Pancreatobiliary Cancer Update
Prevention, Diagnosis and Treatment

January 31, 2009
International Conference Hall
Aichi Cancer Center
Nagoya, Japan
The 14th Aichi International Cancer Symposium

Pancreatobiliary Cancer Update
Prevention, Diagnosis and Treatment

Organizing Committee

Kenji Yamao (Chairperson)
Hidemi Goto
Akira Sawaki
Tsuneya Nakamura
Yasushi Yatabe
Hideo Tanaka
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Hachiro Mori
Hideyuki Fukunaga

President of Aichi Cancer Center: Yuji Nimura
President of Aichi Cancer Center Research Institute: Kazuo Tajima

January 31, 2009
Aichi Cancer Center, Nagoya, Japan
**Scientific Program**

8:55-9:00 Opening Remarks: Yuji Nimura

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**Current view of pathogenesis and epidemiology of pancreatobiliary cancer**

Chairpersons: Nobuyuki Hamajima (Nagoya University)  
Akio Yanagisawa (Kyoto Prefectural University of Medicine)

9:00-9:30 Hideo Tanaka (Aichi Cancer Center Research Institute)  
Current topics on epidemiology of pancreatobiliary cancer

9:30-10:00 Palepu Jagannath (Lilavati Hospital & Research Centre, Mumbai)  
Epidemiology and insights into etiopathology of gallbladder cancer  
the Indo Japan collaboration

10:00-10:30 Noriyoshi Fukushima (University of Tokyo)  
Update on pathology of pancreatobiliary carcinoma:  
Tumor-stromal interaction in pancreatobiliary neoplasms

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**Current view of radiological and endoscopic diagnosis of pancreatobiliary cancer**

Chairpersons: Hiroyuki Maguchi (Teine Keijinkai Hospital)  
Shinji Hirohashi (Osaka Gyoumeikan Hospital)

10:30-11:00 Toshifumi Gabata (Kanazawa University)  
Radiological diagnosis of pancreatic cancer by MDCT and MRI

11:00-11:40 Hsiu-Po Wang (National Taiwan University Hospital)  
Do other diagnostic tools add the benefit to endoscopic diagnosis of difficult cases of biliary cancer?  
Taiwan experience

11:40-12:00 Kazuo Hara (Aichi Cancer Center Hospital)  
Current role of endoscopic ultrasonography in the diagnosis and treatment of pancreatic cancer
<Luncheon Seminar>
Cosponsorship: Eli Lilly Japan K.K.
Chairperson: Masato Nagino (Nagoya University)

12:10-13:10 Peter J. Neuhaus (Charite, Campus Virchow Clinic, Berlin)
Adjuvant chemotherapy for resectable pancreatic cancer

Current view of multidisciplinary treatment of pancreatic cancer

Chairpersons: Katsuhiko Uesaka (Shizuoka Cancer Center Hospital)
Akira Sawaki (Aichi Cancer Center Hospital)

13:20-14:00 Christopher H. Crane (M. D. Anderson Cancer Center)
The use of chemoradiation in locally advanced pancreatic cancer

14:00-14:40 Junji Furuse (Kyorin University)
Treatment strategy of chemotherapy for unresectable pancreatic cancer

14:40-14:55 Hany Elsaleh (Australian National University)
Human equilibrative nucleoside transporter 1 levels predict response to gemcitabine in patients with pancreatic cancer

14:55-15:20 Shigeru Yamada (Hospital for Charged Particle Therapy, National Institute of Radiological Sciences)
Carbon-ion therapy for patients with locally advanced pancreas cancer

15:20-15:45 Yoshiki Hirooka (Nagoya University)
Combination of immunotherapy and chemotherapy improved survival of patients with unresectable locally advanced pancreatic cancer

<Special Lecture>
From cancer genomics to clinics for pancreatic cancer: from hope to reality

Chairperson: Hidemi Goto (Nagoya University)

16:00-17:00 Yusuke Nakamura (University of Tokyo)

17:00-17:05 Closing Remarks: Kenji Yamao
Welcome Remarks
Yuji Nimura
President, Aichi Cancer Center

On behalf of the organizing committee, I am pleased to welcome you to the 14th Aichi International Cancer Symposium. My special thanks are to the speakers, chairpersons and participants who have traveled a long distance to join us here in Nagoya.

Our first international symposium was held in 1994 when Aichi Cancer Center celebrated its 30th anniversary and the International Conference Center was newly built. Since then the symposium has been held annually, and the organizing committee has selected timely topics on basic research, translational research, prevention, diagnosis and treatment of cancer.

The main theme of this year’s symposium is “Pancreatobiliary Cancer Update – Prevention, Diagnosis and Treatment”. This topic was selected since considerable progress has been made in this field in recent years. The symposium consists of 4 sessions and 1 luncheon seminar. The first morning session is “Current view of pathogenesis and epidemiology of pancreatobiliary cancer”, the second is “Current view of radiological and endoscopic diagnosis of pancreatobiliary cancer”. The title of luncheon seminar is “Adjuvant chemotherapy for resectable pancreatic cancer”. The afternoon session is “Current view of multidisciplinary treatment of pancreatic cancer”. Finally, we have a special lecture entitled “From cancer genomics to clinics for pancreatic cancer: from hope to reality”.

I sincerely hope that this meeting will be an excellent opportunity to learn the current status and future perspectives in pancreatobiliary cancer. I also wish that this symposium will contribute toward the victory a conflict with dismal pancreatobiliary cancer all over the world.
Pancreatic cancer is the thirteenth most common type of cancer worldwide. The incidence is somewhat more common in blacks in USA and Japanese population. Smoking and body fatness is considered to be convincing evidence of risk of pancreatic cancer. Food containing folate probably protect against this cancer. Recently we conducted a hospital-based case-control study to assess the impact of alcohol in conjunction with polymorphisms in alcohol-metabolizing enzymes (ALDH2, ADH1B, ADH1C) and found that there was a significant impact of alcohol in the subjects who had high concentration or rapid production of acetaldehyde. We also showed that folate-related enzyme polymorphism (MTHFR C677T, MTR A2756G, MTRR A66G) modifies the association between drinking habit and pancreatic cancer risk.

Cancers of the gallbladder and extrahepatic bile-ducts is more common in Chile, Korea and Japan and is rare in western countries. Probably due to its infrequent occurrence and rapidly fatal outcome, little epidemiologic research has been done on the etiology of biliary tract cancer. The most consistently observed association is that between a history of gallstones or gallbladder disease and the occurrence of gallbladder cancer. Cholecystectomy is associated with a reduced risk of bile duct cancer. Body fatness is also a risk factor for gallbladder cancer through the formation of gallstones.
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EDUCATION
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2007 Chief, Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute
2008 – Principal Investigator of Research Group on cancer control and statistics, and meta-analysis for cancer prevention in East Asia (Grant-in-Aid-from Japanese Ministry of Health, Labour and Welfare)
2008 – Visiting professor of Nagoya University Graduate School of Medicine
Epidemiology and insights into etiopathology of gallbladder cancer - the Indo Japan collaboration

Palepu Jagannath
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Gallbladder cancer (GBC), the commonest malignancy of the biliary tract, is a relatively rare neoplasm, but with high incidence reported from certain world population in Poland, Andean area, North American Indians, Chile and Mexico. In India high incidence is reported from Uttar Pradesh, Bihar, West Bengal and Assam. GBC is about 8 times more in the north India, especially in females than in south. Dietary factors and chronic gallbladder infections have also been associated with the development of GBC.

We conducted an epidemiological field study to determine the prevalence of gallbladder diseases in villages adjoining river Ganga, in Northern India. It included a mass ultrasound screening of 5,100 persons (2,078 men and 3,022 women) on basis of a questionnaire that included 60 villages, 13,334 households and 22,861 persons of 30 years of age and above. An asymptomatic group of 1,448 people served as control group. Gallbladder abnormalities were detected in 3.7% of males and 6.3% of females and gallstones were reported in 2.9% males and 4.8% females. Gallbladder disease was 1.5 times more in those 50 years and above compared to 30-49 years age group. The prevalence of gallbladder cancer was 51/100,000 subjects, while that of chronic cholecystitis 296/100,000 in males and 993/100,000 in females. Abnormal gallbladder and gallstone prevalence was twice higher in symptomatic subjects.

Industrial Toxicology Research Centre, Lucknow, India reports high content of pesticides and heavy metals in water and sediments in downstream locations of river Ganges. Our preliminary results of an International co-operative epidemiologic study on gallbladder cancer in collaboration with Prof. Nimura, Nagoya University hospital, Japan, on heavy metal detection in gallbladder tissue samples are encouraging. Transmission electron microscopy of 7 tissue samples from India (6 cases of GBC and 1 control gallbladder specimen) showed evidence of deposits in stroma of all 6 malignant tissue samples. These deposits were not seen in control samples. A spectrophotometric assessment using freeze dried fresh tissues could detect Cadmium, Chromium, Lead, Arsenic, Mercury and Zinc as heavy metals. A comparative study of 9 tissue samples (5 cases of Ca gallbladder and 4 non-neoplastic gallbladder specimens) from Japanese patients showed very low concentrations of all these metals except Cadmium. Human scalp hair was examined in a preliminary study from areas of high incidence of gallbladder cancer- endemic (n=18) and non-endemic (n=13). Scalp hair analysis of 18
endemic samples revealed significantly high levels of Cadmium, Arsenic, Lead, Mercury and Zinc compared to controls. Higher heavy metal content in the scalp hairs of persons from endemic areas with increased prevalence of gallbladder cancer adds weight to our demonstration of heavy metals in the gallbladder cancer tissues. The specific cause effective relationship of these potential carcinogens needs further evaluation. Presence of heavy metals in hair can serve to identify population at risk in future epidemiological surveys.

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Update on pathology of pancreatobiliary carcinoma: Tumor-stromal interaction in pancreatobiliary neoplasms

Noriyoshi Fukushima
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Desmoplasia is a common feature of pancreatic ductal adenocarcinoma (PDAC). This process is intricately interacted between the host and the neoplastic cells. Recently, by microarray analysis, many genes were identified as a significantly highly expressed gene in pancreatic and/or bile duct cancer tissue. Among them we noted three genes (laminin-5gamma 2 chain, periostin and SPARC/osteonectin) and performed further analysis focusing on tumor-stromal interaction in ductal neoplasms including PDAC, pancreatic intraductal papillary mucinous neoplasms (IPMN) and bile duct cancer.

Secreted protein acidic and rich in cystein (SPARC) is a matricellular glycoprotein involved in diverse biological processes, including tissue remodeling, wound repair, morphogenesis, cellular differentiation, cell proliferation, cell migration, and angiogenesis. In our study, SPARC expression was observed mainly in the cancer stroma of the PDAC on IHC. SPARC was expressed in non-neoplastic ductal epithelial cells, but was not in a majority of PDAC cell lines. The loss of SPARC expression was associated with aberrant hypermethylation of its CpG island. Primary fibroblasts derived from PDAC strongly expressed SPARC and secreted SPARC protein, and treatment of PDAC cells with exogenous SPARC regulated in growth suppression. SPARC expression in fibroblasts from noncancerous pancreatic tissue was augmented by coculture with PDAC cells. These results suggest that SPARC expression in fibroblasts adjacent to PDAC cells is regulated through tumor-stromal interaction.

Next we performed immunohistochemistry (IHC) and in situ hybridization (ISH) to investigate a localization of periostin, and comparatively investigated laminin-5gamma 2 chain expression that is considered to be associated with tumor cell growth and invasion. Periostin is a secreted 90 kDa protein originally identified as an osteoblast-specific factor preferentially expressed in the periosteum in bone tissues. The periostin gene was also identified in pancreatic stellate cells. In our study, periostin expression was observed in the stromal cells around the infiltrating cancer on ISH and IHC in all PDACs. In IPMN, periostin deposition in the periductal stroma increased in frequency and intensity in IPMC compared to IPMA (p=0.014). Furthermore, our results showed higher frequency of periostin deposition was correlated with higher frequency of laminin-5gamma 2 chain expression (p<0.001) in IPMN. These results suggest that tumor-stromal interaction exist not only in invasive carcinoma but also in non-invasive stage of ductal neoplasms of the pancreas.
Noriyoshi Fukushima, M.D.

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ACADEMIC ACTIVITIES
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Radiological diagnosis of pancreatic cancer by MDCT and MRI

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Multidetector-row CT (MDCT) is quite useful for diagnosis of the pancreatic cancer because of its higher spatial resolution. We perform multiphase dynamic CT with high-resolution thin slice images (1.25mm slice thickness). High concentration iodized contrast medium (370mgI/ml) is injected at the rate of 1.6ml/kg during 30 seconds. Multiphase dynamic CT is performed at the arterial, pancreatic, portal and equilibrium phase (4 phase). We are able to get some detailed information about tumor detection, differentiation from benign tumor, and tumor extension to the surrounding tissues and/or organs. Multidirectional MPR (multiplanar reformation: oblique coronal, oblique sagittal, and double oblique axial) images offer correct reorganization of the degree of tumor extension and relationship between pancreatic cancer and neighboring organs. By contrast enhanced multiphase MDCT, we can predict the serosal and retroperitoneal extension of pancreatic cancers, vascular and perineural invasion.

Routine MR pulse sequences for the pancreaticobiliary diseases include T1-weighted images, T2- weighted images with and without fat suppression, diffusion weighted images (DWI: b=800), MRCP (2D and 3D), multidirectional single shot first spin echo (ssfse) T2-weighted images (oblique coronal, oblique sagittal, double oblique axial), multiphase dynamic MR images after administration of Gd-DTPA.

Pancreatic cancer usually shows hypointensity on T1-weighted images, iso or slightly hyperintensity on T2-weighted images, and hyperintensity on diffusion weighted images. On contrast enhanced dynamic MR images, the tumor shows hypovascularity on early phase with delayed enhancement on equilibrium phase. Intratumoral necrosis does not show enhancement on equilibrium phase. Especially, dynamic MR images are useful for the tumor detection. 2D and/or 3D MRCP clearly depict stenosis and dilatation of bile duct and main pancreatic duct (MPD). Because MRCP (heavily T2-weighted images: TE=900msec) cannot show solid tumor itself, we evaluate MRCP findings referring to ssfse T2-weighted images.

Sometimes we may not be able to detect small pancreatic cancer less than 2cm in diameter on CT and MRI, and tumor associated chronic pancreatitis may obscure the
tumor margin or tumor itself. So, we have to pay attention to the secondary signs such as MPD dilatation, distal pancreatic atrophy, and cyst formation to discover the pancreatic cancer at an early stage. Tiny liver metastases (<1cm in diameter) from pancreatic cancer are frequently missed by CT and MRI. Microscopic liver metastases secondary to pancreatic cancer frequently show wedge-shaped enhancement because of peripheral portal venous tumor thrombus, and should not be misdiagnosed as nontumorous arteriportal shunts.

**Toshifumi Gabata, M.D.**

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Do other diagnostic tools add the benefit to endoscopic diagnosis of difficult cases of biliary cancer?  
Taiwan experience

Hsiu-Po Wang  
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Biliary cancer is not common in Taiwan, but sometimes is a challenge to make a definite diagnosis. Biliary cancer with its mimics (benign causes or hepatocellular carcinoma) may have the same clinical presentation and anatomic change - stricture. Before treating the biliary strictures, problems to be resolved are to decide the levels and to clarify the nature of the lesions which determine the ways of treatment. Herein, differential diagnosis of biliary cancer with its mimics is important. Mimics of biliary cancer include primary sclerosing cholangitis, recurrent pyogenic cholangitis, acquired immunodeficiency syndrome cholangiopathy, autoimmune pancreatitis, IgG4 related cholangitis, Mirizzi syndrome, chemotherapy-induced sclerosis, hepatocellular carcinoma and so on. Tissue diagnosis is important for borderline surgical candidates, those with indeterminate nature of strictures or before chemotherapy and radiation therapy. To make the correct diagnosis of biliary cancer, ERCP with cytology sampling, EUS with or without FNA, IDUS, and cholangioscopy with or without biopsy have been the tools for a long time. The yield rate of brushing cytology is not satisfied no matter with dilatation before the procedure or not. Brushing cytology has a high specificity of nearly 100%, but sensitivity is much lower, ranging from 18%-60% in most series. The brushing cytology of ERCP is 66% in NUTH in the past years. The early data of tissue diagnosis through peroral cholangioscopy might increase up to 80% in NTUH, but case number was limited. Cross section images are additional tools physicians choose. Magnetic resonance imaging (MRI) and CT scan (Helical) have been mentioned with good diagnostic power, but they are not as good as EUS. Positron emission tomography (PET) with 2-[18F]fluoro-2-deoxy-D-glucose (FDG) is a well-established technique for oncological functional imaging. 18F-FDG PET/CT has been also applied on biliary cancer. In our study of indeterminate infiltrative hepatic tumors causing hilar stricture, FDG PET/CT provided high accuracy for noninvasive diagnoses of indeterminate infiltrative hepatic lesions on CT or MRI, and offered an incremental value regarding unsuspected occult metastases. Significant statistical difference in SUVmax and TNR between infiltrative hepatic malignancies (especially CC) versus benign lesions was demonstrated in early-phase images (SUVmax, 5.9 ± 2.27 (2.6-10.3) vs 4.5 ± 0.83 (3.7-5.4) P=0.03; TNR, 2.5 ± 1.06 (1.07-4.45) vs 1.9 ± 0.47 (1.31-2.44) P=0.04). These differences were more pronounced in delayed-phase scans when CC was compared to HCC (SUVmax, 7.3 ± 3.28 (2.6-13.9) vs 4.7 ± 1.62 (2.0-6.1) P=0.01; TNR, 3.7 ± 1.85
Infiltrative CC can be differentiated effectively from HCC and benign strictures by FDG PET/CT. But for extrahepatic biliary lesion, sensitivity is high (83%) but specificity is low (57%). For IgG4 cholangitis mimicking infiltrating biliary cancer, the change of pre-treatment and post-treatment FDG PET/CT may gives the clues for benign process. We still consider that EUS is the best tool to define the lesion than other images such as MRI, CT & PET.

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Current role of endoscopic ultrasonography in the diagnosis and treatment of pancreatic cancer

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Endoscopic ultrasonography (EUS) has become an indispensable diagnostic procedure using endoscopy along with intraluminal ultrasonography. EUS provides high resolution images of gastrointestinal malignancies such that depth of tumor invasion can be accurately determined. It also visualizes lesions outside of gastrointestinal tract, particularly those in pancreas. The most important early limitation of EUS was lack of specificity, that is, the differentiation between benign and malignant lesions. In 1992, EUS-guided fine needle aspiration (EUS-FNA) of lesions in the pancreas head was made possible using a curved linear array echoendoscope. Since then, many researchers expanded the indication of EUS-FNA to various kinds of lesions as well as to a variety of therapeutic purposes. In my presentation, I present our experience with interventional EUS, and discuss the present and future roles of this procedure.

1) EUS-FNA for pancreatic cancer

We performed 1355 EUS-FNA in 1208 cases from 1997 to 2007 (718 pancreatic diseases, 192 G.I. tract diseases, 57 biliary diseases, 60 mediastinal diseases, 30 ascites, and 185 other abdominal diseases). The rate of adequate specimens, sensitivity, specificity and accuracy were 99.4% (669/673), 88.7% (485/547), 100% (126/126), 90.8% (611/673), respectively. There were 8 major complications (1.2%) including 5 asymptomatic hemorrhage, 1 symptomatic hemorrhage, 1 acute portal vein thrombosis, and 1 rupture of a splenic pseudoaneurysm, which were all observed after EUS-FNA for pancreatic diseases. We continue to improve the procedure learning from these experiences, we achieve higher sensitivity and lower complication rate according to the more recent data. Moreover, as the amount of tissue sample obtained by FNA increases, we are planning to perform molecular analyses such as gene expression analysis to help determine optimal choices of chemotherapeutic or molecular targeted agents, which was previously not an realistic option due to the limited amount of tissue obtained by FNA.
2) New technique of EUS guided biliary drainage for pancreatic cancer patients

EUS has been investigated for therapeutic purposes in various kinds of diseases, and some of the EUS-guided techniques are now well established. In 2001, Giovannini et al. developed endoscopic-guided transduodenal bile duct drainage, which has been viewed as superior to endoscopic-guided transpapillary bile duct drainage or percutaneous bile duct drainage. However, no large prospective clinical study has been conducted, and clinical safety has not been established. We performed phase I/II study of EUS-guided transduodenal biliary drainage in ACCH. The procedure was successfully performed in all patients. None experienced severe treatment-related toxicities. All patients experienced improvement of liver function. We concluded that the procedure is safe and very effective.

In conclusion, EUS is expected to play more important role in the diagnosis and treatment of pancreatic cancer.

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2008 – Staff, Department of Gastroenterology, Aichi Cancer Center Hospital
Adjuvant chemotherapy for resectable pancreatic cancer

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Pancreatic cancer is the fifth leading cause of cancer mortality with a rising incidence in most European countries. Due to both, the aggressive biology of the disease and the late diagnosis in many cases, pancreatic duct carcinoma is still a disease with a poor prognosis. Today, surgical resection of localized tumor remains the only potentially curative option available for these patients. Advances in surgical technique and perioperative care have improved significantly in the last twenty years causing an extension of indications for surgical intervention. Resections in elderly patients or removal of advanced tumors including resection of the portal vein are feasible with low perioperative mortality rates nowadays. Although the encouraging advances in surgical treatment actuarial 5-year survival rates after pancreatic resection are only at 20%. For that adjuvant therapy concepts are needed for an appropriate postoperative treatment after successfully pancreatic resection. Several randomized clinical trials have been conducted during the last 20 years. Based on the findings of a small study of the Gastrointestinal Tumor Study Group (GITSG) chemoradiation with 5FU is still the gold standard of adjuvant treatment in the US. However, the European Organization for Research and Treatment of Cancer (EORTC) phase III trial failed to demonstrate a significant benefit of adjuvant 5FU-based chemoradiation. A Japanese randomized controlled trial also failed to show long-term efficacy of postoperative 5FU-based chemotherapy. Published in 2001 and 2004 the phase III trial of the European Study Group for Pancreatic Cancer (ESPAC-1), an ambitious European trial, showed several deficiencies such as a very complex design combined with a relative lack of sufficient participants. The trial failed to demonstrate a beneficial impact of chemoradiotherapy on survival in R0 and R1 resection margin category. On the other hand, survival benefit after chemotherapy compared with no chemotherapy was limited to patients with R0 resection. Chemotherapy showed poor results for patients with R1 marginal status.

Treatment with Gemcitabine in patients with advanced pancreatic cancer showed promising results in several randomized trials. Based on these findings the US
Gastrointestinal Intergroup initiated a phase III study (RTOG 9704) adding Gemcitabine or 5FU to an adjuvant 5FU-based chemoradiotherapy. In a subgroup of patients with pancreatic head carcinoma Gemcitabine significantly improved overall survival. The German Charité Oncology (CONKO-001) trial of adjuvant Gemcitabine versus surgery alone, showed a significantly delayed recurrence after resection and treatment with Gemcitabine compared to patients treated with surgery alone. In these data survival was independent from resection status (R0 vs. R1).

In summary, recent results from randomized trials suggest that chemoradiotherapy compared with chemotherapy has no advantage. However, chemotherapy with Gemcitabine seems to offer a promising adjuvant treatment option for patients with resectable pancreatic cancer.

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The use of chemoradiation in locally advanced pancreatic cancer

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Houston, Texas, USA

Gemcitabine based chemotherapy and fluorouracil or gemcitabine based concurrent chemoradiation are frequently used in the treatment of patients with locally advanced pancreatic cancer. Four randomized trials have compared chemotherapy versus chemoradiation1-4 (Table 1). Results have been conflicting: two trials favored a chemotherapy approach1,2 whereas the other two trials supported an initial chemoradiation strategy 3,4. All four studies have illustrated the significant limitations of therapy. Because of this, patients should be encouraged to enroll on a clinical trial. Off study, an emerging strategy is initial chemotherapy for 2-6 months followed by restaging and consideration of chemoradiation (50.4 Gy in 28 fractions) for those patients who do not develop metastases. This strategy reserves chemoradiation for those patients that are most likely to benefit and takes advantage of the modest yet complementary benefits of both modalities. Recent single institutional results reporting greater than 15 months median survival have been achieved with this strategy5-7 (Table 1). In contrast, median survivals of 10-12 months are frequently noted in studies incorporating an initial chemoradiation approach8-10 (Table 1). The only study to report long term survival without surgery (7% at 3 years) used 50.4 Gy with standard fractionation and concurrent 5-fluorouracil and intraoperative radiation therapy to the pancreatic tumor that minimized gastric and duodenal irradiation.11 This experience illustrates the principle that high fractionated doses of radiation therapy to selected primary pancreatic tumors with avoidance of the dose limiting structure (the duodenum) can be curative. In reality, the goals of therapy are to influence the natural history of the disease by enhancing survival with preservation and improvement of quality of life. This is a challenge because patients with pancreatic cancer commonly present with fatigue, exocrine insufficiency, anorexia, weight loss, back and abdominal pain and do not recover well from severe toxicity. In particular, gastrointestinal mucosal toxicity is often very difficult for patients to recover from.

The keys to the successful integration of radiotherapy in the care of patients with localized pancreatic cancer are selection, sequencing, and smaller treatment volumes. Ongoing investigation of novel radiation approaches designed to enhance outcome through the molecular and physical targeting of disease as well as the treatment of unresectable and borderline resectable pancreatic cancer have been investigated and have limitations. The rationale for the application of technological advances such as IMRT in locally advanced pancreatic cancer as well as the most recent data combining novel targeted agents with radiation and outcomes with SBRT will be discussed.


Table I: Selected results of treatment of patients with locally advanced pancreatic cancer. All data are quoted are calculated from the date of enrollment or start of protocol therapy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Radiation (Gy)</th>
<th>Chemotherapy</th>
<th>No. of Patients</th>
<th>Median Survival (Mo)</th>
</tr>
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<tr>
<td><strong>Pre-CT Era Studies</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Moertel et al., 1969</td>
<td>35-40</td>
<td>5-FU</td>
<td>32</td>
<td>10.4</td>
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<tr>
<td>GITSG, 1979,1981</td>
<td>60/40</td>
<td>5-FU</td>
<td>111</td>
<td>11.4</td>
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<tr>
<td>ECOG, 1985</td>
<td>40</td>
<td>5-FU</td>
<td>47</td>
<td>8.3</td>
</tr>
<tr>
<td>GITSG, 1988</td>
<td>54</td>
<td>5-FU and SMF</td>
<td>22</td>
<td>9.7</td>
</tr>
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<td><strong>Modern Phase III Studies - Chemotherapy Alone</strong></td>
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<td></td>
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<tr>
<td>CALGB 308303, 2007</td>
<td>-</td>
<td>Gem +/- Bevacizumab</td>
<td>93</td>
<td>9.9</td>
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<tr>
<td>ECOG 6201, 2006</td>
<td>-</td>
<td>Gemcitabine +/- Oxaliplatin</td>
<td>100</td>
<td>9.1</td>
</tr>
<tr>
<td>ECOG 4201, 2008</td>
<td>-</td>
<td>Gemcitabine</td>
<td>35</td>
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<td></td>
</tr>
<tr>
<td>FFCD-SSRO, 2006</td>
<td>60</td>
<td>5-FU and cisplatin</td>
<td>59</td>
<td>8.6</td>
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<tr>
<td>ECOG 4201, 2008</td>
<td>50.4</td>
<td>Gemcitabine</td>
<td>34</td>
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<tr>
<td>RTOP 9812</td>
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<td>Paclitaxel</td>
<td>122</td>
<td>11.3</td>
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<tr>
<td>RTOP PA-0020</td>
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<td>Paclitaxel / Gemcitabine</td>
<td>154</td>
<td>11.7</td>
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<tr>
<td>RTOP PA-0411</td>
<td>50.4</td>
<td>Capecitabine + Bevacizumab</td>
<td>94</td>
<td>11.9</td>
</tr>
<tr>
<td><strong>Modern Single Institutional Studies - Referral Centers / Chemoradiation</strong></td>
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<tr>
<td>MDACC, 2006</td>
<td>50.4 / 28fx</td>
<td>Capecitabine + Bevacizumab</td>
<td>47</td>
<td>11.6</td>
</tr>
<tr>
<td>UCSF, 2007</td>
<td>50.4 / 28fx</td>
<td>Capecitabine</td>
<td>17</td>
<td>17.0</td>
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<td>MSKCC, 2008</td>
<td>50.4 / 28fx</td>
<td>Erlotinib + Gemcitabine</td>
<td>20</td>
<td>18.7</td>
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<td>MDACC, 2008</td>
<td>50.4 / 28fx</td>
<td>Capecitabine + cetuximab</td>
<td>51</td>
<td>19.1</td>
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<tr>
<td><strong>Stereotactic Body Radiation</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Aarhus University, Denmark</td>
<td>25Gy / 1fx</td>
<td>-</td>
<td>56</td>
<td>6.7</td>
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</table>

*Current Study*
The majority (65%) of patients received prior chemotherapy. Median survival was 14.4 months from the start of any therapy. Chemotherapy followed by chemoradiation in all patients. Staging included laparoscopy. The trial is ongoing and data are not published. Locally advanced patients. Median survival was reported to be 11.5 months from time of diagnosis (approximately 9.5-10.5 months from the start of treatment).

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Member, Radiation Therapy Oncology Group Image Guided Therapy Committee, Radiation Therapy Oncology Group (RTOG), Philadelphia, PA, 1999 – present
Member, New Member committee, American Society of Therapeutic Radiology and Oncology (ASTRO), Fairfax, VA, 2001 – present
Member, Southwest Oncology Group Gastrointestinal Steering Committee, Southwest Oncology Group (SWOG), Ann Arbor, MI, 6/2003 – present
Oral Board Examiner and Written Exam Question Writer, American Board of Radiology, Tucson, AZ, 2004 – present
Treatment strategy of chemotherapy for unresectable pancreatic cancer

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Unresectable pancreatic cancer can be divided to two clinical stages, locally advanced and metastatic disease. Based on some RCTs, 5-FU concurrent chemoradiotherapy with concurrent external-beam radiotherapy (EBRT) has been recognized as a standard therapy in locally advanced pancreatic cancer. However, since gemcitabine has been established as a standard chemotherapy for unresectable pancreatic cancer, chemotherapy using gemcitabine is also applied to patients with locally advanced disease. Recently, two RCTs between gemcitabine alone vs. chemoradiotherapy have been reported, but it is difficult to compare these different treatment modalities. Currently, various new chemoradiotherapeutic regimens are being investigated in an effort to improve the survival rates of these patients. A phase I study of S-1 concurrent chemoradiotherapy showed a full-dose of S-1 with 50.4 Gy of radiation to be feasible, that the median PFS of 8.9 months was promising, and a multicenter phase II study has been completed in 2007. On the other hand, a strategy of induction chemotherapy followed by chemoradiation has recently been proposed in some reports. A phase II study of gemcitabine + S-1 chemotherapy followed by chemoradiation showed that the median PFS and the median OS were 8.1 months and 14.4 months, respectively. A comparative trial using these new treatment methods, S-1 chemoradiotherapy and induction chemotherapy followed by chemoradiotherapy, is warranted to establish more effective chemoradiotherapy for unresectable locally advanced pancreatic cancer.

Gemcitabine has been recognized as a standard therapy for unresectable pancreatic cancer, and it was approved in 2001 in Japan. Following gemcitabine, a phase II study of S-1 showed promising results in patient with metastatic pancreatic cancer; 15 of 40 eligible patients showed partial responses, yielding an objective response rate of 37.5%, and the median OS was 8.8 months; S-1 was also approved in 2006. Thus, gemcitabine and S-1 are currently available for clinical use in Japan. The combination of gemcitabine and S-1 (GS therapy) is expected to be superior to gemcitabine alone, because of high response rates and better survival in a phase II study of GS therapy in which the response rate was 44.4%, and the median OS was 10.1 months. A large RCT comparing gemcitabine alone, S-1 alone, and GS therapy has been under investigation.

Epidermal growth factor receptor (EGFR) is frequently expressed in human pancreatic cancer, and is associated with a poor prognosis and disease progression.
Various sites of the EGF receptor in cellular signaling can be targets of treatments for cancer. Erlotinib is a small molecule compound, which directly inhibits tyrosine phosphorylation, and a combination of gemcitabine and erlotinib showed a survival benefit over gemcitabine alone in an RCT. In Japan, a phase II study of the combination regimen was completed in 2007 to confirm the safety and the efficacy in Japanese pancreatic cancer patients. It would be useful to identify patients who obtain benefit from the combination regimen from the point of view of establishment of an individualized treatment strategy. Some new targeted agents which are focus on antiangiogenesis, VEGF trap and axitinib, are under investigation for unresectable pancreatic cancer as combined with gemcitabine. Japan has contributed in a global phase III trial of axitinib which is a high-affinity VEGFR 1, 2, and 3 tyrosine kinases.

In summary, although gemcitabine alone is still a standard chemotherapy for unresectable pancreatic cancer, some promising therapies have been investigated to improve the survival in patients with unresectable pancreatic cancer.

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May, 1984 Licensed as a Medical Doctor
Human equilibrative nucleoside transporter 1 levels predict response to gemcitabine in patients with pancreatic cancer.

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BACKGROUND & AIMS: The human equilibrative nucleoside transporter (hENT1) protein transports gemcitabine into cells. Small retrospective studies in pancreatic cancer suggest that levels of hENT1 protein or messenger RNA may have prognostic value. We studied the predictive value of hENT1 levels in a cohort of pancreatic adenocarcinoma patients from the large prospective randomized adjuvant treatment trial RTOG9704. METHODS: In RTOG9704, 538 patients were assigned randomly, after surgical resection, to groups that were given either gemcitabine or 5-fluorouracil (5-FU). Immunohistochemistry for hENT1 was performed on a tissue microarray of 229 resected pancreatic tumors from RTOG9704 and scored as having no staining, low staining, or high staining. Associations between hENT1 protein and treatment outcome were analyzed by unconditional logistic regression analysis using the chi-square test and the Cox proportional hazards model. RESULTS: HENT1 expression was associated with overall and disease-free survival in a univariate (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.29-0.91; P = .02; and HR, 0.57; 95% CI, 0.32-1.00; P = .05) and multivariate model in the group given gemcitabine (HR, 0.40; 95% CI, 0.22-0.75; P = .004; and HR, 0.39; 95% CI, 0.21-0.73; P = .003). hENT1 expression was not associated with survival in the group given 5-FU. CONCLUSIONS: In this prospective randomized trial, hENT1 protein expression was associated with increased overall survival and disease-free survival in pancreatic cancer patients who received gemcitabine, but not in those who received 5-FU. These findings are supported by preclinical data; the gemcitabine transporter hENT1 is therefore a molecular and mechanistically relevant predictive marker of benefit from gemcitabine in patients with resected pancreatic cancer.

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Professional Experience:
1988 – 89 Intern: Royal Perth & Hollywood Hospital, Perth, Australia.
1989 – 91 Medical Officer: Western Australian Health Department, Australia.
1991 - 92 Medical Officer: Western Australia Deputizing Medical Service.
1992 – 93 Medical Officer: King Edward Women’s Hospital, Subiaco, Australia.
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2001 – 05  Assistant Professor: School of Medicine UCLA Los Angeles California. USA.
2006 –  Associate Professor Radiation Oncology School of Medicine, ANU Canberra Australia

Honors & Awards:

- Young Clinical Investigators Prize Sir Charles Gairdner Hospital 1997.
- Royal Australasian College of Radiologists “Novartis” Prize 1998.
- The International Academy of Pathology Prize 1999.
- “Varian Prize” Royal Australian & New Zealand College of Radiologists 1999.
- The Medical Research Foundation Clinical Investigators Prize, Royal Perth Hospital 1999.
- Novartis Clinical Investigators Prize Sir Charles Gairdner Hospital 1999.
- Cancer Foundation of Western Australia John Nott Travelling Fellowship 2000
- The American Society of Clinical Oncology Merit Award 2000.
- The American Radium Society Young Oncologist Award 2000.
- Cancer Foundation of Western Australia Award 2001.
- University of Western Australia. Distinction Ph.D. 2001.
- “The Bob Abel Memorial Award” Stop Cancer Seed Grant, California USA 2001.
- American Society of Therapeutic Radiology and Oncology J unior Faculty Award 2002.
- Jonsson Comprehensive Cancer Center Seed Grant, California USA 2002.
- Faculty Career Development Award UCLA California USA 2002.
- Howard Hughes Medical Institute, Frontiers of Science Grant, California USA 2002.
- Radiation Therapy Oncology Group Translational Research Program Grant USA 2002.
- American Radium Society Travel Grant USA 2003.
- The European Society of Therapeutic Radiation Oncology (ESTRO) Travel Grant USA 2003.
- NIH Early Detection Research Network Grant 2004

Other Professional Experience:

Carbon-ion therapy offers the potential advantages of improved dose localization and enhanced biological effect. Our results have shown that carbon ion therapy has the promising potential of delivering a sufficient dose to the tumor with acceptable morbidity in the surrounding normal tissues. Tumors that appear to respond favorably to carbon ions include locally advanced tumors with a non-squamous histology such as adenocarcinoma. Carbon-ion therapy may very well improve tumor control of pancreas cancer. The purpose for which the phase I/II trial of carbon ion radiotherapy for locally advanced pancreas cancer was performed was to establish the safety of carbon ion radiotherapy, determine the recommended dose and substantiate the effectiveness of preoperative carbon ion radiotherapy. Patients and methods: Patients and methods Between April 2003 and February 2007, 47 patients judged according to the staging criteria of Japanese Pancreas Society as being clinical stages IVa or IVb without distant metastasis were enrolled into this trial. One patient was excluded because he received chemotherapy before treatment. Forty-six patients were eligible for this analysis. Patients eligible for study entry had histologically or cytologically confirmed with locally advanced unresectable pancreatic ductal carcinoma. Eligibility criteria were: confirmation of ductal carcinoma by CT findings, age of 80 years or younger, ECOG performance score 0, 1, or 2, and adequate hepatic, renal and cardiopulmonary function sufficient for undergoing surgery. The criteria of the CT findings for non-resectability of the tumor included tumor encasement of the celiac trunk and/or superior mesenteric artery. Carbon ion therapy was given once daily, 4 days a week, for fixed 12 fractions in 3 weeks. The dose was set at 38.4 GyE and escalated to 52.8 GyE at 5% increments. Toxicity on organs such as the skin, bladder and digestive tract was assessed according to the NCI-CTC classifications. Tumor response was defined by the RECIST scoring system as the maximum tumor response observed during the first 6 months after the initiation of carbon ion radiotherapy. Local recurrence was defined in terms of lesions occurring in the tumor bed. Results: All patients completed the scheduled treatment course. Seven grade 3 acute
and one grade 3 late toxicities were observed. Six of 7 grade 3 acute toxicities were anorexia and one was cholangitis. Tumor response was evaluated in 46 lesions. CR was observed in one lesion, PR in 7, SD in 37, and PD was observed in one lesion. The local control rate at one year in the 46 analyzed patients and in the patients receiving 45.6GyE or more were 76% and 95% respectively. The one year overall survival rate were 44% at all patients, and 40% at lower than 43.2GyE and 73% at higher than 45.6GyE respectively. The maximum acute reaction of the grade 3 was observed in two-thirds of the patients (67%) on the 52.8GyE. From these results, we concluded that the maximum tolerance dose of carbon ions is 52.8GyE/12fractions/3weeks.

Conclusion On the basis of the literature on drugs with a sensitizing effect in conjunction with heavy particle beams, further studies were scheduled in an effort to find even more effective treatment modalities based on a combination of chemo- and radiotherapy. We started a phase I clinical trial of Gemcitabine Combined with Carbon-ion therapy for patients with local advanced pancreas cancer from April 2007.

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1991 – 1992  Medical Staff in Surgery, Chiba University, Chiba, Japan  
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2005 – present  Associate Professor, Department of Gastroenterological Surgery, Chiba University, Chiba, Japan  
2005 – present  Associate Professor, Department of Surgery, Teikyo University, Tokyo
Combination of immunotherapy and chemotherapy improved survival of patients with unresectable locally advanced pancreatic cancer

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Pancreatic cancer has a poor outcome with conventional therapies, including chemotherapy and radiotherapy. Therefore, there is great need for a novel therapeutic approach for pancreatic cancer.

Dendritic cells (DCs) are the most potent antigen-presenting cells that play a central role in innate and acquired immunities. For the treatment of cancers, tumor antigen-loaded DCs have been considered as a therapeutic vaccine for inducing tumor-specific immunity. Autologous tumor cell lysates are most frequently used in clinical trials for cancers where no tumor-associated antigens are defined. It has been reported that antigen-presenting cells (APCs) that phagocyte apoptotic tumor-derived cells are potent tumor vaccines and that apoptotic tumor cells and apoptotic bodies may effectively cross-prime the T-cell response and induce more potent immunity than tumor lysates.

However, it is difficult to obtain sufficient quantities of tumor cells for loading DCs ex vivo for therapy; it would be highly conceivable that the in vivo provocation of immunity by the direct injection of DCs into tumors after apoptosis-inducing therapy such as radiotherapy or chemotherapy is more applicable since, among APCs, DCs can most efficiently uptake and process extracellular antigens derived from apoptotic cells.

This is the first clinical report on the safety and bioactivity of the combination of GEM administration and immunotherapy including DCs for the treatment of inoperable locally advanced pancreatic cancer. Moreover, this study shows for the first time the induction of tumor antigen-specific CTLs following GEM administration with immune cells including DCs for a patient with the advanced pancreatic cancer.

DC therapy frequently induces a measurable immune response. However clinical responses are seen in a minority of patients, presumably due to insufficient expansion of antigen-specific CTLs capable of eradicating tumour cells. Here, to increase
therapeutic efficacy of DC-based vaccination, we have undertaken the first clinical trial involving a combination therapy of GEM with immunotherapy for patients with inoperable locally advanced pancreatic cancer.

Patients (n=5) received the treatment course, which consisted of intravenous GEM administration at 1000mg/m² (day 1) and the endoscopic ultrasound-guided fine-needle injection of OK432-pulsed DCs into a tumour followed by intravenous infusion of CD3-LAKs (day 4), at 2-week intervals.

No serious treatment related adverse events were observed during the study period. Three of the five patients demonstrated effective responses to this clinical trial; one had PR and two had long SD more than 6 months. In the patient with PR it has been shown that DC-based vaccination combined with GEM administration induces tumour antigen-specific CTLs.

In our conclusion, this combined therapy was considered to be synergistically effective and may have a role in the therapy of pancreatic cancer for inducing tumour antigen-specific CTLs.

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From cancer genomics to cancer treatment; from hope to reality

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cDNA microarray technologies have enabled us to obtain comprehensive data for gene expression profiles of human cancers. To isolate novel targets for diagnosis (predictive marker for the efficacy of treatment as well as tumor marker) and for treatment of cancer (molecular-targeting drug, cancer vaccine, antibody, and small molecular compound), we constructed expression profile database of cancer cells originated from various organs with their corresponding non-cancerous tissues using a cDNA microarray that consisted of more than 30,000 genes. These experiments disclosed a number of genes that appeared to be involved in development and/or progression of cancers in those tissues. So far, we have analyzed more than 1,300 clinical cancer samples of the liver, pancreas, stomach, colon, esophagus, bile duct, uterus, lung, ovary, kidney, urinary bladder, testis, prostate, breast, and soft tissues as well as acute and chronic myeloid leukemias. We have selected hundreds of candidate genes by the following criteria; (1) gene expressions were transactivated in a large proportion of cancer tissues in comparison with their corresponding normal tissues and (2) expression was not observed or hardly detectable in any of important vital organs. The further functional analysis identified dozens of genes that are likely to function as oncogenes in various cancers. The suppression of expression of such genes with siRNA induced cell cycle arrest, apoptosis, or suppression of anchoring-dependent cell growth. We screened 9- or 10-amino-acid peptides corresponding to a part of such oncoantigens that induced cytotoxic T lymphocytes that would specifically kill cancer cells in an HLA-A restricted manner. We have already isolated nearly 60 peptides (HLA-A02 or HLA-A24 restricted) derived from about 50 oncoantigens and started translational research using some of them in August 2006. We are now running more than 20 different protocols and more than 250 cancer patients have been enrolled by the end of November 2008. We also developed antibodies that showed growth-suppressive effect in vivo and/or in vitro. The promising mice data and clinical output of our translational
research will be introduced in the meeting. These results indicated that systematic expression analysis should be a very effective approach for identification of molecules that are potential targets for development of novel therapeutic drugs and diagnostic tools.

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1995 – Director, Human Genome Center, Institute of Medical Science, The University of Tokyo  
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# List of Speakers and Chairpersons

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
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