invasion. Based on these two findings, we came up with a new strategy to regenerate bone, which is a relatively well vascularized organ. Instead of separately regenerating bone and vasculature and subsequently combining and transplanting them to create viable bone tissue, we have proposed to graft hypertrophic chondrocytes to have them induce both bone and vasculature simultaneously. To realize this unique strategy, we are trying to improve methods to derive chondrocytes from various stem cells, differentiate them further into hypertrophic chondrocytes, and combine them with appropriate scaffolds to create new osteogenic-angiogenic biomaterial.

2. Control of pathological bone destruction

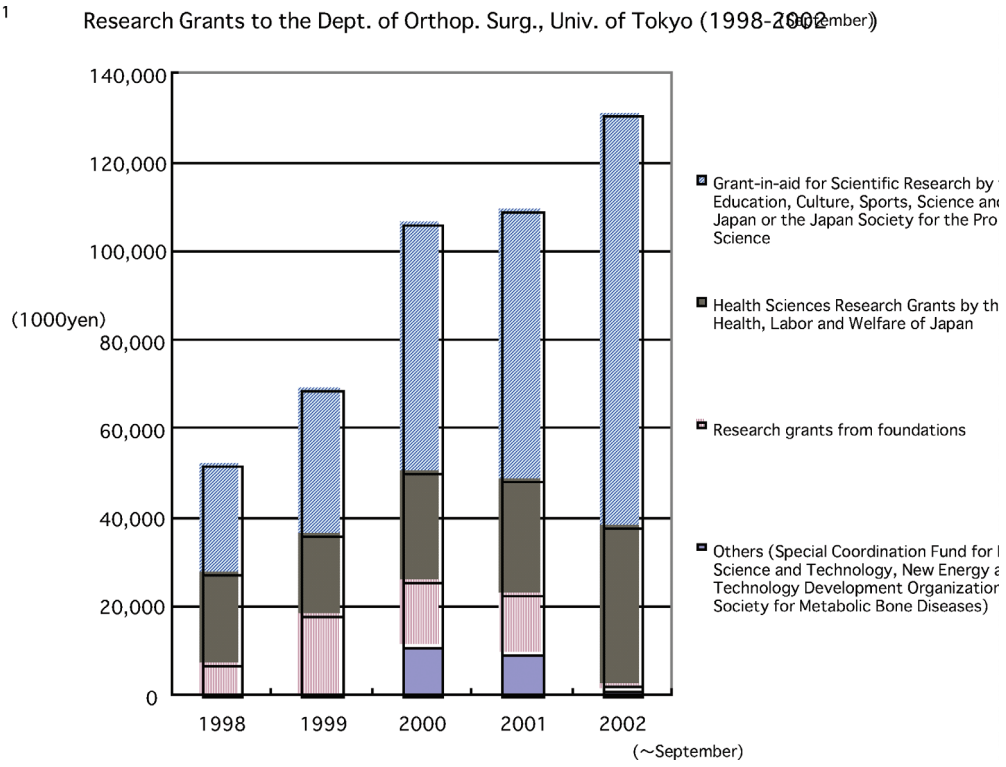
In the future, we will be able to establish novel treatments for pathological bone destruction, and the RANKL/RANK pathway can be a good therapeutic target. RANKL vaccination technology is a promising preventive therapy. By identifying the genes and signal transduction pathways that regulate osteoclast differentiation, activation, and survival, we will be able to regulate bone resorption much more precisely and meticulously. Adenovirus vector-mediated gene transduction will be a good means of gene therapy targeting osteoclasts by modulating intracellular signals.

3. Surgical navigation system with intuitive three-dimensional display and navigation robot

We are developing a new surgical navigation system which superimposes the real, intuitive three-dimensional (3-D) image of the patient's internal structure on the patient's body, and helps surgeons to perform surgery. The system consists of a personal computer, a lens array, a supporting stage, a liquid crystal display and a half-silvered mirror. The 3-D images are generated by real-time computer-generated integral photography, and superimposed on the patient's body via a half-silvered mirror, as if they were seen through the body. Because of the simplicity and the intuitiveness of the navigation image, this system will become applicable for clinical use in the near future in combination with the navigation robot system described above.

Research Grants (Figure 1)

Figure 1



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Department of Ophthalmology

Outline and Research Objectives

The Department of Ophthalmology University of Tokyo was established in 1889. Since then, over a century, our department has played a crucial role as a pioneer in every aspects of ophthalmology in Japan and delivered a lot of international leaders in both clinical and research fields of ophthalmology. The chairman Jujiro Komoto (1889-1922) introduced Western ophthalmology into Japan and established the basics in Japanese ophthalmologic society. The chairman Shinobu Ishihara (1922-1940) developed Ishihara test plate for color blindness, which is still a world-wide golden standard as a screening examination for color blindness. The chairman Yoshiharu Shoji (1940-1949) investigated on the pathogenesis of cataract and the chairman Hagiwara (1915-1964) conducted basic and clinical research on Behcet's disease, the cornea, and the extra-ocular muscles. The chairman Shinichi Shikano (1964-1971) performed research on Behcet's disease and autonomic nervous system in the eye. The chairman Saiichi Mishima (1971-1987) controlled comprehensive research on the physiology of the cornea, ocular pharmacology, and surgical biology, and served as a chief organizer of international congress of ophthalmology held in Kyoto in 1978. The chairman Kanjiro Masuda (1987-1997) conducted research on the pathogenesis and therapy of uveitis. The chairman Makoto Araie (1997-present) has organized thorough research on ocular pharmacology, ocular blood-flow, and clinical and basic aspects of glaucoma and cornea transplantation.

Faculties and Students:

Professor and Chair	Makoto Araie, MD., Ph.D. (1997~)
Associate Professor	Hidetoshi Kawashima, MD., Ph.D.
	Goji Tomita, MD., Ph.D.
Lecturer	Yasuyuki Suzuki, MD., Ph.D.
	Yasuhiro Tamaki, MD., Ph.D.
	Satoru Kato, MD., Ph.D.
	Miyuki Nagahara, MD., Ph.D.

Associate 10
Postdoctoral Fellow 1
Secretary 2

Past Researches and Major accomplishments

1) Evaluation of important parameters of ocular physiology by means of in vivo fluorophotometry or in vivo measurements of protein concentration in the aqueous humor:

Effects of various anti-glaucoma eye drops on both the aqueous flow rate and blood-aqueous-barrier (BAB) permeability were first and quantitatively determined in human eyes and anti－inflammatory effects of topical NSAID were first quantitatively determined in patients undergoing cataract surgery. Further, a method to non-invasively monitor the aqueous production reducing effects of anti－glaucoma drugs in human eyes or toxic effects of intra-ocular irrigating solution in animal eyes have been first developed. The techniques thus establish were used in developing a new anti-glaucoma drug, which is now marketed.

2) Study of cornea:

Permeability to the cornea is the rate-limiting factor for intra-ocular penetration of topically instilled drugs. A pre-existing method for in vivo determination of corneal endothelial (CE) permeability was improved so that status of its harrier function can be estimated more systematically. A new in-vitro method for quantitative evaluation of CE permeability was established, which was world-wide used for comparing safety of various intra-ocular irrigating solutions, and the lowest Ca^{2+} concentration needed to maintain the CE integrity was first determined. Further, molecular biological features of corneal endothelial cells were investigated and the above studies are followed by the present investigation of regenerative medicine of corneal graft for corneal transplantation.

3) Study of ocular pharmacokinetics:

Using the 2-compartment computer model, ocular pharmacokinetics of topically instilled beta-blockers, one of the most important anti-glaucoma drug, were studied and binding of topically instilled beta-blockers to uveal pigment and its clinical implication were first

demonstrated. Trans-corneal and intravitreal kinetics of flourophores were studied to determine factors to facilitate intra-ocular penetration of topically instilled and systemically administered drugs.

4) Clinical study of glaucoma:

Glaucoma is the leading cause of blindness in developed countries and open angle glaucoma represents 75% of all glaucomas in Japan. Surgical techniques of glaucoma were improved by introducing antimetabolites and basic features of adjunctive use of anti metabolites investigated. By computer analysis of visual field results, IOP-dependent damages in the visual field were elucidated, optimal sectorization of test points determined and it was also found that IOP is a risk factor for progression also in normal tension glaucoma. And, effects of glaucoma surgery or calcium antagonists on the visual field progression in normal tension glaucoma were first qualitatively determined. New image analysis techniques, psychophysical methods and new anti－ glaucoma eye drops were evaluated and one anti－glaucoma eye drop could be successfully developed and marketed.

5) Basic study of glaucoma:

Clinical study of glaucoma demonstrated that IOP is not the only factor contributing to progression of glaucoma, which lead to experimental studies on neuroprotection. Conditioned medium from human amniotic epithelial cells was first found to have neurotrophic effects on cultured neurons including retinal ganglion cells (RGCS) and interaction between retinal glial cells or NO and isolated RGCs were determined. Novel gene mutation in Japanese glaucoma patients was found and MYOC, one of glaucoma genes, was cloned in the bovine eye.

6) Study of ocular blood flow:

Clinical studies of glaucoma revealed that local circulation is also involved in progression of glaucoma. Apparatuses which can non-invasively estimate the blood flow in the iris, retina, choroids or optic nerve head utilizing laser speckle phenomenon in living eyes were constructed, establishing the laser speckle method as an in-vivo, non-invasive peripheral blood flow measurement method which can be applied in human subjects. Using this method, effects of calcium antagonists, topical eye drops or surgical procedures on ocular circulation of various ocular tissues could be first systemically studied. It was first found that the ocular tissue most effectively affected is different depending on the Ca^{2+}-antagonist used (nicardipine selectively affects choroidal circulation, lomerizine ONH circulation etc). The important new finding obtained by the ocular blood studies was, topically instilled drugs can influence the circulation in the posterior parts of the eye through their direct penetration to the posterior part of the eye, which have been considered to be impossible. This finding not only has great clinical implication in ocular therapeutics, but also prompted the current study to confirm that topically instilled drugs penetrate to the posterior retina, choroids or retrobulbar tissues at pharmacological concentrations.

Current Researches and Future Prospects.

1) Study of Cornea:

To cope with very limited supply of donor corneas and allograft rejection in corneal transplantation, the reconstruction of artificial cornea has been attempted using the tissue engineering technology. A method to culture human corneal endothelial cells (HCEC) has been first established and, using cultured HCFCs and human corneal stroma the cornea could be successfully reconstructed. Thus reconstructed cornea has 70-80% of cell density, pump function and barrier function of normal HCECs. The reconstructed cornea transplanted to rabbit eye stayed transparent during postoperative 6 months, showing transplanted HCEC normally functioning. Animal corneal stroma as a carrier of cultured HCECs is being investigated. The cornea reconstructed with porcine corneal stroma and HCECs showed average cell density pump function of about 60-70% of normal HCECs and bone marrow cells injected into rat anterior chamber were found to transform into CE-like cells, suggesting that self immature cells can transform into CEs. Possibility of utilizing cultured HCEC from fetus is now investigated. Antigen-specific T cell activation is a critical step in the rejection of transplanted allografts. To activate T cells, two kinds of signal are necessary: signal mediated by T cell receptor (TCR)/CD3 complex and the costimulatory signal by cell surface adhesion molecules such as CD80/86 and ICAM-1. As novel therapies for rejection after corneal transplantation, the feasibility of anti-CD80/86 antibodies is being investigated using murine corneal transplantation model with a complete mismatch at major and minor histocompatibility. Clinical usage of reconstructed cornea, first in high-risk corneal transplantation cases, is planned in 5 years, to resolve very limited supply of donor corneas in Japan. By incorporating gene technology, grafts much better functioning with much less chance to be rejected than the donor cornea may be constructed. To reduce allograft rejection, therapy with anti-CD 80/86 antibodies and chemokine receptor antagonist such as CCRI antagonist, which is also involved in induction of rejection, may be also possible.

2) Study of ocular pharmacokinetics:

Our new finding suggesting penetration of topically instilled drug to the posterior parts of the eye at pharmacological concentrations will be a break-through in medical treatment of diseases of posterior parts of the eye such as the retinal, choroidal or optic nerve disorders. Whole-head autoradiography and a new method of isolation of posterior ocular tissues are now being carried out and confirmed the above findings. Factors and routes contributing to the posterior penetration of instilled drugs will be elucidated, and systemically safe, local treatment of retinal, choroidal or optic nerve disorders is to be developed.

3) Clinical study of glaucoma:

As one of the three chief investigators, Makoto Araie conducted an epidemiological study of glaucoma and related ocular diseases in Tajimi area and now is analyzing the obtained results as a chief of data analysis committee. This is the first ophthalmological epidemiological study carried out in mongoloids and its result will have a great impact in the field of ophthalmology. Several longitudinal, some of them randomized and prospective, studies are being conducted by Makoto Araie as a chief investigator a) A 3－year prospective, randomized, multi-centered and comparative study of nipradilol and timolol on the progression of normal tension glaucoma. The result of this study will first elucidate if non-IOP dependent risk factors of glaucoma can be treated by topical drugs or not, and if a positive result is obtained, it will be a great break-through in the medical treatment of glaucoma. b) The multi-centered, randomized, placebo-controlled study on the effects lomerizine, a Ca^{2+}-blocker, on the retinal blood flow is the first to study if retinal blood flow can be selectively increased by systemically safe oral Ca^{2+}-antagonis, lomerizine, and if a positive result is obtained, it will be a break-through in the medical treatment of retinal diseases. Other longitudinal or cross-sectional studies now ongoing includes disk bleeding study to investigate whether myopic-type disc is associated less disc bleeding but more progression of damage as compared with non-myopic type disc, advanced stage glaucoma study where disability in daily life in the late stage of the disease is prospectively questioned, frequency doubling technology visual field study where this new psychophysical test is prospectively evaluated from view point of early detection of glaucoma progression and scanning laser ophthalmoscopy study where morphometry of the optic disc in Japanese patients is quantitatively estimated on multicenter-based protocol, development of visual disability questionnaire designed to evaluate visual disability in Japanese glaucoma patients who vertically read and write, analysis of filtering bleb characteristics after trabeculectomy in Japanese patients to find contributing factors to the late stage bleb-related complications, the most vision-threatening complication of glaucoma surgery. The result obtained from the above studies in future will shed new light on the diagnosis, follow-up, treatment and rehabilitation of glaucoma, the second leading cause of blindness in Japan, of which prevalence in adults was found to be as high as 5% (unpublished result of the above mentioned Tajimi Study).

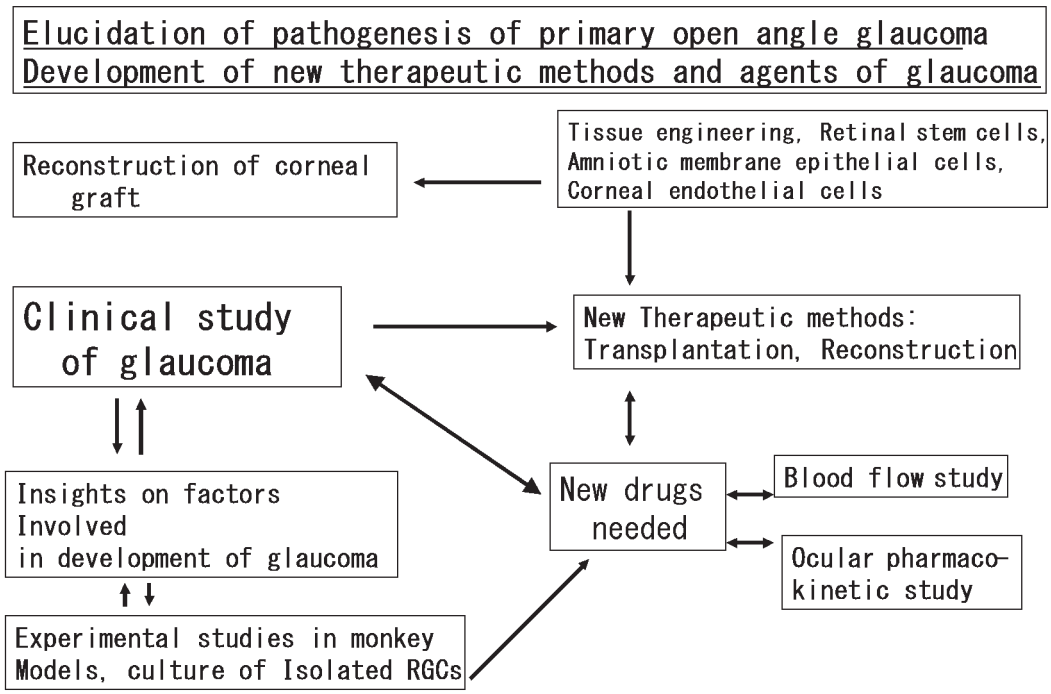
4) Basic study of glaucoma:

Makoto Araie is serving as a chairman of Glaucoma Optic Neuropathy Study Group and established monkey glaucoma model is used to study how glaucomatous damaging processes impair the optic nerve head (ONH) structure, ONH circulation and neural functions (visual field, receptor field of neurons in lateral geniculate body, etc) and how the potential drugs can modify them, which is impossible to study in humans. ONH is the tissue primarily involved in glaucomatous damage and ONH damage results in loss of retinal ganglion cells in retina. Using established system of culture of isolated retinal ganglion cells and isolated Müller cells, factors, affecting survival of these cells, including therapeutic agents, are now intensively studied. Mammalian retina is composed of seven major cell types, Müller glia, and six neural cell types, retinal ganglion cell (RGC), bipolar cell, horizontal cell, amacrine cell, rod and cone photoreceptor cell. Unlike amphibian or fish, adult mammalian retina has been considered to be devoid of stem or progenitor cells and that substantial regeneration dose not take place.

However, a recent study has unexpectedly demonstrated the presence of retinal stem cells in adult mice, suggesting the possibility that these cells can be utilized as a potential cell source of transplantation therapy for damaged retinal cells including RGCs. Animal model is pre-requisite for the realization of the transplantation therapy, and rabbit is one of the most suitable animals because of its relatively large-sized eyes, easiness in handling and reasonable price. Method to isolate retinal stem cells from ciliary epithelium using neurosphere-forming assay has been established not only in mice but also rabbits and monkeys. Ongoing studies address factors involved in differentiation of retinal stem cells and how these cells can be utilized as cell source of transplantation therapy of retinal degenerative disorders including glaucoma. In culturing isolated RGCs and retinal stem cells, and in providing substrate for transplantation, human amniotic epithelial cells and our experience on them should be of considerable use.

5) Study of Ocular blood flow:

In addition to the laser speckle method that were



already developed for non-invasive measurement of peripheral blood flow in ocular tissues, an apparatus for Color Doppler Imaging and that for Laser Doppler Velocimetry have been recently introduced. The former measures the absolute blood velocity of vessels in the orbit (diameter > 100μ) and the latter that of large retinal vessels (diameter ≒100μ). Our laboratory is the only one in the world that equipped with the above 3 apparatuses and using 3 apparatuses, physiology, pathology and pharmacology of ocular circulation from feeding vessels to peripheral circulation can be first systematically investigated. The subjects of the on-going studies are: Measurement of peripheral resistance in normal subjects with genetically high risk for systemic hypertension; Change in autoregulatory capacity of retinal and ONH circulation with aging, development of glaucoma or development of diabetic retinopathy; and Assessment of hemodynamic parameters most correctly and sensitively reflecting status of peripheral vascular bed. The results obtained by above studies will shed light not only on further understanding of pathophysiology of systemic hypertension and ocular disorders associated with circulatory abnormalities, but also lead to establishment of hemodynamic parameters most sensitively reflecting therapeutic effects of various drugs on retinal or ONH disorders including glaucoma.

Research Grants

Grant-in-aid for scientific research from Ministry of Education, Culture, Sports, Science and Technology:

1. Tenkai-Kenkyu (A)2, No.10357016, 1998-1999:| Chief investigator, ¥19,500,000
2. Kiban-Kenkyu (A)1, No. 11307036, 1999-2001: Chief investigator, ¥41,010,000
3. Kiban-Kenkyu (B)2, No. 12557146, 2000-2001: Chief investigator, ¥19,700,000
4. Kiban-Kenkyu (A)1, No. 14207069, 2002-2004: Chief investigator, ¥49,998,000

Grant-in-aid for scientific research from Ministry of Health, Labour and Welfare

. H-10-Sensory Organ-005, 1998-2000: Chief investigator, ¥73,500,000

Select Publications

1. Makoto ARAIE, Masahiro TAKASE, Yasuo SAKAI, Yukihisa ISHII, Yukio YOKOYAMA & Masatoshi KITAGAWA: Beta-adrenergic blockers: ocular penetration and binding to the uveal pigment. Japanese Journal of Ophthalmology 26:248-263, 1982
2. Makoto ARAIE: A Reevaluation of corneal endothelial permeability to fluorescein. Experimental Eye Research 41: 383-390, 1985
3. Makoto ARAIE: Barrier function of the corneal endothelium and intraocular irrigating solutions. Archives of Ophthalmology, 104;435-438, 1986
4. Makoto ARAIE & David M MAURICE: The rate of diffusion of fluorophores through the corneal epithelium and stroma. Experimental Eye Research 44: 73-87, 1987
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6. Makoto ARAIE, Eiichi SHIRASAWA & Koji HIKITA: Effects of oxidized glutathione on the barrier function of the corneal endothelium. Investigative

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10. Makoto ARAIE, Eiichi SHIRASAWA & Tokie OHHASHI: Intraocular irrigating solutions and permeability of the blood-aqueous barrier. Archives of Ophthalmology, 108: 882-885, 1990
11. Makoto ARAIE, Koichi HAMANO, Shuichiro EGUCHI & Shun MATSUMOTO: Effect of calcium ion concentration of the permeability of the corneal endothelium. Investigative Ophthalmology & Visual Science 31:2191-2193, 1990
12. Makoto ARAIE & David M Maurice: The loss of fluorescein, fluorescein glucuronide and FITC-dextran from the vitreous by the anterior and retinal pathways. Experimental Eye Research 52: 27-39, 1991
13. Mikiro MORI & Makoto ARAIE: A simple method of determining the time course of timolol's effects on aqueous flow in humans. Archives of Ophthalmology 109: 1099-1103, 1991
14. Tetsuro OSHIKA, Makoto ARAIE, Tetsuya SUGIYAMA, Masayuki NAKAJIMA & Ikuo AZUMA: Effect of bunazosin hydrochloride on intraocular pressure and aqueous humor dynamics in normotensive human eyes. Archives of Ophthalmology 109: 1569-1574, 1991
15. Mikiro MORI, Makoto ARAIE, Masahiro SKURAI & Tetsuro OSHIKA: Effects of pilocarpine and tropicamide on blood-aqueous barrier permeability in man. Investigative Ophthalmology & Visual Science 33: 416-423, 1992
16. Yasuyuki SUZUKI, Makoto ARAIE & Yazuo OHASHI: Sectorization of central 30∞ visual field in glaucoma. Ophthalmology 100: 69-75, 1993
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21. Makoto ARAIE, Maki SEKINE, Yasuyuki SUZUKI & Nobuyuki KOSEKI: Factors contributing to the progression of visual field damage in eyes with normal-tension glaucoma. Ophthalmology 101: 1440-1444, 1994
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24. Minoru KIMURA, Makoto ARAIE & Satoru KOYANO: Movement of carboxyfluorescein across retinal pigment epithelium-choroid. Experimental Eye Research 63: 51-56, 1996
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26. Nobuyuki KOSEKI, Makoto ARAIE, Shiroaki SHIRATO & Seiichiro YAMAMOTO: Effect of trabeculectomy on visual field performance in central 30∞ visual field in progressive normal tension glaucoma. Ophthalmology 104: 197-201;1997
27. Makoto ARAIE, Mariko KITAZAWA & Nobuyuki KOSEKI : Intraocular pressure and central visual field of normal tension glaucoma. British Journal of Ophthalmology 81:852-856,1997
28. Makoto ARAIE & Minoru KIMURA: Intraocular irrigating solutions and barrier function of retinal pigment epithelium. British Journal of Ophthalmology 81: 150-153;1997
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45. Saiko UCHIDA, Yasuyuki SUZUKI, Makoto ARAIE, Takashi SHIGEEDA, Takeshi HARA, Shiroaki SHIRATO. Long-term follow-up of initial 5-fluorouracil trabeculectomy in primary open-angle glaucoma in Japanese patients. Journal of Glaucoma 2001;10:458-465
46. Kiyoshi ISHII, Atsuo TOMIDOKORO, Miyuki NAGAHARA, Yasuhiro TAMAKI, Mikiko KANNO, Yasuhiro FUKAYA, Makoto ARAIE. The effects of topical latanoprost on optic nerve circulation in rabbits, monkeys and humans. Investigative Ophthalmology & Visual Science 2001;42:2957-2963
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Department of Otorhinolaryngology, Head and Neck surgery

Outlines

The Department of Otorhinolaryngology was founded in 1899 by Prof. Waichiro Okada. This is the first department of otorhinolaryngology of the medical school and the university hospital in Japan. The first professor, Waichiro Okada (1902-1924), the 2nd, Taneji Masuda (1924-1946), the 3rd, Kotoji Satta, the 4th, Ichiro Kirikae (1947-1969), the 5th, Yasuo Sato (1970-1980), the 6th, Yasuya Nomura (1980-1991), the 7th, Kimitaka Kaga (1992-)

Research Objectives

Our department covers all of otorhinolaryngological diseases and associated systemic diseases, and has specialized clinical and basic research in middle ear and inner ear diseases, peripheral and central deafness in infant and children, adult and elderly, facial paresis, vertigo and balance disorders, olfactory disorders, paranasal diseases, voice and speech disorders, cleft palate, taste and swallowing disorders, head & neck cancer, psychosomatic medicine and medical education.

1) Hearing research; Morphology and neurophysiology of the inner ear focusing on sensory neural deafness: human temporal bone pathology, electron microscopic study in animal models with gene abnormality, clinical application of otoacoustic emissions and auditory brainstem responses. Hair cell physiology of synaptic transmission.
2) Facial nerve research; Morphology of the facial nerves focusing on degeneration and regeneration.
3) Head and neck cancer research; Molecular biology and gene therapy of head and neck cancers.
4) Evoked potential research; Generators of auditory evoked potentials in the central auditory system.
5) Auditory perception and cognition research; normal subjects and patients with central deafness and cochlear implant using event related potentials and MEG.
6) Voice research; Morphology and electrophysiology of the larynx and voice production.
7) Basic research on auditory brainstem implant.
8) Vestibular research; The oculomotor and balance system in the brainstem, cerebellum and cerebrum. Vestibular myogenic evoked potential and its origin and clinical application.
9) Taste research; Taste perception and disorders.
10) Olfactory research; Olfactory epithelium morphology and function of olfaction.
11) Language research; Development of hearing, speech and language in neonates and infants.
12) Artificial organ research; Development of artificial sensory and motor organs.

Faculties and Students

Professor	Kimitaka Kaga, MD,PhD (1992-)
Associate Professor	Masashi Sugasawa, MD,
	Tatsuya Yamasoba, MD
Lecturer	Toshihisa Murofushi, MD,PhD,
	Naonobu Takeuchi, MD,PhD
	Ken Ito, MD,PhD,
	Kenichiro Ishio, MD
	Ryuzaburo Higo, MD,PhD

Associate 10
Postdoctoral Fellow 2
Graduate Student.....6
Research Student 4
Secretary 3

Past Research and Major Accomplishments

Otology and neurotology

1. Development of new surgical procedure: total middle ear reconstruction and auricle, canal plasty and ossicular reconstruction for congenital microtia and atresia.
2. Comprehensive study on central auditory system and central auditory disorders.
3. Demonstration of origins of auditory evoked potentials in animal and human subjects: auditory brainstem response and middle latency.
4. Introduction of gene therapy into inner ear diseases. 5. Demonstration of sound lateralization of bone conduction hearing.
6. Invention of bilateral bone conduction hearing aid.
7. Discovery of a new hearing disorder of auditory nerve disease.
8. Proposal of new critical age of language development.
9. Mechanism of perception and cognition of music and environmental sounds.
10. Discovery of a new antibody of inner ear.

Head and Neck Cancer:

1. Long term follow up study on different treatment of maxillary cancer and proposal of the best treatment.
2. Identification of adeno virus in nasopharyngeal cancer.
3. Development of new chemotherapy of head and neck cancer.
4. Development of new surgical procedure for parapharyngeal tumor.

Rhinology:

Demonstration of developing and aging changes of olfactory neuroepithelium.

Laryngology:

Development of new artificial voice production system for patients after total laryngectomy.

Bronchoesophagology

Development of electrophysiological swallowing system.

Medical eduacation:

1. Introduction of clinical counselling with head and neck cancer patients for medical students in bedside learning.
2. Evaluation system of teachers in medical school by medical students.

Current Research

Otology and neurotology

I. Clinical research

1. Early operation of cochlear implant around two years of age.
2. Music perception of children and adults with cochlear implant.
3. Sound lateralization perception and time-intensity trading ability in normal subjects with absolute pitch and patients with brain damage.
4. Development of super-low noise bone conduction hearing aid.
5. Cooperative reconstruction surgery of auricle and canal plasty for congenital microtia and atresia by plastic surgeons and otological surgeons.
6. New total middle ear reconstruction surgery for infectious radicalized ears.
7. Implantation of bone anchored hearing aid for children with Treacher Collins syndrome.
8. Early discovery of congenital deafness in neonates and early hearing aid fitting and education of speech and language.
9. Contribution to double handicapped children with hearing problem.
10. Perception and cognition of cortical deafness.

II. Basic study

1. Development of polyimide multiple-site surface microelectrode for epidural cortical recording of high spatial resolution evoked-potentials.
2. Development of independent component analysis of multiple-site auditory evoked potentials.
3. Molecular biology of inner ear hair cell differention.
4. Molecular biology of experimental noise induced deafness.
5. Regeneration mechanism of inner ear hair cells in chick.
6. Development of gene therapy for experimental inner ear diseases.
7. Origin of binaural interaction of hearing using midline section of brainstem and localized lesions of brainstem in animal models.
8. Plasticity of central auditory system.

Head and neck surgery

1. Development of a new procedure of skull base surgery.
2. Molecular biological study on hypopharyngeal cancer.
3. Development of a new procedure of partial laryngectomy.

4. Quality of life between conservative and surgical treatment.
5. Development of navigation to support safer head and neck surgery.

Rhinology

1. Olfaction change of human subjects under environment of modern society.
2. A study on distribution of histamine receptor in human nasal mucosa.
3. Application of navigation system for endoscopic nasal surgery.

Laryngology, Bronchoesophagology

1. Application of Botulinus toxin to treat spastic dysphonia.
2. A new procedure to treat hoarseness in elderly patients inplanting fascia in the vocal cord.
3. Language development of children using tracheal canula in the first year of life.
4. Comparative study of vocal cords in differential species.
5. Measurements of pressure changes of swallowing system in patients with dysphagia.
6. Surgical procedures to treat dysphagia.

Medical education

1. How to teach humanity in medical education.
2. Development of assessment of teachers activity in lectures, seminars and bedside learning in medical education.

Future Prospects

New artifial sensory and motor organs and gene therapy will be new directions checked by gene analysis of each cancer individually and treated by

1. Otology: After present cochlear implant for profound sensory deafness, we will challenge to create a new cochlear implant for music perception, auditory brainstem implant for neural deafness and super low noise bilateral bone conduction hearing aids for conductive deafness.
2. Head and neck surgery: Head and neck cancer treatment will be checked by gene analysis of each cancer individually and treated by gene therapy due to phylosophy based on tailored medicine.
3. Rhinology: Allergic rhinitis is incurable diseases but will be challenged by new immunotherapy. Sensory and neural anosmia is desperate to recover at present but will be challenged to innovate artificial sensory device for implantation in olfactory bulb.
4. Laryngology: Voice is very important in communication. Loss of vocal cord result from total laryngectomy because of surgical cancer treatment. Now we are challenging to innovate new computerized devices for providing the same voice from the oral cavity before surgery which uses voice synthesis technology and orally fitted voice generating system.

Research Grants

1998 Hatamura Y, Ishii T, Kaga K: Advanced medical tools for clinicians and development of fine instruments. Ministry of Welfare. 1998-2001, Total ¥400,000,000.

1999 Kaga K, et al: Basic study on auditory brainstem implant. Ministry of Education. 1999-2001, Total ¥14,000,000.

2000 Kaga K, et al: Study on auditory space in higher brain. Ministry of Education. 2000-2001, Total ¥6,000,000.

2001 Kaga K: Identification of sound localization in human brain. Ministry of Education ¥2,100,000.

2002 Kaga K, et al: Neonatal universal screening and long term follow up. Ministry of Welfare and Labor ¥1,260,000.

Select Publications

1. Kaga K, Uebo K, Sakata H, Abe Y, Haebara H, Kosakai M: Auditory brainstem responses and temporal bone and brainstem pathology in brainstem death, with special reference to autolysis of red blood cells. Acta Otolaryngol (Stockh) 115:183-186,1995.
2. Kaga K, Tanaka Y: Auditory air and bone conduction brainstem responses and damped rotation test for young children with bilateral congenital atresia of the ears. Int J Pediat Otorhinolaryngol 32:13-21,1995.
3. Kaga K, Tamai F, Kitazumi E, Kodama K: Auditory brainstem responses in children with Cornelia de Lange syndrome. Int J Pediat Otorhinolaryngol 31:137-146,1995.
4. Kaga K, Nakamura M, Shinogami M, Tsuzuku T, Yamada K, Shindo M: Auditory nerve disease of both ears revealed by auditory brainstem reponses, electrocochleography and otoacoustic emissions. Scandinavian Audiol 25:233-238,1996.
5. Ismail Noorhassim, Kaga K: Pure tones audiometry and auditory brainstem responses in noise-induced deafness. American J Otolaryngol 17:31-35,1996.
6. Suzuki M, Kaga K: Effect of cisplastin on the negative charge barrier in strial vessels of the guinea pig. A transmission electron microscopic study using polyethyleneimine molecules. Eur Arch Otorhinolaryngol 253:351-355,1996.
7. Yamada K, Kaga K, Uno A, Shindo M: Sound lateralization in patients with lesions including the auditory cortex: comparison of interaural time difference (ITD) discrimination and interaural intensity difference (IID) discrimination. Hearing Research 101:173-180,1996.

8. Yamasoba T, Oka Y, Tsukuda K, Nakamura M, Kaga K: Auditory findings in patients with maternally inherited diabetes and deafness harboring a point mutation in the mitochondrial transfer RNAleu(UUR) gene. Laryngoscope 106:49-53,1996.
9. Yamasoba T, Suzuki M, Kaga K: Influence of chronic kanamycin administration on basement membrane anionic sites in the labyrinth. Hearing Research 102:116-124,1996.
10. Kaga K, Shindo M, Tanaka Y: Central auditory information processing in patients with bilateral auditory cortex lesions. Acta Otolaryngol (Stockh) Suppl 532:77,82,1997.
11. Tanioka H, Kaga K, Zusho H, Araki T, Sasaki Y: MR of the endolymphatic duct and sac: findings in Meniere disease. AJNR Am J Neuroradiol 18:45-51,1997.
12. Suzuki M, Kaga K: Effect of cisplatin on the basement membrane anionic sites in the ampulla, macula, and strial vascularis of guinea pigs. Ann Otol Rhinol Laryngol 106:971-975,1997.
13. Nakamura M, Yamasoba T, Kaga K: Changes in otoacoustic emissions in patients with idiopathic sudden deafness. Audiology 36:121-135,1997.
14. Yamada K, Kaga K, Sakata H, Uno A, Tsuzuku T: Auditory evoked potentials under total spinal anesthesia in rats. Ann Otorhinolaryngol 1087-1092,1997.
15. Suzuki Y, Kaga K, Sugiuchi Y, Ishii T, Suzuki J-I, Takiguchi T: Sudden bilateral hearing loss due to gastric carcinoma and its histological evidence. J Laryngol Otol 111:1142-1146,1997.
16. Kojima Y, Kaga K, Shindo M, Hirose A: Electromyographic examination of patients with unilateral cortical facial paralysis. Otolaryng Head Neck Surg 117:S121-124,1997.
17. Kaga K, Uebo K, Sakata H, Suzuki J: Auditory and vestibular pathology in brainstem death revealed by auditory brainstem response. Acta Otolaryng (Stockh) Suppl 503:95-103,1993
18. Uno A, Kaga K, Tsuzuku T, Kuroki M: Middle-latency responses of awake and anesthetized Japanese macaques. Audiology 32:302-307,1993.
19. Kim LS, Kaga K, Tsuzuku T, Uno A: Effects of primary auditory cortex lesions on middle latency responses in awake cats. A.N.L. (Tokyo) 20:155-165,1993.
20. Yamada K, Kaga K, Tsuzuku T, Uno A: Analysis of auditory brain stem response with lidocaine injection into the cerebrospinal fluid in rats. Ann Otol Rhinol Laryng 103:796-800,1994.
21. Yamada K, Kaga K, Suzuki J-I: Temporal bone pathology in patients without caloric response. Acta Otolaryngol (Stockh) 114:586-594,1994.
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23. Kaga K, Uebo K, Sakata H, Abe Y, Haebara H, Kosakai M: Auditory brainstem responses and temporal bone and brainstem pathology in brainstem death, with special reference to autolysis of red blood cells. Acta Otolaryngol (Stockh) 115:183-186,1995.
24. Kaga K, Ichimura K, Kitazumi E, Kodama K, Tamai F: Auditory brainstem respnses in infants an children with anoxic brain damage due to near-suffocation or near-drowning. Int J Pediatr Otorhinolaryngol 36:231-239,1996.
25. Kaga K, Nakamura M, Shinogami M, Tsuzuku T, Yamada K, Shindo M: Auditory nerve disease of both ears revealed by auditory brainstem responses, electrocochleography and otoacoustic emissions. Scandinavian Audiol 25:233-238,1996.
26. Iwasaki S, Kaga K, Yagi M, Kuroda M: Vestibular findings syndrome. ORL 58:343-346,1996.
27. Kaga K, Shinoda Y, Suzuki J-I: Origin of auditory brainstem responses in cats: Whole brainstem mapping, and a lesion and HRP study of the inferior colliculus. Acta Otolaryngol (Stockh) 117:197-201,1997.
28. Kaga K, Ichimura K: A preliminary report clinical effects of otic solution of ofloxacin in infantile myringitis and chronic otitis media. Int J Pediaric Otorhinolaryngol 42:199-205,1998.
29. Suzuki M, Yamasoba T, Kaga K: Development of the blood-labyrinth barrier in the rat. Hearing Research 116:107-112, 19989.
30. Suzuki M, Yamasoba T, Kaga K: Effects of chronic administration of Kanamycin on the basement membrane anionic sites in the crista ampullaris of guinea pigs. Laryngoscope 108:81-86,1998j.
31. Sakamoto M, Sugasawa M, Kaga K, Kamio T: Average thresholds in the 8 to 20 kHz range as a function of age. Scand Audiol 27:189-192,1998.
32. Kaga K, Ono M, Yakumaru K, Owada M, Mizutani T: Brainstem pathology of infantile Gaucher's disease with only wave I and II of auditory brainstem response. J Laryngol Otol 112:1069-1073,1998.
33. Kaga K, Takeuchi N, Sakurai H: Facial nerve pathology of two patients with herpes simplex encephalitis. A temporal bone study. Facial Nerve, pp 1-6, Proc VIII International Symposium on the Facial Nerve. Kugler Pub, The Netherlands, 1998.
34. Kaga K, Yamada K, Tsuzuku T, Uno A: The long-term effect of bilateral inferior colliculus ablation on auditory brainstem response in awake cats. Acta Otolaryngol (Stockh) 119:128-131m1999.
35. Kaga K: Vestibular compensation in infants and children with congenital and acquired vestibular loss in both ears. Int J Pediatr Otorhinolaryngol 49:215-224,1999.
36. Naito R, Murofushi T, Mizutani M, Kaga K: Auditory brainstem responses, electrocochleograms, and cochlear microphonics in the myelin deficient mutant hamster 'bt'. Hearing Research 136:44-48,1999.
37. Yamasoba T, Tsukuda K, Oka Y, Kobayashi T, Kaga K: Cochlear histopathology associated with mitochondrial transfer RNALeu(UUR) gene mutation. Neurology 52:1705-1707,1999.

38. Kaga K, Shindo M, Tanaka Y, Haebara H: Neuropathology of auditory agnosia following bilateral temporal lobe lesions: A case study. Acta Otolaryngol 120:259-262,2000.
39. Takegoshi H, Kaga K, Kikuchi S, Ito K: Mandibulofacial dysostosis: CT evaluation of the temporal bones for surgical risk assessment in patients of bilateral aural atresia. Int J Pediatric Otorhinolaryngol 54:33-40,2000.
40. Yamada K, Kaga K, Tsuzuku T, Uno A: Long-term changes in middle latency response and evidence of retrograde degeneration in the medial geniculate body after auditory cortical ablation in cats. Acta Otolaryngol 120:744-949,2000.
41. Itoh K, Yumoto M, Uno A, Kurauchi T, Kaga K: Temporal stream of cortical representation for auditory spatial localization in human hemispheres. Neruoscience Letters 292:215-219,2000.
42. Kaga K, Setou M, Nakamura M: Bone-conducted sound lateralization of interaural time difference and interaural intensity difference in children and a young adult with lateral microtia and atresia of the ears. Acta Otolaryngol 121:274-277,2001.
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49. Kondo K, Sagara H, Hirosawa K, Kaga K, Matsushima S, Mabuchi K, Uchimura H, Watanabe T: Hair cell development in vivo and in vitro: analysis by using a monoclonal antibody specific to hair cell in the chick inner ear. J Comp Neurol 445:176-198,2002.
50. Ishimoto S, Ho K, Sasaki T, Shinogami M, Kaga K: Total middle ear reconstructive surgery for the radicalized ear. Otol Neurotol 23:262-266,2002.

Department of Rehabilitation Medicine

Outline and Research Objectives

The Department of Rehabilitation Medicine was established by Ministry of Education, Culture, Sports, Science and Technology in April 2001. It is one of the newest fields in the University of Tokyo Graduate School of Medicine. It belongs to the Sensory and Motor System Medicine Course of the Surgical Sciences Study Major. Current staff is only one professor. We have accepted the graduate school student formally since fiscal year 2001 when the Rehabilitation Medicine Field was installed in. Two students of the first year class of graduate school and two of the second year class started some rehabilitation research. An activity of our department is at one with the Central Rehabilitation Service of the university hospital. As for the staff of the rehabilitation service of the university hospital, there are one lecturer, one associate and three part-time medical doctors. In addition, one temporary associate has accompanied in April 2002, and he takes charge of the day hospital in psychiatry rehabilitation.

The Central Rehabilitation Service derives from the establishment of the exercise therapy room in 1963 in the central medical service department. It aimed at the development of the medical rehabilitation in our country corresponding to needs of rehabilitation service that had become clear in the health care of the 20th century middle.

In the university hospital, the rehabilitation section increased and maintained a hydrotherapy room and the occupational therapy room, etc., and it was renamed the rehabilitation center in 1966. Then, it became an independent section by changing the title as the central rehabilitation service in 1970. Both were names by measures in the hospital. A formal name of the section was a department of physical therapy. The professor employment was set up as a full-time medical director in 1984. However, a formal name of the section was still a physical therapy department.

Rehabilitation medicine is a comprehensive medical management of disability including its diagnosis and treatment. It was born in the flow of the health care and medical service at modern ages by which it came to value the enhancement of not only extending years of patient's life but also adding life to years. In Declaration of Alma-Ata by World Health Organization (WHO) of 1978, it was described, "primary health care addresses the main health problems in the community, providing promotive, preventive, and curative and rehabilitative services". Regardless of rapid expansion of those needs, acknowledgment of medical rehabilitation was delayed in the frame of conventional diagnosis and treatment department. In our country, it was 1996 that the rehabilitation department was authorized as the formal clinical department in the health insurance system by the former Ministry of Health and Welfare. On the other hand, the professor of the physical therapy department was positioned as an assistance instructor in the sensory and motor system medicine course by the University of Tokyo Faculty of Medicine having shifted to the graduate school course system between fiscal year 1995 and fiscal year 1997.

In the university hospital, the name was changed from the physical therapy department to the rehabilitation medicine department by the budget measures in fiscal year 2001. Now we integrated related occupational categories, which had historically belonged to the orthopedic surgery department and the former physical medicine department, and started the maintenance of the department. The Central Rehabilitation Service includes 14 physical therapists (one person is a part-time) and 5 occupational therapists and 5 acupuncture therapists as a rehabilitation team staff other than current medical doctors.

Our mission is to provide exceptional rehabilitation for our patients through clinical excellence and compassionate care, all dedicated to helping patients achieve their maximum functional capacity and highest quality of life. Another significant focal point of the Department is research. The research objectives of the Department are to make clear configuration of disabilities and to develop measures to reduce the obstacles for patients' independent living as well as to promote reintegration in their society.

Faculties and Students

Professor and Chair	Eto, Fumio, MD, Ph. D (1998~)
Lecturer	Kodama, Yoshiaki, MD, Ph. D
Associate	2
Visiting Fellow	1
Graduate student	4
Secretary	1 (part-time employment)

Past Research and Major Accomplishments

The rehabilitation medicine field had not been admitted as an established course before reorganization of the graduate school course system. Therefore, there is still no own laboratory space. There is yet no space of doctor's medical office and other staff's duty rooms in the university hospital though the physical therapy department has been engaged in the medical service activity of rehabilitation since 1963. In our conventional research activity, a clinical research that adheres to a daily medical management in rehabilitation has been a major subject.

Research topics that have been executed so far are the following content.

1. The influence of the trouble in patient's daily life due to various diseases is analyzed, and an appropriate treatment program is developed. It is included to describe natural course of the disease and the trouble clearly in life cycle of physically handicapped person. A study to make clear a pattern of the disorder type change in cerebral palsy by the development process from infancy was done. Natural course of Werdnig-Hoffmann disease and congenital muscular dystrophy, which were a rare pediatric disease, was described, and the indication of rehabilitation was clarified.
2. Proper management of the factor disturbing rehabilitation process is important in everyday medical rehabilitation care. The pain management was a typical problem, and the pathophysiological study on shoulder-hand syndrome in poststroke patients was done.
3. Most of activities in daily life depend on walking and locomotion ability. Especially, a study about evaluation method of gait abnormalities and development of specific treatment of an abnormal gait is necessary for regain of useful mobility in physically disabled. The effect of various shoe insoles including arch support as apparatus for treatments was clarified by the gait analysis system.
4. We have studied on development of rehabilitation therapy to promote independent living of the patients with higher brain dysfunction due to cerebrovascular disorders, traumatic brain injury, Alzheimer's disease and so on. Such a study included the development of assessment tools to evaluate the effectiveness of the rehabilitative intervention.
5. The ordering a bed rest is one of the treatment measures. We have clarified the meaning of disuse syndromes in the rehabilitation as the adverse effect, which includes the deconditioning state. Moreover, decreased activity in daily life after discharge from hospital may be a significant cause of disuse syndromes, especially in the older people. The research on risk factors of accidental fall has revealed that incidence of fall is higher in the older people with decreased daily activities.
6. The disuse syndromes and hypoactive daily life may be serious matter in the poststroke patients living in the community. We have examined the influence of daily activity on changes in the physical fitness of people with poststroke hemiplegia. Then, we have concluded that they can improve their physical fitness without formal supervised training by simply increasing their daily activities.
7. We have developed the comprehensive assessment tool of activities of daily living (ADL) for the elderly based on the hierarchical structure of the ADL. In rehabilitation of the dementia patients the usefulness of ADL measurement has been revealed for classification of the severity of dementia as well as for evaluation of the effect of rehabilitation program.
8. A basic research including animal experiment is also necessary to improve the rehabilitation management. In collaboration with some outside laboratories we have studied a causative mechanism of muscle atrophy, joint contracture and bone atrophy, which are main components of disuse syndromes. In addition, we have examined the effect of physical agents in such a condition; for example, effects of dietary calcium depletion and repletion on tibial bone volume, influences of exercise and mechanical loading on bone strength, effects of electrical stimulation for reducing the degree of joint contracture, and so on.

Current Research

The department's research interests are directed towards reduction of the major disabilities of the handicapped persons, namely immobility, instability and intellectual impairment. The approach is both theoretical, by seeking a better understanding of the baneful processes which produce disability in daily life of the handicapped persons; and practical by the introduction and evaluation of new methods of management. Research workers of variety of medical and non-medical backgrounds shall work together on these problems. Such a research policy is the future

directionality, but the present state is in extension of the past research activities.

Two or more equipment (force platform, video operation analysis system, surface electromyography, and ataxiameter, etc.) are usually combined for the evaluation of walking and motion disturbances. This combined operation analysis system is arranged for the synchronized determination. In addition, synchronous measurements such as the torque machines for the muscular power measurement and the surface electromyography are possible. We have been analyzing human locomotion activities, and also examining the effects of shoes with various insert or heel wedges for walking in normal subjects and physically impaired persons. The present research addresses examining the effects of heel elevation of shoes on walking of the patient with Parkinson's disease. Moreover, a biomechanical change in the walking pattern after surgical operation on the ligaments of the knee has been analyzed with those devices.

The accomplishment of human activities such as locomotion requires the functional integration of at least three major organic systems; the bone, joint, and muscular system that carries out various motions in daily activities; central and peripheral nervous system that controls musculoskeletal system organs; cardiopulmonary system that supplies oxygen and glucose to the former two system organs. Therefore, clinical research interests of rehabilitation medicine are in the development of integrated physical exercise program, the improvement of cardiopulmonary management during rehabilitation therapy, and restorative design for brain damage and nerve injuries. Now we are studying on the evaluation of higher brain dysfunction concerning everyday activities and also on the physical fitness measurement by using the ergometer for the development of an appropriate rehabilitation program.

The clinical practice of rehabilitation is characterized in the team approach by multidisciplinary cooperation. Because two or more specialized professionals work together in practice, the area of research needed is broad. There are a lot of necessary, but unsettled research topics for development and enhancement of rehabilitation practice. However, the physicians and non-medical staffs cannot afford to spend time in the research work because the needs of rehabilitation medical service nowadays increase rapidly in the university hospital. Our present research environment is under a poor condition, and therefore, more cooperation with the outside laboratory or organization including other faculty of the university may be recommended to accomplish the research plan in order to investigate a problem thoroughly.

Future Prospects

Rehabilitation medicine is an important task of primary health care. Theories of disability in health practice and research are area of a new frontier. A research on treatment and prevention of disability depends on the concept and the hypothesis of disability. In addition to an experimental study, a narrative based study in ethnography is important so that the subjective problems like disability experiences may be discussed. Then, not only a biological approach but also a sociological approach should promote it concurrently.

Our academic field has just started. We have requested a laboratory to accomplish experimental study, but it is not given yet. Since historical process and the financial situation of a current university, it is pessimistic to set up the research environment on the university campus. We should struggle with the matter connected directly with the activity of the university hospital, which is a training organization of a medical doctor, though there are an enormous number of unsolved research topics. We have entrusted the attending lecturer to the staff of outside institutions and the organization in order to support our clinical and educational tasks. We are now arranging the cooperation system with staffs of these external institutions for research and development of the welfare equipments to facilitate the independence of the disabled persons. This system may be of help to the research activity coherent to clinical practice in rehabilitation.

The physical therapist and the occupational therapist are new type of jobs in our country in the development process, and they are positioned as medical service staffs in the hospital. It is necessary to increase the chance that those co-medical professionals also participate in the research activity in order to activate a clinical research.

The research of rehabilitation medicine is a new field, internationally. There increases a number of inquiries to hope for studying at our department from several foreign researchers of other Asian nations. Unfortunately, our present environment is insufficient to accept them. Nevertheless, one Chinese doctor and one Mongolia doctor are working with us now. The former has already completed the doctor degree thesis, and the latter is about to start a study now. Professor Eto was invited to Chinese Rehabilitation Medicine Association Conference held in Beijing in China in October 2001 and gave a lecture, entitled "the current situation of rehabilitation medicine in Japan, from a viewpoint of medical education". In addition, he lectured several topics on stroke rehabilitation at the university hospitals in Wuhan city and Shijiazhuang city in China. International cooperation in the rehabilitation medicine research is the future matter.

Table 1. Representative subjects for research grants

Fiscal year	Resource	Subject (Author)	Amount of money (yen)
1998-1999	The MEXT Scientific Research Fund, Basic Research (C)	Study on effect of electric stimulation in prevention of disuse changes of bone and soft tissues (Dr. Akai, M)	1,500,000
2000-2002	The MEXT Scientific Research Fund, Basic Research (C)	Study on effect of heel elevation for Parkinsonian gait (Dr. Eto, F)	4,100,000
2000	The MEXT Scientific Research Fund, Basic Research (C)	Study on functional recovery and ADL of stroke patient's with higher brain dysfunction (Dr. Ohtsuru, I)	1,900,000
2000	The MEXT Scientific Research Fund, Basic Research (C)	Study on evaluation of joint lesion by using noninvasive measures such as vibration response (Dr. Akai M)	3,100,000
2001-2002	Ministry of Health, Labor and Welfare, Research Consignment Expense for Psychiatric and Neurological Disease	Study on functional recovery and ADL in higher brain dysfunction (Dr. Eto, F)	1,600,000

(Abbreviation, MEXT: Ministry of Education, Culture, Sports, Science and Technology)

Research Grants

The total of the competing research expense, which the doctor researcher who belonged to the Central Rehabilitation Service of the university hospital acquired, is 13,200,000 yen since 1998. Five representative research topics and the capital sources are as follows in table 1.

Select Publications

1. Ueda S, Miura T, Eto F. Shoulder-Hand Syndrome as an important complication of hemiplegia. J Jap Ass Phys Med Balneol Climatol 38: 35-42, 1975.
2. Eto F, Yoshikawa M, Morimatsu M, Hirai S, Ueda S. Shoulder-hand syndrome as a complication of hemiplegia. Jpn J Geriat 12: 245-251, 1975.
3. Eto F, Ueda S. Long-term change of motor patterns in cerebral palsy. Jpn J Rehabil Med 14: 261-266, 1977.
4. Eto F, Yoshikawa M, Ueda S, Hirai S. Posthemiplegic shoulder-hand syndrome, with special reference to related cerebral localization. J Am Geriatr Soc 28: 13-17, 1980.
5. Eto F. Complications due to prolonged or excessive rest in rehabilitation medicine. J Clinical and Experimental Medicine (Igaku no ayumi) 116: 416-422, 1981.
6. Eto F. Activities of daily living of the patients with dementia in the long-stay psychogeriatric wards. In: Flax HJ, Matta AA, eds. New Frontiers that Influence Disease and Rehabilitation, IRMA IV, Puerto Rico, 1983, pp.125-129.
7. Watamori T, Eto F. A longitudinal study of linguistic and nonlinguistic functions in a patient with Alzheimer's disease. Rinshou Seishin Igaku (Clin Psychiatry) 12: 1155-1168, 1983.
8. Eto F, Harasawa M, Hirai S. Hand dexterity related to age: Pegboard test as an indicator of aging and brain dysfunction. Jpn J Geriat 20: 405- 409, 1983.
9. Eto F, Yoshikawa M. A dose-response study of Dihydroergotoxine (DHET) Mesylate for cerebrovascular disturbances. In: Gaitz CM, Samorajaski Y, eds. Aging 2000: Our Health Care Destiny, vol 1: Biomedical Issues, Springer-Verlag, New York, 1985, pp.421-431.
10. Ueda S, Hasegawa T, Ando K, Sakuma A, Kusunoki T. Standardization of the finger function test and upper extremity ability test for hemiplegia. Jpn J Rehabil Med 22: 143-160, 1985.
11. Okawa Y, Ueda S, Eto F, Kikuchi N. The analysis of the course of motor impairment in Fukuyama type congenital muscular dystrophy. Jpn J Rehabil Med 22: 197-202, 1985.
12. Okawa Y, Eto F, Ueda S. The analysis of the course of disability in Werdnig-Hoffman disease (chronic type). Jpn J Rehabil Med 22: 115-120, 1986.
13. Eto F. Treatment of degenerative neurological diseases in the elderly: a rehabilitation approach. Jpn J Geriat 23: 35-40, 1986.
14. Eto F. Rehabilitation of post-stroke patients with cardiac disease. J Clinical and Experimental Medicine (Igaku no ayumi) 139: 691-695, 1986.
15. Ueda S, Eto F, Okawa Y. Standardization of a functional test for hemiplegia for the evaluation of total body motion. Scand J Rehabil Med 17 (Suppl): 163, 1988.
16. Eguchi K, Eto F, Ohkawa Y, Ueda S. Factors affecting return to work following stroke in youth and young adults. Jpn J Stroke. 10: 124-126, 1988.
17. Eto F. Physical disability and dementia. Jpn J Rehabil Med 25: 85-86, 1988.
18. Eto F. Rehabilitation of the elderly patients. In: Hsu C-J, Orimo H, eds. Problems of the aged. Asia &

Pacific Council for Science & Technology, Taipei, 1989, pp64-88.
19. Majima M, Ueda S. Major factor of the deterioration of physical fitness in poststroke hemiplegics. Jpn J Rehabil Med 27: 53-57, 1990.
20. Eto F. Activities of daily living and mental status in elderly patients with organic brain disorders. In: O'Neill D ed. Carers, Professionals and Alzheimer's Disease, John Libbey & Company, London, 1991, pp323-327.
21. Eto F. Falls and immobilization: A vicious circle in the elderly. In: Orimo H, Fukuchi Y, Kuramoto K, Iriki M eds. New Horizons in Aging, Univ of Tokyo Press, Tokyo, 1992, pp.280-281.
22. Eto F, Tanaka M, Mizoguchi T. Comprehensive activities of daily living (ADL) index for the elderly. In Beregi E, Gergely IA, Rajczi K, eds.: Recent Advances in Aging Science, vol.2, Monduzzi Editore, Bologna, 1993, pp.2183-2187.
23. Obana M, Eto F. Progressive pes equinovarus complicated with Parkinson's disease. J Clin Rehabil 2: 78-80, 1993.
24. Kakurai S, Akai M. Clinical experiences with a convertible thermoplastic knee-ankle-foot orthosis for post-stroke hemiplegic patients. Prosthetics and Orthotics International 20:191-194, 1996.
25. Eto F, Saotome I, Akiya N, Furuichi T. Early intervention of rehabilitation service for acute stroke patients. Eur J Neurol 3(Suppl 2): 102, 1996.
26. Akai M, Shirasaki Y, Tateishi T. Electrical stimulation on joint contracture; an experiment in rat model with direct current. Arch Phys Med Rehabil 78:405-409, 1997.
27. Eto F. Rehabilitation of memory. Jpn J Rehabil Med 34: 395-399, 1997.
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29. Kodama Y, Nakayama K, Fuse H, Fukumoto S, Kawahara H, Takahashi H, Kurokawa T, Sekiguchi C, Nakamura T, Matsumoto T. Inhibition of bone resorption by pamidronate cannot restore normal gain in cortical bone mass and strength in tail-suspended rapidly growing rats. J Bone Miner Res 12: 1058-1067, 1997.
30. Usuba M, Akai M, Shirasaki Y. Effect of Low-Level Laser Therapy (LLLT) on viscoelasticity of the contracted knee joint; Comparison with whirlpool treatment in rats. Lasers in Surgery and Medicine 22:81-85, 1998.
31. Yokota K, Itsukaichi K, Kakurai S, Asakura K. Consideration of training for walker-assisted gait: From the investigation of the load under walker's tips. Bull Jpn Soc Prosthetics Orthotics 14: 76-81, 1998.
32. Itsukaichi K, Kaneko H, Kakurai S, Tazawa E. Habilitation of the congenital limb deficient children. Bull Jpn Soc Prosthetics Orthotics 14: 88-94, 1998.
33. Eto F, Saotome I, Furuichi T, Ogasawara M. Effects of long-term use of benzodiazepines on gait and standing balance in the elderly. Annals of New York Academy of Sciences 860: 543-545, 1998.
34. Kodama Y, Takeuchi Y, Suzawa M, Fukumoto S, Murayama H, Yamato H, Fujita T, Kurokawa T, Matsumoto T. Reduced expression of interleukin-11 in bone marrow stromal cells of senescence-accelerated mice (SAMP6): relationship to osteopenia with enhanced adipogenesis. J Bone Miner Res 13: 1370-1377, 1998, 1998.
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36. Kodama Y, Dimai HP, Wergedal J, Sheng M, Malpe R, Kutilek S, Beamer W, Donahue LR, Rosen C, Baylink DJ, Farley J. Cortical tibial bone volume in two strains of mice: effects of sciatic neurectomy and genetic regulation of bone response to mechanical loading. Bone 25: 183-190, 1999.
37. Linkhart TA, Linkhart SG, Kodama Y, Farley JR, Dimai HP, Wright KR, Wergedal JE, Sheng M, Beamer WG, Donahue LR, Rosen CJ, Baylink DJ. Osteoclast formation in bone marrow cultures from two inbred strains of mice with different bone densities. J Bone Miner Res 14: 39-46, 1999.
38. Eto F. Recent advances in geriatric rehabilitation. Jpn J Geriat 36: 153-161, 1999.
39. Xu H, Akai M, Kakurai S, Yokota K, Kaneko H. Effect of shoe modifications on center of pressure and in-shoe plantar pressures, Am J Phys Med Rehabil 78:516-524, 1999.
40. Fujitani J, Ishikawa T, Akai M, Kakurai S. Influence of daily activity on changes in physical fitness for people with post-stroke hemiplegia, Am J Phys Med Rehabil 78:540-544, 1999.
41. Akai M, Shirasaki Y, Tateishi T. The effect of electricity on joint contracture due to immobilization; Direct current stimulation in rat experiment. In: Electricity and Magnetism in Biology and Medicine. Bersani F ed., Kluwer Academic/Plenum Publishers, New York, 1999, p.883-886.
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43. Nara A, Umishima M, Imase A, Mineshima T. Study on the effects of pulp-to-pulp distance in measuring the pinch strength - compare the young with the aged in a nursing home -. Sagyo Ryoho (J Jpn Ass OT) 19: 338-345, 2000.
44. Hirose K, Eto F. Exercise training for internal disability in the elderly. J Clin Rehabil 9: 3 42-350, 2000.
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46. Kodama Y, Miyakoshi N, Linkhart TA, Wergedal J, Srivastava A, Beamer W, Donahue LR, Rosen C, Baylink DJ, Farley J. Effects of dietary calcium deple-

tion and repletion on dynamic determinants of tibial bone volume in two inbred strains of mice. Bone. 27: 445-452, 2000.
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49. Ohtsuru I, Eto F, Wada N, Saotome I, Furuichi T. New reliable and valid motor assessment scale for stroke patients: Hemiplegic motor behavior tests. Geriatrics Gerontology Int 1: 45-51, 2001.
50. Kodama Y, Eto F. How to find out patients with a high risk for falls. J Clin Rehabil 10: 961-964, 2001.

Department of Anesthesiology

Outline and Research Objectives

The department of Anesthesiology was established in1952. Our department has residents and eight researchers from China. We give lectures and provide clinical education for postgraduate students and medical students.

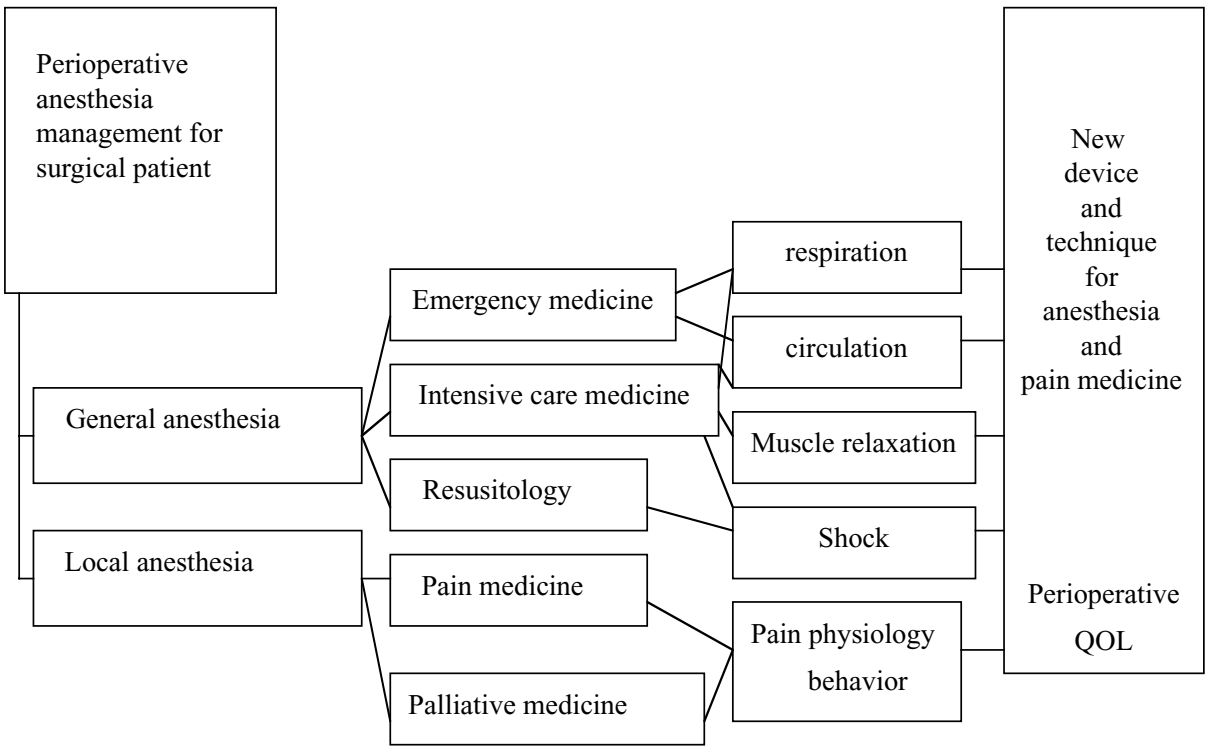
We have pain clinic services in our department, which was established in 1962. It is provided for not only out-patients but also including patients in the ward of the other departments on a daily basis in all areas of painful diseases.

Anesthesia service including pre-and post-operative care is provided every day for elective and emergency surgical procedures. Recently, we have started acute pain service for postoperative pain relief and palliative medicine for cancer pain relief and terminal care.

Research activities:

There are eight laboratories in our department, which are investigating clinical and basic project of anesthesia research.

These themes of the research groups of our department are listed as bellow.



Anesthesiology, basic and clinical respiration

- Measurement of pulmonary vascular resistance of normal and pulmonary edema using rabbit
- The effect of anesthetics upon pulmonary function
- The model of neurogenic pulmonary edema of rabbit
- Basic research of lipopolysaccharide which interact with apoprotein from the lung of neonatal mouse
- Basic research of the changes in transmission and distribution of gas with pulmonary lesion
- Clinical assessment of pulse-oximeter

circulation

- Relationship between sympathetic nervous system and cardiac function
- Clinical assessment of anti-hypertensive agents during anesthesia
- Prostaglandins and tissue blood flow of the liver and kidney

pain mechanism (neurobiology, neuro-physiology, behavior investigation)

- Relationship between noxious stimuli and catecholamines in the anesthetized rat
- Physiology of pain and the mechanisms of analgesia using spinal rat
- The effect of midazolam upon the spinal analgesical mechanisms
- The effect of peripheral sensory nervous activities by acupuncture
- Basic and clinical assessment of benzodiazepine antagonist
- Basic and clinical assessment of enkepharinase inhibitor
- Analgesic mechanism of nociceptin in spinal rat
- Assessment of bispectral index monitor
- Clinical evaluation of drug challenge test
- Analgesic mechanism of laser treatment
- Analgesic mechanism of oriental medicine
- Clinical assessment of acupuncture

muscle relaxation

- Mechanism and the pharmacological analysis of non-depolarizing muscle relaxants in human
- Clinical assessment of malignant hyperthermia
- Basic and clinical assessment of non-depolarizing muscle relaxants

new devices and techniques for anesthesia

- Mechanism of H-type epidural-spinal anesthesia
- Development of skin surface anesthetics by lidocaine tape
- Clinical assessment of the induction by midazolam combined with barbiturates
- Anesthetic method by low dose buprenorphine with inhalational anesthetics
- The effect of epidural buprenorphine and morphine on post-operative pain control
- Clinical usefulness of patient-controlled analgesia (PCA)
- Clinical assessment of stellate ganglion block
- Assessment of anesthetic machines
- Development of device for intubation

mechanism of anesthesia

- Mechanism of anesthetics from auditory brainstem response and Fourier analysis of EEG
- Inhalational anesthetics and rate potential
- Analgesic mechanisms of hyperventilation
- The interaction of central analgesic and spinal analgesic mechanisms

shock

- Response to immunological system against the endotoxin in the blood
- The effect of poly-enzyme inhibitor upon tissue microcirculation
- Effects of anesthetics upon liver cell and Kupffer cell

QOL in surgical patients during perioperative period and chronic pain patients

- Perioperative QOL in case of surgical patient
- QOL of donor of blood
- QOL of intractable chronic pain patient such as post-herpetic neuralgia and low back pain

Faculty and Students

Professor and Chair	Kazuo Hanaoka, MD, Ph., D. (1991~)
Associate Professors	Hideko Arita, MD, Ph.,D.
	Tomoki Nishiyama MD, Ph., D
Lecturer	Cyoku Yajima, MD, Ph., D
	Yasuo Ide, MD, Ph.,D.
	Masakazu Hayasida MD, Ph.,D.

Associate.....13
Postdoctoral Fellow 12
Graduate student 9
Research student.....6
Secretary 3

Past Research and Major Accomplishments

In Anesthesiology, Respiration, Circulation, Pain, Muscle relaxation, New devices and techniques for anesthesia, Mechanism of anesthesia, Shock and Perioperative QOL are mainly involved.

For each project, we are investigating both basically and clinically. The main purpose of these investigation is that the safety and quality of perioperative anesthesia care are sought, and also the treatments of patients with intractable pain as chronic pain and postoperative pain as acute pain are important field of pain management.

We investigated the effect of Drug Challenge Test (DCT) for chronic intractable pain patient and established the easy and accurate method of DCT. This DCT were applied to many chronic patients and got good results by the treatment of administered adequate drugs orally. Epidurascopy for chronic lumbar pain are investigated and developed clinically.

Postoperative pain management are also investigated and established guideline for the method using local anesthetics combined with narcotics via epidural catheter to the epidural space. Patient Controlled Analgesia (PCA) and pre-emptive analgesia are also investigated.

Current Research

Respiration, circulation, pain, muscle relaxation, new devices and techniques for anesthesia, mechanism of anesthesia, shock and perioperative QOL are being investigated. Each project is progressing well. Especially new devices for epiduroscopy with useful attachment such as manipulating device are being developed.

We are making of the animal model of post herpetic neuralgia (PHN), which is very useful for the investigation of PHN. The number of patients with PHN will increase because of large population of high aged people in the near future. Therefore, this is very important investigation.

Future Project

We are seeking the method of safe anesthesia including perioperative period. Also safe management of pain is really necessary in 21 century, because the population of aged people will be tremendously increased. Therefore, the investigated area of above mentioned will be continued. Palliative care medicine will be important field also in the near future. Therefore, we will investigate this field. Actually clinical investigation of palliative care medicine has started from this year as a field study.

Research Grants

1. 1998-2001 Research Grant (C2), #10671404 The Involvement of NMDA receptor in the intrinsic analgesia evoked by hyperventilation.
2. 1998-2001 Research project. Grant-in-aid for scientific research (B)#10470315 The effects of vasoactive drugs upon the spinal pain modulation.
3. 1999-2002 Research Grant (C2), #11671480 The effects of inhalational anesthetics and nitric oxide upon the activities of spinal dorsal horn neuron.
4. 2000-2002 Research Grant (C2), #12671453 Investigation of network by analgesic mechanisms of spinal cord
5. 2002-2004 Research Grant(C2), #14571422 The development and clinical application of cheeper and more accurate neuromuscular monitoring devices now in use.

Select Publications

respiration

1. Kitamura T, Uchida K, Tanaka N, Tsuchiya T, Watanabe J, Yamada Y, Hanaoaka K, Seymour JF, Schoch OD, Doyle I, Inoue Y, Sakatani M, Kudoh S, Azuma A, Nukiwa T, Tomita T, Katagiri M, Fujita A, Kurashima A, Kanagasaki S, Nakata K:Serological diagnosis of idiopathic pulmonary alveolar proteinosis. American Journal of Respiratory & Critical Care Medicine 162:658-662, 2000

circulation

2. Nishiyama T, Hanaoaka K,: Nicardipine did not activate rennin-angiotensin- aldosterone system during isoflurane or sevoflurane anesthesia. Canadian Journal of Anaesthesia 47(12):1249-1252,2000
3. Nishiyama T, Hanaoaka K: Free hemoglobin concentrations in patients receiving massive blood transfusions during emergency surgery for trauma. Canadian Journal of Anaesthesia 47(19): 881-885, 2000
4. Nishiyama T, Yokoyama T, Matsukawa T, Hanaoka K: Continuous nicardipine infusion to control blood

pressure after evacuation of acute cerebral hemorrhage. Canadian Journal of Anaesthesia 47(12):1196-1201,2000
5. Orii R, Sugawara Y, Hayashida M, Yamada Y, Kubota K, Takayama T, Harihara Y, Makuuchi M, Hanaoaka K:Peri-operative blood lactate levels in recipients of living-related liver transplantation. Transplantation 69(10):2124-7, 2000
6. Takeda K, Sawamura S, Tamai H, Hagihara R, Hanaoaka K: Reversible tricuspid valve obstruction during removal of renal cell carcinoma with intracardiac tumor extension. Anesthesia & Analgesia 91:1137-38, 2000
7. R. Orii, Y. Sawamura, M. Hayashida, Y. Yamada, K Chang, T. Takayama, M. Makuudhi and K.Hanaoka: Effects of amrinone on ischaemia-reperfusion injury in cirrhotic patient undergoing hepatectomy: a comparative study with prostaglandin E_1. British Journal of Anaesthesia 85(3): 389-95, 2000
8. Orii R, Sugawara Y, Hayashida M, Uchida K, Yamada Y,Takayama T., Makuuchi T., Hanaoka K: Lactate is correlated with the indocyanine green elimination rate in liver resection for cirrhotic patients. Anesthesia & Analgesia 92(4):1064-070,2001
9. Kazuo Hanaoka, Akiyoshi Namiki, Shiji Dohi, Yoshihisa Koga, Osafumi Yuge, Yasushi Kayanuma, Kazuyuki Hidaka, Tadashi Kusunoki; A dose-ranging study of midazolam for postoperative sedation of patients: A randomized, double- blind, placebo-controlled trial. Crit Care Med. 30 (6): 1256-1260, 2002
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pain mechanism (neurobiology, neuro-physiology, behavior investigation)

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Department of Emergency and Critical Care Medicine

Outline

Department of Emergency and Critical Care Medicine was established in 1965, as the emergency service within the Central Clinical Service Facilities of the University of Tokyo Hospital and at the same time as the intensive care service for in-hospital patients, it became a tertiary emergency care and critical care center in the metropolitan Tokyo and also became the principal teaching facility of the University of Tokyo. It is a designated Level I Trauma Center, and also the home of one of the newest Life Flight aeromedical services in the country.

The Emergency Center sees approximately 15000 patients per year. It contains major trauma and cardiac resuscitation rooms complete with STAT X-ray and full monitoring and resuscitation equipment. There are 9 treatment spaces including space for orthopedic, gynecology, and optho-ENT evaluation. X-ray, rapid spiral CT, ultrasound, angiography and STAT Lab are located adjacent to the Emergency Center.

The Critical Care Center contains adult intensive care unit (ICU) of 8 beds, cardiac care unit (CCU) of 6 beds, surgical high care unit (SHCU) of 36 beds, medical high care unit (MHCU) of 15 beds, pediatric intensive care unit (PICU) of 6 beds, and neonatal intensive care unit (NICU) of 6 beds.

The Emergency Center and Critical Care Center sees an excellent mix of multiple traumas, high-acuity medical, surgical, pediatric, and gynecological patients. The Life Flight service provides another opportunity for exposure to critically ill patients. Consult services are available from each of the clinical departments of the Hospital.

Faculties and Students

Professor and Chairman Naoki YAHAGI, M.D., Ph.D.
Associates 9
Staff 3
Research student.....1
Secretaries 3

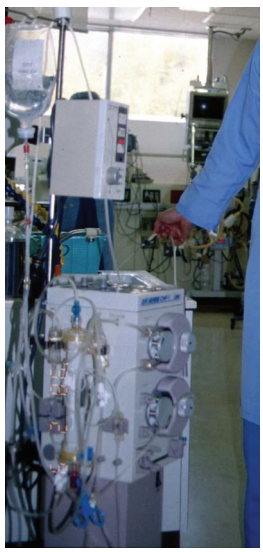
Past Research and Major Accomplishments

- Study of the effect of anesthetics on the threshold for transpulmonary passage of venous air emboli. (*Resuscitation* 13: 81-86, 1986, *Anesthesiology* 67: 905-909, 1987, *Anesth Analg* 75: 720-723, 1992) .

  We found that the threshold for transpulmonary passage of venous air was significantly lower during halothane anesthesia (0.01-0.05 ml/kg), as compared with pentobarbital (1.0 ml/kg), fentanyl (0.5 ml/kg), or ketamine (0.35 ml/kg) anesthesia.
- Study on the effect of catecholamine on regional cerebral blood flow in dogs (Masui 36: 1176-1180, 1986)

Development of Hemoperfusion System (HF)

1) For the patients of cardiac surgery
2) For the regulation of water balance in the patients of renal insufficiency
3) For the expansion of the indication of bloodless priming for cardiopulmonary bypass by hemoconcentration using HF.



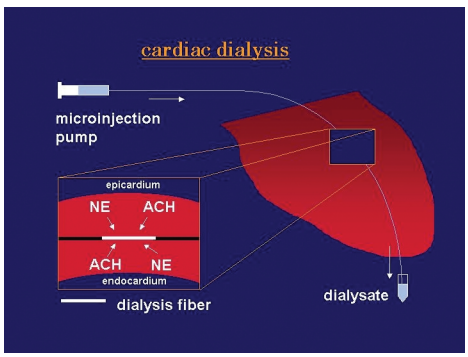
The usage of HF during cardiopulmonary bypass in NCVC

1985	1986	1987	1988	1989	1990	
Total	644	623	593	573	586	594
HF	13	78	115	84	120	180
HF in adults	13	56	83	44	67	97
(%)	2.0	9.0	12.0	7.8	11.6	16.3
HF in infants	0	22	32	40	52	83
(%)	0.0	3.5	5.4	7.0	8.9	14.0

- Development of HF pump system for the perioperative management of cardiac surgical patients suffering from renal insufficiency and deteriorated cardiac function. (Ube-Junken; 1984)
- Induction of hypothermia for the management of the patient who undertaken open heart surgery complicated by acute cerebral infarction (Kyukyu-igaku 18:917-921, 1994) (1984).
- We elucidated the structural parts involved in activation and inactivation of Na channel by bioengineering and electrophysiology. (*FEBS Letters* 228: 195-200, 1987, *Nature* 339: 597-603, 1989) .
- Effect of low molecular weight dextran for ARDS induced by oleic acid (*Am J Emerg Med*18: 180-183, 2000)(1988).
- Yahagi cared 5300 cases of critically ill patients including cardiac surgical patients, severely ill patients of all categories in NCVC, and emergency cases. Yahagi developed a handy bronchofiberscope. (Easyscope:FiberTech, 21000BZZ00571000, 1998). Yahagi engaged in the preparation of a manual for cardiac transplantation, and established The International Society of Medical Gas in 1995.
- Induction of mild hypothermia for the management of severe cardiac insufficiency (*Anesth Analg* 79: 581-582, 1994, *J Clin Anesth* 10: 120-125, 1998) (1991)

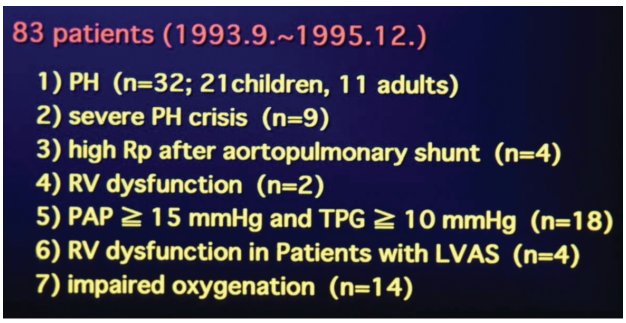
Evaluation of Airway

1) Effect of change of position (*Ann Thorac Surg* 67: 894, 1999)
2) Ultrasound detection of diaphragmatic paralysis after cardiac operations (*Ann Thorac Surg* 65: 1841, 1998)
3) Double lumen endobronchial tube Broncho-Cath II (*Anesthesiology* 81: 781-782, 1994)
4) The cause for needing airway maneuvers to maintain a patent airway during the use of cuffed oropharyngeal airway (COPA) using endoscope, and the difficulty of maintaining patent airway during COPA use might by collapse of the larynx at the level of the hyoid bone. (*Resuscitation* in press)
5) Diagnosis of airway obstruction (*Anesth Analg* 76: 207, 1993, *Anaesthesia* 50: 91-92, 1995, *Anesth Analg* 85: 1180-1181, 1997)
6) Bronchial lavage of the infant using a laryngeal mask airway (*Anaesthesia* 49: 450, 1994) (*Anaesthesia* 49: 450, 1994)
7) Development of a handy-type bronchofiberscope



Inhaled nitric oxide (NO)

1) Indication and the 2-4years follow up of the cases (*Artif Organs* 21: 17-20, 1997, *Artif Organs* 21: 83-84, 1997, *Artif Organs* 22: 886-891, 1998, *Artif Organs* 23: 169-174, 1999)



2) Fontan type operation (*Ann Thorac Surg* 57: 1371-1372, 1994)
3) LVAS (*Artif Organs* 19: 557-558, 1995, *Ann Thorac Surg* 65: 345, 1998)

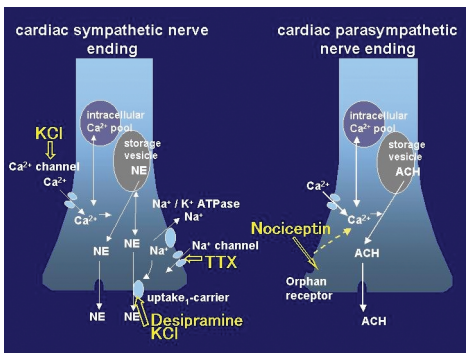
- Helium inhalation (*Anesth Analg* 80: 1042-1045, 1995, *Artif Organs* 21: 24-27, 1997) We demonstrated the beneficial effect of helium/oxygen to improve oxygenation of the postcardiac surgical patients who showed impairment of oxygenation without physiological findings and with normal chest radiographs despite having a positive end expiratory pressure of up to 10 cmH2O.

The effect of helium-oxygen on oxygenation and lung parameters

min		-90 min	baseline	He 90 min
56*	PaO2/FiO2	117±45	113±39	174±56*
±5*	Qs/Qt (%)	27±7	29±6	19±5*
18*	Cdyn (ml/cm H2O)	60±18	60±18	65±18*
±4	PIP (cm H2O)	25±4	25±3	25±4

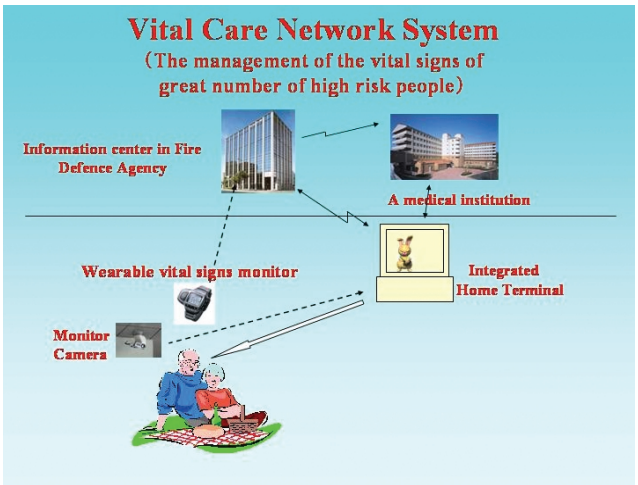
*: $p<0.05$ vs baseline values.

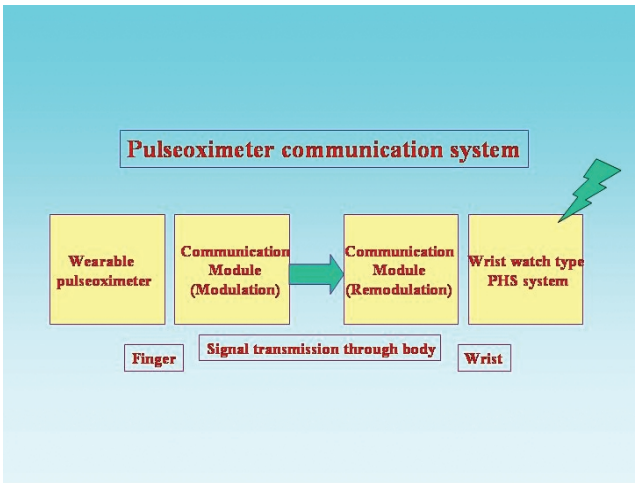
- Autotriggering caused by cardiogenic oscillation during flow-triggered mechanical ventilation (*Crit Care Med* 28: 402-407, 2000)
- Clinical use of electrolyzed water (*Artif Organs* 21: 39-42,1997, *Artif Organs* 24:984-987, 2000).
- Elucidation of peripheral neural regulation of heart (*Brain Res* 761: 329-332, 1997, *J Autonom Nerv System* 68: 43-48, 1998, *Brain Res* 794: 146-150, 199, *Brain Research* 864: 157-161, 2000)



Current Research and Future Prospects

We are now concentrating to develop "the Vital Care Network System" which is to manage the great number of high risk people continually. The system is composed of wearable monitor, wrist watch type PHS which is to amplify the signal, the information center to receive and manage the vital sign signals and to call on hospitals for aid. (The Next Generation Software Project of Information-technology Promotion Agency, Japan. "Vital Care Network System". 2002)





Research Grants

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4. Grants-in-aid for Innovative Project of Industry-University-Government Cooperation in Ministry of Education, Culture, Sports, Science and Technology "The research for practical use of medical integral videography" 2000-2003. ¥130,000,000
5. Tokyo Metropolis Grants-in-aid for Industry-University-Government "Electrolyzed water for the bacterial wound healing" April 1999~Feb 2000. ¥6,569,000

Select Publications

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