Asia-Pacific Congress on Pancreas and Biliary Tract Cancer

in conjunction with the

14th Annual Meeting of the Taiwan Cooperative Oncology Group

&

2010 International Conference on Translational Cancer Research

November 20-21, 2010

Howard International House Taipei, Taiwan

Program and Abstracts

Taiwan Cooperative Oncology Group
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### Congress Program

**Saturday, November 20, 2010**

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<tr>
<td>9:00 – 9:15</td>
<td>Opening Remarks</td>
<td>Mei-Ling Hsiao (蕭美玲)</td>
<td>Jang-Yang Chang (張俊彥)</td>
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<td>Ing-Kang Ho (何英剛)</td>
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<td>Wen-Ta Chiu (邱文達)</td>
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<tr>
<td>9:15 – 9:30</td>
<td>Take Photographs (all Participants)</td>
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<td>10:15 – 10:30</td>
<td>Break</td>
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<tr>
<td>10:30 – 11:15</td>
<td>Forcing Tumor Progression and Treatment Response</td>
<td>Valerie M. Weaver</td>
<td>Jang-Yang Chang (張俊彥)</td>
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<td>11:15 – 11:40</td>
<td>Disease Progression of Pancreatic Cancers Relates to a Core Gene Expression Profile Associated with Glandular Differentiation</td>
<td>Kelvin K.-C. Tsai (蔡坤志)</td>
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<td>11:40 – 12:05</td>
<td>In Search of Cancer Stem Cells from Pancreatic Ductal Adenocarcinoma</td>
<td>Chia-Ning Shen (沈家寧)</td>
<td>Ann-Lii Cheng (鄭安理)</td>
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<td>12:05 – 12:30</td>
<td>Molecular Genetics of Pancreatic Cancer and Potential Translational Promises</td>
<td>Ming-Chu Chang (章明珠)</td>
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<tr>
<td>12:30 – 13:30</td>
<td>Lunch</td>
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<td>14:15 – 14:40</td>
<td>EUS and EUS-guided Aspiration in the Diagnosis of Pancreatic Lesion: the NTUH Experience</td>
<td>Hsiu-Po Wang (王秀伯)</td>
<td>Lein-Ray Mo (牟聯瑞)</td>
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<td>14:40 – 15:05</td>
<td>General Management of Malignant Biliary Obstruction</td>
<td>Chiu-Yung Chen (陳炯瑜)</td>
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<td>Alice Lin-Tsing Yu (陳鈴津)</td>
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<td>Risk Factors for Biliary Tract Cancer in Taiwan: a Population-based Case-control Study Using the National Health Insurance Research Database</td>
<td>Jeffrey Shu-Ming Chang (張書銘)</td>
<td>Cheng-Hsiung Wu (吳正雄)</td>
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<td>Cheng-Chung Wu (吳誠中)</td>
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<td>16:55 – 17:20</td>
<td>Systemic Therapy for Advanced Biliary Tract Carcinoma: Promises and Controversies</td>
<td>Chiun Hsu (許駿)</td>
<td>Yee Chao (趙毅)</td>
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# Congress Program

## Sunday, November 21, 2010

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<td>9:00 – 9:45</td>
<td>Recent Progress in Surgical Resection and Multidisciplinary Therapy for Cholangiocarcinoma</td>
<td>Michiaki Unno</td>
<td>Miin-Fu Chen (陳敏夫)</td>
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<td>9:45 – 10:10</td>
<td>Cholangiocarcinoma: from Bedside to Bench</td>
<td>Miin-Fu Chen (陳敏夫)</td>
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<td>Surgical Management of Pancreatic Cancer in Taiwan</td>
<td>Yan-Shen Shan (沈延盛)</td>
<td>Cheng-Hsi Su (蘇正熙)</td>
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<td>Kun-Huei Yeh (葉坤輝)</td>
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<td>Management of Pancreatic Cancer in Japan</td>
<td>Takuji Okusaka</td>
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<td>15:45 – 16:10</td>
<td>Drug Development for Pancreatic Cancer in Taiwan</td>
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Committee Members

Organizers

- Taiwan Cooperative Oncology Group (TCOG), National Institute of Cancer Research, National Health Research Institutes (NHRI)
- The Chinese Oncology Society (COS)
- Formosa Cancer Foundation
- Asian Clinical Oncology Society (ACOS) Taiwan Branch
- Center of Excellence for Cancer Research (CECR), Taipei Medical University (TMU) and Center of Excellence for Cancer Research (CECR), National Taiwan University Hospital (NTUH) on behalf of Establishment of Cancer Research System Excellence Program, DOH

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- **Chairperson:**
  Jang-Yang Chang (張俊彥)

- **Co-Chairperson:**
  Jacqueline Whang-Peng (彭汪嘉康) Miin-Fu Chen (陳敏夫)
  Shu-Wen How (侯書文)

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  Tsann-Long Hwang (黃燦龍) Cheng-Hsiung Wu (吳正雄)
  Lein-Ray Mo (牟聯瑞) Pin-Wen Lin (林炳文)
  Chen-Guo Ker (柯成國) Jaw-Town Lin (林肇堂)
  Li-Tzong Chen (陳立宗)

  **CECR**
  Wen-Ta Chiu (邱文達) Ming-Fong Chen (陳明豐)

- **Secretary General:**
  Tsang-Wu Liu (劉滄梧)
Committee Members

Scientific Committee

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  - Jen-Hsi Chen (陳仁熙)
  - Yi-Yin Jan (詹益銀)
  - Yan-Shen Shan (沈延盛)
  - Wu-Chou Su (蘇五洲)
  **CECR**
  - Gi-Ming Lai (賴基銘)
  - Lu-Hai Wang (王陸海)

- **Members:**
  - Yee Chao (趙毅)
  - Ching-Kuo Yang (楊國卿)
  - Cheng-Chung Wu (吳誠中)
  - Chang-Fang Chiu (邱昌芳)
  - Kun-Huei Yeh (葉坤輝)
  - Jaw-Ching Wu (吳肇卿)

Co-organizers

- **Establishment of Cancer Research System Excellence Program, DOH –**
  Centers of Excellence for Cancer Research (CECR) in National Health Research Institutes, Taipei Veterans General Hospital, Chang Gung Medical Foundation, Chang Gung Memorial Hospital, Linkou Branch, China Medical University Hospital, National Cheng Kung University Hospital, Kaohsiung Medical University Chung-Ho Memorial Hospital

Secretariat

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**CECR**
Center of Excellence for Cancer Research (CECR), Taipei Medical University (TMU)
Julia Yang (楊綵瑜), Christine Wang (王瑞君), Yarden Lu (盧郁伶)
Center of Excellence for Cancer Research (CECR), National Taiwan University Hospital (NTUH)
Amanda Sun (孫菩謙)
"Novel Targeted Agents": Are They Really Different and Can They Overcome or Avoid Resistance Mechanisms?

Antonio Tito Fojo

Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, USA

The advent of the era of “target therapies” in cancer began with the identification of Gleevec® (imatinib) as an active agent in chronic myeloid leukemia (CML). Enthusiasm for this approach was understandably high and was accompanied by suggestions that these “novel targeted agents” would not be vulnerable to the mechanisms of resistance that had encumbered “classical cytotoxic agents”. Soon after the introduction of imatinib, reports of resistance began to appear and at first the data suggested that resistance would be simple and confined to acquired mutations in the bcr-ABL target and by inference readily manageable with a different agent. However, subsequent experience has shown that in fact resistance even to imatinib is much more complex.

As we acquire experience with newer agents we are becoming increasingly aware that (1) drugs have changed some but mostly not much, (2) new paradigms will emerge and old ones will be validated, (3) in new drugs we will find new paradigms and validate old paradigms while, (4) in old drugs we will find new paradigms when examined with new technology and validate old paradigms.

We come to understand these issue if we compare “novel targeted agents” with our “classic cytotoxic agents”. As we do these comparisons we find that our older agents are just as if not more specific than our novel agents and conversely that novel agent as just as cytotoxic if not more. The specificity of microtubule targeting agents for example exceeds that of any novel tyrosine kinase inhibitor while the cytotoxicity that occurs with drugs such as sunitinib is comparable to that of our older agents. Furthermore, while novel agents have been advocated as cytostatic agents, such a designation is not supported by the available data; and certainly not by the data in patients with tumors, where doubling times are so much longer than found in preclinical models.

Once it is recognized that our resistance paradigms are for the most part not changing, then it follows that much if not all that we have previously learned with regard to drug resistance is of value and applies to our novel targeted agents. Evidence for this can be found in new models of drug resistance that allow us to compare our older agents with our newer agents and that illustrate their common mechanisms of resistance and similar ways of overcoming tolerance.

We can also appreciate why mutations may have occurred in patients treated with imatinib and contrast this with the lack of mutations previously reported with “classic cytotoxic agents”. At the core of this understanding is an awareness that drugs currently being synthesized are often of such high specificity that even small changes in structure can adversely impact activity.
and also the fact that the targets of these drugs while valid in a cancer cell, in fact are all too often proteins that are not indispensable to most cells. The new parading of “addiction” to a protein or pathway has no example that can match the extent to which a cell is “addicted” to microtubules.

To be sure, we are learning new lessons about mechanism of drug resistance, but whether any of these are specific to our novel agents or simply represent new knowledge and new approaches to understanding the workings of a cell remains to be determined. Increasingly, for example, we are discovering that resistance to older cytotoxic agents can also be accomplished by the use of cellular pathways in varying ways, much in the same as some novel targeted agents appear to escape the effects of an inhibitor.

Finally our clinical data is given us insight into how drug resistance develops allowing us to further understand how this might be managed clinically. It is clear that the cassette of genes that confer drug tolerance and that which regulate cellular growth and proliferation are two different cassettes and that these are developed independently in the evolution of a cell. Consequently one can find in a tumor differential resistance to chemotherapies but at the same time observe that the basic biology of the tumor as manifested by growth and proliferation do not change even as a resistant clone emerges.

We conclude:
1. Novel drugs are really no different than older drugs. They are cytotoxic and like older drugs vulnerable to drug resistance.
2. Older drugs are really no different than newer drugs. They are cytolentic and vulnerable to drug resistance.
3. What we have learnt to date is valuable.
4. New mechanisms of resistance will emerge. We will describe them with new drugs and with old drugs as we look to old drugs with new understanding.
Forcing Tumor Progression and Treatment Response

Valerie M. Weaver

Center for Bioengineering and Tissue Regeneration, Departments of Surgery, Anatomy and Bioengineering and Therapeutic Sciences, Bay Area Center for Physical Sciences and Oncology, University of California, USA

Carcinogenesis is initiated by a series of genetic and epigenetic events that occur in a cell population that exists within a complex multi-cellular tissue. Tumor progression and metastasis proceed in the context of a tissue microenvironment that consists of a heterogeneous mixture of diverse cell types including fibroblasts, endothelial cells and immune cells that interact within a non-cellular proteinaceous stroma or extracellular matrix (ECM). Accordingly, cancer evolution is a tightly regulated process that is influenced by tissue organization and modified by interactions between multiple cell types and an evolving extracellular microenvironment. The dynamic interchange between the transformed cancer cells and their tissue microenvironment not only modifies the pathogenesis of malignancy but also modifies tumor histophenotype and dictates treatment response. In addition and not previously recognized, all cells experience force, and cell and tissue level forces evolve during malignancy and can and do exert pleiotrophic effects on cell and tissue behavior. Thus in a direct challenge to the traditional view of cancer, biophysical and biomechanical factors also play critical roles in tissue development and homeostasis. Moreover, when these cell and tissue levels forces are corrupted, they profoundly influence tissue health and disease and can significantly regulate tumor development and progression and modulate treatment response. In this presentation we present evidence regarding the role of mechanical force in tissue homeostasis and illustrate how heritable or oncogenically-induced physical changes in cells and their surrounding microenvironment modify tumor evolution and treatment response. Using examples from our own work in which we have been studying the role of stromal-epithelial interactions in breast, skin and pancreatic cancer we illustrate how mechanical force can significantly regulate tumor initiation, progression and treatment. For instance, we found that ECM remodeling and cross-linking significantly stiffen the tissue to drive focal adhesion assembly, enhance growth factor signaling, disrupt tissue integrity and promote malignant progression and metastasis, and that inhibiting ECM remodeling and stiffening inhibits tumor progression and metastasis. We discuss how genetic aberrations in cancer cells can disrupt biophysical and biomechanical homeostatic mechanisms that regulate normal cell and tissue behavior at the molecular, cellular and tissue level and suggest how modifications of such physical parameters may contribute to cancer and regulate treatment efficacy. We conclude with recent findings assessing the role of force on tumor metastasis and treatment efficacy. We discuss how biomechanical cues could promote tumor metastasis and treatment response by influencing inflammation. This work was supported by a W81XWH-05-1-0330 grant from the DOD BCRP, and a U54CA143836-01 and CA138818-01A1 grant from NCI to VMW.
Disease Progression of Pancreatic Cancers Relates to a Core Gene Expression Profile Associated with Glandular Differentiation

Jimmy J.-M. Su1, Chi-Rong Li2, Michael T.-L. Lee3, Patrick Y.-W. Chu1, Valerie M. Weaver4,5, Kelvin K.-C. Tsai1 (蔡坤志)

1 National Institute of Cancer Research and Translational Center for Glandular Malignancies, National Health Research Institutes, Tainan, Taiwan;
2 Center for Education and Research on Geriatrics and Gerontology and School of Nursing, Chung Shan Medical University, Taichung, Taiwan;
3 Department of Computer Science, Kun Shan University, Tainan, Taiwan;
4 Department of Surgery and Center for Bioengineering and Tissue Regeneration, University of California San Francisco, San Francisco, CA;
5 Departments of Anatomy and Bioengineering and Therapeutic Sciences, Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research and Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA

Glandular malignancies such as pancreatic adenocarcinoma display considerable tissue architectural heterogeneity while the prognostic role of the associated molecular changes awaits further exploration. We recapitulated the morphogenetic and structural differentiation process of pancreatic acini or tumor spheroids using three-dimensional (3D) organotypic culture models and profiled their associated transcriptome. Intriguingly, interrogation of genes differentially expressed between monolayer and 3D culture demonstrated a significant association between overall survival in a cohort of 102 pancreatic cancer patients and the organoid structures recapitulating a “normal-like” acinar structure. We further explored this association by prioritizing the gene profiles and applying supervised classification algorithms. Using this strategy we identified a core structure-associated prognosis signature (CSPS) that strongly predicts recurrence-free or overall survival ($P < 0.001$). Importantly, the CSPS predicts pancreatic cancer survival independent of standard clinicopathological variables and performs excellently in the prognostic prediction of other glandular malignancies, including prostate and breast cancers. Our results suggest mechanisms contributing to “normal” glandular structural pancreatic morphogenesis also participate in treatment resistance.

(Supported by NHRI CA-099-PP-19 and Department of Health of Taiwan H99-TD-C-111-004 to KKT).
In Search of Cancer Stem Cells from Pancreatic Ductal Adenocarcinoma

Chia-Ning Shen (沈家寧)1,2, Chi-Che Hsieh1,2, Wen-Ying Liao3, Yi-Ming Shyr4, Tien-Hua Chen4, Shian-Ying Sung2,5

1 Stem Cell Program, Genomics Research Center, Academia Sinica, Taipei, Taiwan; 2 Program for Cancer Biology and Drug Discovery, China Medical University, Taichung, Taiwan; 3 Graduate Institute of Pharmaceutical Chemistry, China Medical University, Taichung, Taiwan; 4 Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan; 5 Graduate Institute of Cancer Biology, China Medical University, Taichung, Taiwan

Background
The current prognosis of pancreatic cancer remains poor with median survival of approximately 6 months and the overall five years survival rate is less than 4%. It is largely because pancreatic cancer patients were encountering for sever radio- or chemo-resistance. Existence of pancreatic cancer stem cells (CSCs) has been considered as a possible cause of resistance to chemotherapy. Therefore, to identify molecular features of pancreatic cancer stem cells could improve pancreatic cancer therapeutics.

Methods
We investigated whether drug-resistant pancreatic cancer stem/initiating cells existed by analyzing specimen obtained from patient of pancreatic adenocarcinoma and human pancreatic ductal adenocarcinoma cells lines.

Results
Initially, we demonstrated that the majority of pancreatic cancer cells are negative to CD24 and ABCG2; however, we identified CD44+CD24+ABCG2+ subpopulation had self-renewal capability and higher tumorigenicity. We found the CD44+CD24+ABCG2+ subpopulations can be maintained constantly in culture and were able to generate different subpopulations in vitro and to produce the heterogeneous tumor engraftment in NOD/SCID mice. In addition, these cells displayed drug resistance and had multipotency that can be induced to differentiate into insulin-producing endocrine cells, hepatocytes or even neuron-like cells. Based on using extracellular flux analyzer, we also revealed that the CD44+CD24+ABCG2+ subpopulation produced higher levels of lactate and had higher oxygen consumption rate indicating the entire metabolism (in particular glycolysis and the TCA cycle) is reorganized. And this alteration was only seen in the sorted CD44+CD24+ABCG2+ subpopulation at 1-3 days after isolation. In contrast, alterations in mitochondrial functions were not seen in either CD44+CD24−ABCG2+ or CD44+CD24−ABCG2− subpopulation.

Conclusions
It has been proposed by Otto Warburg that mitochondrial alterations in cancer cells as the driving force of tumorigenesis and the cause of the resistance against apoptosis associated permeabilization. Our current work provided evidences to show that this metabolic transformation possibly linked to self-renewal expansion and differentiation potential of pancreatic cancer stem/initiating cells and thereby mediates resistance to anti-cancer drugs.
Molecular Genetics of Pancreatic Cancer and Potential Translational Promises

Ming-Chu Chang (章明珠)

Department of Internal Medicine, National Taiwan University Hospital, Taiwan

Pancreatic ductal adenocarcinoma (PDCA) is one of the most aggressive cancers in human. The genetic alterations accumulated from noninvasive precursor lesion, so called pancreatic intraepithelial neoplasia (PanIN), include K-ras, TP53, SMAD4 and p16/CDKN2a genes. PanINs show graded histologic abnormalities and increasing cytogeneic aberrations consistent with neoplastic progression. PDAC is consistent with the theory of multistep process with accumulation of multiple alterations of critical growth regulatory factors. The pancreatic cancer genome project has recently been completed, proving a unique understanding of the genetic change underlying the development of PDAC. These targeted signaling pathways include apoptosis, DNA damage control, regulation of G1/S phase transition, hedgehog signaling, hemophilic cell adhesion, integrin signaling, K-ras signaling, JNK signaling, regulation of invasion, small GTPase-dependent signaling, transforming growth factor β signaling, and wnt/notch signaling. It is now hoped that our improved knowledge of the molecular profile of PDCA could be translated into better diagnostic and therapeutic options to deal with this dismal disease. The progress made in understanding the carcinogenesis in PDCA is critical for improvement the treatment in the future.
Endoscopic Stenting for Palliation of Malignant Biliary Obstruction

Joseph Leung

Mr. & Mrs. C. W. Law Professor of Medicine, University of California, Davis School of Medicine, Chief of Gastroenterology, VA Northern California Health Care System, USA

Management of Malignant Obstructive Jaundice

Malignant obstructive jaundice is associated with considerable morbidity with intractable itching and an increased risk of biliary sepsis. Surgical resection is the only hope of cure for pancreaticobiliary malignancies. Palliative biliary drainage can be achieved with endoscopic (ERCP) stenting or percutaneous transhepatic biliary drainage (PTBD).

Endoscopic (plastic) Stents

Endoscopic stenting is an established palliation for malignant biliary obstruction. It can be achieved with insertion of a large bore (10 Fr) plastic stent following selective bile duct cannulation and negotiating a guide wire across the malignant stricture. Dilation of the stricture using a dilation balloon or catheter facilitates stent insertion and also allows tissue sampling to confirm underlying malignancy. Insertion of a plastic stent is relatively easy as long as a guide wire is negotiated beyond the obstruction. A prior papillotomy is not necessary as the incidence of post ERCP pancreatitis following plastic stenting alone remains low. The length of the stent is defined as the separation between the two anchoring side flaps. The distal tip of the stent is usually left in the duodenum for ease of subsequent removal. Plastic stents tend to become blocked after a few months and may require elective stent exchange to prevent cholangitis. In situations where endoscopic drainage failed after the bile ducts are filled with contrast, especially in patients with hilar obstruction, there is an increased risk of cholangitis and percutaneous transhepatic drainage of the obstructed system may be necessary for biliary decompression.

Self Expandable Metal Stents (SEMS)

A different form of endoscopic stenting is the placement of larger expandable metal stents (up to 1 cm expanded diameter). Deployment of a self expandable metal stent (SEMS) is technically more challenging as some SEMS tends to shorten to 2/3 of its pre-deployment length (e.g. Wallstent) whereas others do not shorten while being deployed (e.g. Zilver stent). Correct positioning and deployment with the help of radiopaque markers is necessary to insure proper drainage of the biliary system. The lengths of SEMS are limited and sometimes it may be necessary to leave the stent entirely inside the bile duct especially in patients with hilar obstruction.

Multiple Stenting

In patients with distal CBD obstruction, a single stent is sufficient to relieve the jaundice. In patients with hilar obstruction, the level of involvement is better defined by the Bismuth classification. Patient with CHD obstruction and communicating right and left systems can still be drained with one stent. For those patients who have the right and left hepatic system obstructed separately, two or more stents are required to drain the bile ducts. Stenting for hilar...
obstruction will benefit from initial balloon dilation as some of the hilar strictures (e.g. Klatskin cholangiocarcinoma) are tight. Dilation facilitates the insertion of both plastic and SEMS.

For plastic stenting of hilar obstruction, two stents can be inserted parallel to each other following placement of two guide wires into the right and left hepatic ducts. The SEMS can be placed parallel to each other but when stents with larger mesh size are used; double stenting can be achieved with a stent-in-stent approach or a Y configuration. A more recent introduction of the smaller 6 Fr Zilver stents allows the insertion of two SEMS in a parallel fashion with simultaneous deployment to drain the right and left hepatic systems.

**Complications of Endoscopic Stenting**

Stent blockage is a significant late complication of stenting. For plastic stents, it is often related to bacterial contamination secondary to duodenal biliary reflux. As a result of bacterial biofilm formation, sludge forms and occludes the stent. This may give rise to recurrent jaundice and cholangitis. The average stent patency for a 10 Fr plastic stent is about 3 months, even shorter for the smaller 7 or 8 Fr stents. The management will involve endoscopic removal of the blocked plastic stent and replacement of a new stent.

For patients receiving SEMS, in particular the open mesh stents, tissue or tumor ingrowth leads to stent blockage. Because of the larger diameter, patency of SEMS is usually longer than the plastic stents. The open mesh SEMS are more difficult if not impossible to be removed once deployed. The treatment of a blocked SEMS is to insert a second plastic stent through the lumen of the blocked SEMS to provide drainage. The use of covered SEMS (with a plastic membrane lining the inside of the stent) tends to prevent tissue ingrowth and prolong stent patency. However, increased risk of stent migration has been reported and even the covered SEMS can become blocked because of tumor overgrowth or ingrowth as a result of breakdown of the cover membrane.

**Prevention of Stent Blockage**

Bacterial contamination and biofilm formation is believed to be the cause of plastic stents blockage. In vitro studies have been done to determine the effects of special plastic surfaces and the role of antibiotic therapy to prevent bacterial attachment and stent blockage. Drug eluting stents which provide a local concentration of antibiotic may have a potential role in prevention of bacterial adherence. Duodenal biliary reflux is believed to contribute to plastic stent blockage. In the context of plastic stents which contain side flaps and where the distal tip is left in the duodenum, two modifications in design have been made in an attempt to minimize bacterial contamination. The use of the Tanenbaum stent with side flaps but no side holes is associated with less turbulent flow and may delay bacterial colonization. However, it is only useful for stenting of distal bile duct stricture and does not offer significant improvement in stent patency over the usual polyethylene stents. A further improvement is the attachment of a sleeve or an anti-reflux valve to the distal end of the stent to minimize duodenal biliary reflux. Controlled studies have reported a longer patency of the stent with the anti reflux design although there was no difference in the overall survival. Metal stents with the tip left in the duodenum are at risk of the same complication of duodenal biliary reflux but because of the larger stent diameter, cholangitis tends to occur later. Preliminary data on a newly designed SEMS with an anti-reflux valve is associated with a much lower risk of ascending cholangitis.
**Oral Abstract**

**Choice of Stents for Palliation**

Current recommendation on the choice of stents used for palliation depends on the expected survival of the patient. Even for an un-resectable tumor, the size of the lesion predicts survival. Patient with a smaller tumor is more likely to survive for longer than 6 months and therefore may benefit from the use of the more expensive SEMS whereas patients with significant co-morbidities or extensive disease are less likely to survive for a long period and can then undergo plastic stent placement only.

**Other Forms of Palliative Treatment**

A study involving small number of patients reported usefulness of photodynamic therapy in combination with endoscopic stenting for palliation of unresectable cholangiocarcinoma. Brachytherapy using special biliary stents with radioactive implants is technically feasible but long term studies involving large number of patients is required to define its true benefits in inoperable peri-pancreatic head cancers.

**Future Research**

A meta-analysis reported in the Cochrane review suggested that endoscopic stenting is the treatment of choice for palliative biliary drainage. What the literature lacks is large scale randomized controlled studies on the palliative treatment of malignant obstructive jaundice, to define the role of plastic versus metal stents in patients with different life expectancies especially for those with survival less than 6 months. Future research should include studies that improve plastic stent patency (from a better design to prevent ascending infection to better material(s) to prevent bacterial biofilm formation) in order to make it a more cost effective alternative to metal stents, and also studies to evaluate the specific indications for covered versus uncovered metal stents as well as the role of newer therapeutic modalities.

**References**

EUS and EUS-guided Aspiration in the Diagnosis of Pancreatic Lesion: the NTUH Experience

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Endoscopic ultrasonography (EUS) has been applied for clinical use for more than 20 years. Nowadays, it has changed the role of diagnosis to intervention. EUS-guided aspiration (EUS-FNA) was introduced by P Vilmann (1992), M Giovannini (1993) and KJ Chang (1994). EUS-FNA is one of the methods to get the tissue of pancreas which locate retroperitoneally. EUS-FNA is believed better than trans-cutaneous approach such as ultrasound-guided and CT-guided.

EUS-FNA was started in NTUH in 1999-2000. We have applied the technique on different diseases, including mediastinal, pancreatic, bile duct, hepatic, adrenal and submucosal tumor of GI tract. Among the indications, EUS-FNA is requested most frequently. From Dec. 2001 to May 2010, 244 patients received EUS-FNA for pancreatic mass sampling at NTUH. The pathology included ductal cell carcinoma, IPMN, neuroendocrine tumors, small cell carcinoma, SPEN, metastasis and TB, etc. The associated parameters of EUS-FNA diagnosis were as follows, sensitivity 96.0%, specificity 98.5%, positive predictive value 99.4%, negative predictive value 90.5%, and accuracy 96.7%. On-site cytology evaluation with rapid staining methods, Hemacolor and Ultrafast Papanicolaou staining, was done routinely for EUS-FNA specimens in NTUH. Only two cases (0.8%) of significant bleeding complication (blood transfusion) after EUS-FNA occurred. No mortality related to the procedure.

WE conclude that EUS-FNA is good tool to get the tissue from pancreatic lesion. It is effective and safe procedure in our experience.
General Management of Malignant Biliary Obstruction

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Biliary drainage is usually conducted as a part of treatment of malignant biliary obstruction. Biliary drainage is performed to reduce liver damage, to abolish bacterial infection, and to facilitate drug metabolism. Drainage may be needed before surgery if patient has cholangitis or overt liver function impairment. It is generally recommended to use percutaneous drainage for high biliary obstruction and endoscopic drainage for low biliary obstruction. For percutaneous drainage, internal-external drainage is more physiological and can prevent electrolyte imbalance and dehydration associated with external drainage. More bile output does not necessary imply a faster improvement of liver function. Contrarily, post-obstructive choleresis and light bile implies more serious liver function impairment and will take more times for recovery of liver function. Unless, there is an effective regimen for cancer treatment, patients with terminal cancer are usually benefited less by biliary drainage and may not require a biliary drainage for palliation. Every patient is unique; we have to treat them individually by applying knowledge of biliary excretion and techniques of biliary drainage to achieve the best benefit of patient.
Gemcitabine in Pancreatic Biliary Cancer Therapy

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Adenocarcinoma of the pancreatic, gallbladder and biliary tract is uncommon, but not rare; and it caused high mortality. Although tumors arising distally in the Ampulla of Vater are generally discovered at an early stage and are associated with a relatively good prognosis, tumors arising in the pancreatic, gallbladder or other parts of the biliary tract are associated with a poor prognosis. Gemcitabine has been reported to have some clinical activity in pancreatic and biliary tumors, with variable response rates of approximately 30% or less. A recent trial demonstrated a survival benefit for the cisplatin-gemcitabine combination compared with gemcitabine alone (median survival 11.7 vs. 8.2 months, p = 0.002). However, survival remains generally poor, and new therapeutic targets and options are needed. Ribonucleotide reductase (RR) is a gemcitabine targeted enzyme. It catalyzes the reduction step converting nucleotide diphosphates to their 2’-deoxy forms, the rate limiting step in the synthesis of the 2’-deoxy nucleoside triphosphates from purine and cytidine-based DNA precursors. RR is a heterodimeric compound consisting of two subunits, M1 and M2. M1 composed substrate and activator binding sites. M2 is composed iron and tyrosine free radical and acts in concert with various activated oncogenes. M2 overexpression is associated with increased Raf-1 membrane associated protein and mitogen activated kinase (MAPK) activity and resistance to gemcitabine therapy. Here, we report the RR related pharmacogenomics study and potential circumvention of RR resistant in pancreatic and biliary tumors.
Risk Factors for Biliary Tract Cancer in Taiwan: a Population-based Case-control Study Using the National Health Insurance Research Database

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Background
The incidence of biliary tract cancer, including gallbladder cancer (GC), and intra- and extrahepatic cholangiocarcinoma (ICC and ECC), has been rising in Taiwan. Most of the studies published to date on the risk factors of biliary tract cancer were hospital-based studies with a small sample size. In addition, most studies did not examine whether the three types of biliary tract cancer have different risk factors. The current study utilizes a population-based case-control design using data from the National Health Insurance Research Database (NHIRD) of Taiwan to assess the risk factors associated with biliary tract cancer by disease sites.

Methods
Patients newly diagnosed with biliary tract cancer during 2004 to 2008 were included in the analysis. For each cancer case, 4 cancer-free controls matched on sex, age, and time of diagnosis (reference date for the controls) were identified. Possible risk factors for biliary tract cancer were assessed in a 4-year period one year prior to the diagnosis of biliary tract cancer (reference date for the controls). Multivariable conditional logistic regression was performed to evaluate the association between biliary tract cancer and the possible risk factors.

Results
6,517 cases of biliary tract cancer (2,978 ICC, 2,432 ECC, and 1,107 GC cases) and 26,068 controls were identified for analysis. Factors associated (p < 0.05) with an increased risk of all three biliary tract cancers included cholangitis, cholelithiasis, diabetes, Crohn’s disease, and peptic ulcer. Factors associated with an increased risk for only ICC and ECC included non-specified cirrhosis of liver and hepatitis B. Chronic pancreatitis was positively associated with ICC and GC, but not ECC. Thyrotoxicosis was positively associated only with GC, whereas alcoholic liver disease and hepatitis C were only associated with an increased risk of ICC.

Conclusions
The current study shows risk factors that are common across and unique to different types of biliary tract cancer. The results of the current study may help devise effective prevention strategies for biliary tract cancer.

(This study was supported by the Establishment of Cancer Research System Excellence Program, Grant number: DOH99-TD-C-111-004)
Perspectives of Molecular Targeting Therapy in Biliary Cancer

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The incidence of cholangiocarcinoma is steadily increasing worldwide. Surgical resection offers the only chance for cure; whereas most of patients with cholangiocarcinoma are unfit for surgical management either due to intrahepatic metastasis and/or distant metastasis at the time of initial diagnosis. Currently, gemcitabine associated with platinum-compound is considered the gold-standard for palliative chemotherapy of cholangiocarcinoma; nevertheless, again, the response rate is disappointing as low as 20-30%. Therefore, emergence of novel therapeutic regimens, such as target therapy, is eagerly needed. In this article, we present our animal cholangiocarcinoma model, screening methodology of new drugs either alone or in combination, determination of synergism, platform of therapeutic assessment, relevant molecular mechanics, and early prediction of therapeutic response and prognosis. We hope this preclinical research platform might efficaciously trigger application of novel target therapy in clinical trials.
Systemic Therapy for Advanced Biliary Tract Carcinoma: Promises and Controversies

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Biliary tract carcinoma is a heterogeneous group of cancers. Different tumor types (intra-hepatic cholangiocarcinoma, extra-hepatic bile duct carcinoma, and gallbladder carcinoma) have different pathogenesis and natural history. Systemic therapy for advanced or metastatic diseases is further complicated with the frequently concomitant biliary tract obstruction and infection. Therefore, most of the reported clinical trials of systemic therapy for biliary tract carcinoma are single-arm studies with different patient characteristics and heterogeneous outcome. The recent report of survival benefit of gemcitabine plus cisplatin chemotherapy ushers in a new era of clinical trials for biliary tract carcinoma. Meanwhile, the roles of molecular targeted therapy for biliary tract carcinoma were also explored.

Despite these promising results, there are caveats in design, conduct, and interpretation of clinical trials of systemic therapy for advanced biliary tract carcinoma. Gemcitabine plus platinum is the current standard systemic therapy, but the optimal dosing regimen remains to be defined. Patients with biliary tract obstruction are especially susceptible to treatment-related complications and multi-disciplinary treatment is needed for optimal patient care. Studies of novel therapeutic targets and predictive biomarkers have been limited by tissue availability and lack of pre-clinical model systems for hypothesis testing. In this presentation the current status of systemic therapy for advanced biliary tract carcinoma will be reviewed and future perspectives of clinical and translational research will be discussed.
Cholangiocarcinoma is an uncommon cancer that arises from the biliary epithelium. It is classified into 3 categories as intrahepatic, hilar or distal. Surgical resection is the gold standard for treatment for all types of cholangiocarcinoma, however, the surgical outcomes have not been satisfactory. 5-year survival rates as high as 30-50% have been reported. Recently, the outcome of the surgical treatment for hilar cholangiocarcinoma has markedly improved. Before 1997, the overall 5-year survival rate of patients with hilar cholangiocarcinoma at Tohoku University Hospital was only 11%, but increased to almost 40% after 1998. The probable causes are as follows: 1) improvement of preoperative diagnosis by multi-detector row CT, 2) improvement of perioperative management, such as percutaneous transhepatic portal embolization (PTPE) and preoperative biliary drainage, 3) improvement of surgical skill to achieve curative resection, such as combined resection of portal vein and/or hepatic artery. On the other hand, the surgical outcomes of the patients with distal cholangiocarcinoma have not improved, although the surgical strategy for distal cholangiocarcinoma has been established for pancreaticoduodenectomy with lymph node dissection for more than 25 years. The 5-year survival rate has been 30-40% and the outcomes have not changed for 25 years. These results suggest that surgical resection alone is insufficient to successfully treat advanced cholangiocarcinoma and that multidisciplinary therapy including surgery, chemotherapy, and radiation is needed.

In this paper, we review our surgical experiences with hilar and distal cholangiocarcinoma at Tohoku University Hospital. Moreover, I would like to talk about our phase I/II trials of neoadjuvant chemoradiation therapy for advanced cholangiocarcinoma.
Cholangiocarcinoma: from Bedside to Bench

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Cholangiocarcinomas (CCA) are devastating cancers that are increasing in both their worldwide incidence and mortality rates. The challenges posed by these often lethal biliary tract cancers are big, with conventional treatment options being limited and the only hope for long-term survival being that of complete surgical resection of the tumor. Unfortunately, the vast majority of patients with CCA typically seek treatment with advanced disease, and often these patients are deemed poor candidates for curative surgery.

A total of 218 consecutive patients with histopathologically proven CCA undergoing hepatectomy at CGMH between 1977 and 2004 were investigated. Favorable prognostic factors influencing overall survival consisted of early tumor stage, presence of mucobilia, papillary tumor type, hepatic resection, and post-operative chemotherapy. Moreover, absence of physical findings, presence of mucobilia, early staged tumor, and curative hepatectomy could independently predict CCA patients with long term overall survival (more than 5 years) after hepatectomy.

Moreover, conventional chemotherapy and radiation therapy have not been shown to be effective in prolonging long-term survival. Thus, there is a real need to develop novel chemopreventive and adjuvant therapeutic strategies for CCA based on exploiting selected molecular targets that would impact in a significant way on clinical outcome.

We have established a study system for cholangiocarcinogenesis including rat model for CCA. In addition, applying DNA microarray for rat and human CCA and proteomics to explore molecular alterations related to dysregulation of CCA growth and survival, aberrant gene expression, invasion and metastasis, and tumor microenvironment are described in this presentation. We also developed animal PET for rat CCA model for preclinical study to find out the potential therapeutic agents. Moreover, an emphasis is placed on the importance of clinical study based on translational study to find potential molecular therapeutic targets and prognostic markers for CCA.
Hepatocellular carcinoma (HCC) is the number one of the ten leading cancer death in Taiwan and has been picked up as the target diseases by National Research Program for Genomic Medicine (NRPGM). We have proposed and organized a liver cancer research network that could coordinate the major medical centers in Taiwan to conduct a prospective study. This network (Taiwan Liver Cancer Network, TLCN) currently includes five major medical centers in northern, central, and southern parts of Taiwan (NTUH, CGMH-Linko, VGH-Taichung, CGMH-Kaohsiung, VGH-Kaohsiung) to conduct a prospective study, so that we will be able to collect HCC patients with various socioeconomic, ethnical and life style backgrounds as well as regional representativeness. The resected liver tumor and non-tumor tissues will be separated and snap-frozen at each collaborating hospital and periodically shipped to the central tissue bank at NHRI, Zhunan. Other biosamples, such as serum, plasma and blood cells will be stored in the tissue bank, too. By the end of July, 2010, we have collected 4576 liver cancer patients with tissue or blood samples and sufficient clinical pathological and virological information. Among them, 3263 were HCC, 171 were chholangiocarcinoma, 72 were focal nodular hyperplasia, and etc. Currently, the tissue bank has more than 2500 fresh frozen specimens. This network has started to accept applications for biosamples from individual PI in Taiwan since 2007, including DNA, RNA, paraffin tissue sections and tissue fragment for protein extraction. So far, we already have 36 applicants, and all of them are professors from national universities and medical centers. Eight types of HCC tissue arrays of various groups of HCC tissues were also completed and ready for application. Currently, we have started to build up follow up database. After the follow up database is completed, our liver cancer network will be one of the largest and best liver cancer patient database and tissue bank in the world.
Surgical Management of Pancreatic Cancer in Taiwan

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Pancreatic cancer is a devastating disease, though significant efforts have been made, the annual cancer death is nearly identical to the annual incidence. Surgical resection remains the potential curative option for pancreatic cancer. However, there are only 15%-20% of patients are candidates for pancreatic resection. Low tumor resectable rates, early tumor recurrence after resection, and resistance to chemotherapy and radiotherapy contribute to its poor prognosis.

From above, resection of small pancreatic cancer and increasing the resectability are the detrimental to improve patient survival. Detection of small pancreatic cancer is difficult due to nonspecific symptoms. Blind pancreaticoduodenectomy with or without biopsy for pancreatic head lesion has been advocated by experienced surgeons. But there still exists contradictory viewpoint from gastroenterologist for consideration of postoperative morbidity. Preoperative chemoradiation for locally advanced pancreatic cancer is another way to increase the resectability, it can increase the median survival from 9 months to 20 months. But the difficulty in exploration is much higher than usual operation, so it was only performed in high experienced medical center. After improvement in surgical techniques and postoperative care, the surgical mortality rate of high volume centers in Taiwan was lower. Finally, in this report, we will collect the experience of management of pancreatic cancer in 10 medical centers.
Accuracy and Reproducibility of Pancreatic Pathology and its Impact on Patient Management, Multicentre Trials and Clinical Research

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Histopathology is usually regarded as the gold standard for correct diagnosis of the specific tumour entity, for cancer staging, and for accurate identification of tumour characteristics that are believed to be of prognostic relevance, including tumour size and extension, grade of differentiation, lymphovascular and perineural tumour propagation, lymph node or distant metastasis. Management of individual patients, clinical trials and research projects are based on these key data, which are provided by the reporting pathologist.

In recent years, however, several studies have raised awareness about the lack of standardization in gross and microscopic examination, the existence of different definitions regarding margin involvement, and the use of confusing nomenclature for resection margins and specimen surfaces. This lack of (inter-)national consensus is most likely partially the cause for the significant divergence of published data on tumour stage and rates of lymph node metastasis and margin involvement, which seems to be at odds with the universally uniform (poor) outcome of pancreatic cancer patients following surgical resection with curative intent.

The existence of significant differences in several aspects of pathology examination and the impact thereof on the reported data are currently the topic of a rapidly growing body of literature. Several studies demonstrated a significant increase of microscopic margin involvement (up to over 80%) in pancreatic cancer specimens following introduction of a rigorous and fully standardized pathology examination protocol. The latter also had a major impact on the reported origin of the pancreatic head cancers, ie. carcinomas arising from the pancreas, ampulla or distal common bile duct. The impact of these differences on adjuvant treatment, prognosis and trial participation is obvious.

First successful attempts at standardisation and introduction of a quality monitoring system of pancreatic pathology reporting are currently being undertaken at a local, regional or national level in several countries. This should set the trend for a global consensus to ensure that pathology is indeed the gold standard for the provision of key tumour-related data. Multicentre clinical trials are urgently needed to assess the impact of changes in patient management and use of new treatment modalities. However, without robust and reliable pathological data, these are unlikely to succeed in producing compelling evidence.
The Characterization of Signalling Pathway and Clinical Role of Kruppel Like Factor 10 (Klf10) in Pancreatic Cancer

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Pancreatic adenocarcinoma is one of the most lethal tumors among all cancer types, and is the fourth-highest cause of cancer deaths in the industrialized world. Only 10-20% of patients with pancreatic adenocarcinoma are currently undergone surgical therapy, and, even in resected cases, the 5-year survival rate is only 15-25% due to their high recurrences. At present, clinical staging and histopathological criteria are the only parameters in clinical use to stratify patients according to the risk of developing metastasis after curatively intended surgery. However, current staging classifications are not able to accurately predict patient outcome, illustrating a highly heterogeneous population of cells with considerable diversified biological reactions exist in tumors of even the same stage. To further classify patients into different risk categories and to aid clinicians in choosing suitable treatments, new and better prognostic markers are urgently needed. Several have been proposed, however, none of them have so far been proven robust enough to be incorporated into routine practice.

The human homologue of Klf10 (Kruppel like factor 10) was originally identified as the product of a transforming growth factor (TGF) beta-inducible early-response gene1 using osteoblastic cells and differential display PCR. Since then, it has been shown that Klf10 can also be specifically induced by E2, TGF-β1, -β2, -β3, EGF, NGF and BMP-2. Further studies on TGF-β1’s regulation of Klf10 transcription have indicated that increased intracellular levels of Klf10 mimic the anti-proliferative and apoptotic effects of TGF-β1 on epithelial cell growth, suggesting that Klf10 is an important factor for mediating TGF-β1 signaling. However, Klf10’s targets and the related signal transduction pathways remain largely unknown. Using protein- and ChIP-chips, we were able to screen for possible targets of Klf10 based on the specific binding sites for transcription regulation. Among the 1,200 candidates identified, about 90 genes including Id1/2, BI-1, IKKα, MDC-1 etc were categorized as belonging to programmed cell death or apoptosis network. The Klf10 regulating mechanisms and their biological significances on some of these genes have been confirmed individually by our laboratory. Furthermore, we used a cancer profiling array to examine Klf10 expression in paired tumor versus normal tissues. With the 7 cases of pancreatic tissue examined, all showed significant less Klf10 expression in the tumor tissue when compared with the matched normal tissue. As a one step further, clinical specimens were collected for a complete evaluation on the correlation between Klf10 expression and clinic pathological features of pancreatic adenocarcinoma, especially on the prognosis of patients who underwent curative pancreatectomy.
The Klf10 expression of 95 formalin-fixed paraffin-embedded tissue samples of resected pancreatic adenocarcinomas were examined by immunohistochemistry using a Klf10-specific monoclonal antibody, forty three were female and the median age was 62 \pm 12 years. Sixty-six tumors were located over pancreatic head. There were 8, 25, 32, 13 and 17 patients of stage I, IIa, IIb, III, IV respectively. Low expression of KLF10 correlated significantly with advanced staging (65.2\% vs 89.7\%, \( p = 0.01 \)) and distant metastasis (67.9\% vs 94.1\%, \( p = 0.03 \)).

Univariate analysis revealed that baseline CA19-9 level, stage, surgery and KLF10 predicted disease progression; while tumor location, stage, surgery and KLF10 correlated with overall survival. Results of multivariate analysis showed that distant metastasis and loss of immunostaining of KLF10 were two independent prognostic factors for rapid progression and shorter survival. In order to elucidate the mechanism which leads to diminished Klf10 expression, we analyzed 40 pancreatic cancer patient specimens for methylation status by methylation specific PCR.

These studies demonstrate Klf10 silencing is associated with promoter region hypermethylation in pancreatic cancer and suggest that the expression of Klf10 is a valuable prognostic factor as well as an attractive target for the purpose of therapeutics development.

(The study was supported by grants of Department of Health (DOH99-TD-C-111-004, Taiwan, R.O.C.)
Update of Systemic Chemotherapy for Biliary Tract Cancer

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While anti-cancer drugs such as gemcitabine, 5-FU, and cisplatin are often used in the treatment of advanced biliary tract cancer, no standard chemotherapy based on a large-scale phase III study has been established yet for this cancer. Recently, the combination of gemcitabine and cisplatin (GC therapy) was investigated in randomized clinical trials (RCTs) conducted in the United Kingdom and Japan. GC therapy showed statistically significant survival benefits over gemcitabine alone in the RCT in the UK. Although the Japanese RCT was smaller, similar results to those of the UK trial were obtained. GC therapy is now recognized as a global standard for the treatment of advanced biliary tract cancer. A randomized phase II study comparing S-1 monotherapy and gemcitabine plus S-1 (GS therapy) is currently being conducted by the Japanese Clinical Oncology Group (JCOG 0805), for which enrollment was completed in April, 2010. We are now planning a large-scale RCT to compare the more promising of these two regimens with GC therapy. Furthermore, investigations of the usefulness of molecular-targeted agents against biliary tract cancer are also proposed. As biliary tract cancer is relatively rare, collaborative global clinical trials are important.
Shifting Paradigms in Our Therapeutic Approach to Pancreatic Cancer: Is There Reason for Optimism?

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Pancreatic adenocarcinoma represents the fourth leading cause of cancer-related mortality in the United States amongst both women and men, and will be responsible for an estimated 36,800 deaths nationwide in 2010. Treatment options for this disease have remained fairly limited over the past couple of decades, as the vast majority of gemcitabine-based combinations, including those evaluating promising targeted agents, have failed to demonstrate significant survival benefit in phase III trials compared to single-agent therapy alone. However, recently completed or ongoing therapeutic trials, both informed by and leading to further preclinical discoveries, may force us to reconsider our strategic approaches for the treatment of pancreatic cancer. These “paradigm-shifting” ideas can be grouped into 3 categories:

1. Moving away from gemcitabine-based therapy as the chemotherapeutic backbone on which to develop novel regimens. The recent phase III French trial (ACCORD 11) demonstrating the efficacy of FOLFIRINOX provides the most compelling evidence for this tactic.

2. Focusing our attention not just on tumor cells, but also on the surrounding tumor stromal compartment. As primary pancreatic tumors are often characterized by a dense desmoplastic reaction, our ability to overcome and harness the supporting elements that may affect drug penetration becomes an important way to optimize intratumoral delivery of concurrently administered drugs. Preclinical models have tested this “stromal depletion” hypothesis using Hedgehog signaling inhibitors and nanoparticle albumin-bound chemotherapy; these agents are now under active investigation in clinical trials.

3. Exploring new and different targets beyond the “usual suspects”. Included amongst these novel targets are those representing core signaling pathways (such as TGF-beta) known to be genetically altered in the majority of pancreatic cancers.

Recognizing that not all of these strategies have yet been fully realized in the clinical arena, we have reason to hope that they may ultimately translate into improved survival for patients with pancreatic cancer. In the meantime, accompanying efforts should focus on identifying specific clinical characteristics and candidate biomarkers that may help refine our decision-making as to which patients are most likely to benefit from any or all of the above approaches.
Management of Pancreatic Cancer in Japan

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Pancreatic cancer accounts for only 3% of all cancers in Japan, but it is now the fifth leading cause of death from cancer in the country. These statistics indicate a rapid increase in the number of deaths from this disease in Japan. The prognosis of patients with this disease is extremely poor, with fewer than 5% of patients remaining alive at 5 years after the diagnosis. Of all the treatment modalities available for pancreatic cancer, only resection offers the opportunity for cure, however, only a small proportion of patients are eligible for surgery. Even in patients with resectable disease, the long-term outcome remains unsatisfactory, because of the high frequency of early recurrence after resection. Therefore, to improve the prognosis of these patients, the development of effective non-surgical treatments is essential.

A landmark study reported in 1997 suggested that single-agent treatment with gemcitabine provided superior survival benefit to 5-fluorouracil, and the agent was approved in 2001 in Japan after a small feasibility study conducted in Japanese patients. At around the time of approval of gemcitabine, early and late phase II studies for S-1 were conducted, and S-1 was approved for use in the treatment of pancreatic cancer in 2006. Until date, 8 chemotherapeutic agents have been approved for use in the treatment of pancreatic cancer by the Japanese government. However, only two agents, gemcitabine and S-1, are considered by Japanese physicians as having any true therapeutic potential against this cancer. We are conducting a phase III study of gemcitabine vs. S-1 vs. gemcitabine+S-1 in collaboration with Taiwanese investigators. Gemcitabine + erlotinib was the only combination that showed survival prolongation in comparison with single-agent gemcitabine in a global phase III study, and a relatively large-scale phase II study, on 100 Japanese patients, of gemcitabine + erlotinib was conducted in Japan.

Some phase III studies of adjuvant therapy and several early and late phase studies of newer agents are also ongoing in Japan. I would like to introduce these clinical trials and practices for Japanese pancreatic cancer patients in my presentation.
Drug Development for Pancreatic Cancer in Taiwan

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Gemcitabine is the standard therapy for APC with modest anti-tumor efficacy, 6-11% of overall response rate and 5-6 months of overall survival time. Our first study for APC was weekly gemcitabine (800 mg/m^2) plus 24-hr infusion of high-dose 5-FU/LV, which resulted in an overall and clinical benefit response rate of 22% and 46%, respectively; and a median progression-free and overall survival of 4.1 and 6.9 months, respectively. Subsequently, we explored the feasibility and efficacy of a triplet chemotherapy consisting of biweekly gemcitabine (fixed rate infusion of 800 mg/m^2) followed by oxaliplatin and 48-hr infusion of 5-FU/LV (3000 and 300 mg/m^2, respectively), the GOFL regimen in fragile APC patients. The MTD of oxaliplatin for the combination was determined as 85 mg/m^2 in phase I part of study. Of the 45 patients in phase II study, the overall response rate and disease-control rate was 33.3% (95% CI, 19.0-47.7%) and 68.9% (95% CI, 54.8-83.0%), respectively. The median progression-free survival and overall survival was 4.7 (95% CI, 3.3-6.0) months and 9.8 (95% CI, 7.0-12.6) months, respectively. Based on the exciting results, we initiated a multicenter phase II study to evaluate induction GOLFL followed by CCRT in patients with unresectable LAPC, the TCOG T1204 study. Among the 50 accruals (96% with definitive unresectable diseases), the median overall survival of ITT population and patients who completed both induction GOFL and CCRT was 14.5 (95% CI, 10-27.4) months and 18.1 (6.1-45.7) months, respectively. To further improve the therapeutic index of the triplet chemotherapy, we shall try using S-1, a 3\textsuperscript{rd}-generation of oral fluoropyrimidine with better clinical activity against APC than infusion 5-FU, to substitute 5-FU, and the new phase I/II trial will be launched in the near future. Recently, we have also completed the recruitment of a phase II trial, which evaluates a new formulation irinotecan (encapsulated, liposomal irinotecan, PEP02) as 2\textsuperscript{nd}-line therapy for gemcitabine-failure APC. In addition, a phase Ib trial of 1\textsuperscript{st}-line gemcitabine plus nano-cisplatin (NC-6004) aiming to determine the MTD of NC-6004 in APC is also ongoing.

Furthermore, we have also established 3-dimention culture system as well as orthotropic xenograft model in our laboratory, and expecting these new facilities will enhance new drug discovery for the management of pancreatic cancer in the future.

(The study was supported by grants of Department of Health (DOH99-TD-C-111-004, Taiwan, R.O.C.)
EGFR Nuclear Import in Gallbladder Carcinoma: Nuclear Phosphorylated EGFR Upregulates iNOS Expression and Confers Independent Prognostic Impact

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Background
The understanding of epidermal growth factor receptor (EGFR) deregulation in carcinogenesis remains incomplete.

Methods
We comprehensively investigated the implications of EGFR gene status and EGFR nuclear translocation in gallbladder carcinoma (GBCA). Subcellular localization of EGFR and phosphorylated EGFR (pEGFR) were analyzed by fractional immunoblotting and confocal immunofluorescence in GBCA cell lines. pEGFR binding to iNOS promoter was assessed by chromatin immunoprecipitation with iNOS promoter activity evaluated by luciferase assay. EGFR, pEGFR, and iNOS were immunohistochemically assessable for localization and level in 104 GBCAs, with 76 analyzed for EGFR gene by chromogenic in situ hybridization (CISH) and mutant-enriched PCR targeting exons 19 and 21. The results were correlated with clinicopathological factors and disease-specific survival (DSS). The prognostic impact of nuclear pEGFR (N-pEGFR) was also immunohistochemically examined for 58 independent GBCAs.

Results
Endogenous nuclear expression of EGFR and pEGFR was substantiated in vitro with augmented activity of iNOS promoter elicited by pEGFR binding upon EGF treatment. Despite no mutation, EGFR amplification, identified in 11 cases (15%) by CISH, strongly correlated with cytoplasmic EGFR expression (p < 0.001) but not with DSS. Immunohistoexpression of nuclear EGFR (N-EGFR), cytoplasmic pEGFR, and N-pEGFR was strongly related to that of iNOS (all ≤ 0.005). N-pEGFR independently predicted worse DSS in both testing (p = 0.0468, HR = 2.024) and validation cohorts (p = 0.0223, HR = 5.573).

Conclusions
In conclusion, N-EGFR and N-pEGFR indeed express in GBCA cells and specimens and may confer clinical aggressiveness partly through iNOS transactivation. Lacking response-predicting mutation, EGFR gene status, albeit amplified in 15% of GBCA, is neither related to nuclear EGFR translocation nor prognostically useful.

(The study was supported by grants of Department of Health (DOH99-TD-C-111-004, Taiwan, R.O.C.)
Risk Factors for Biliary Tract Cancer in Taiwan: a Population-based Case-control Study Using the National Health Insurance Research Database

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Background
The incidence of biliary tract cancer, including gallbladder cancer (GC), and intra- and extrahepatic cholangiocarcinoma (ICC and ECC), has been rising in Taiwan. Most of the studies published to date on the risk factors of biliary tract cancer were hospital-based studies with a small sample size. In addition, most studies did not examine whether the three types of biliary tract cancer have different risk factors. The current study utilizes a population-based case-control design using data from the National Health Insurance Research Database (NHIRD) of Taiwan to assess the risk factors associated with biliary tract cancer by disease sites.

Methods
Patients newly diagnosed with biliary tract cancer during 2004 to 2008 were included in the analysis. For each cancer case, 4 cancer-free controls matched on sex, age, and time of diagnosis (reference date for the controls) were identified. Possible risk factors for biliary tract cancer were assessed in a 4-year period one year prior to the diagnosis of biliary tract cancer (reference date for the controls). Multivariable conditional logistic regression was performed to evaluate the association between biliary tract cancer and the possible risk factors.

Results
6,517 cases of biliary tract cancer (2,978 ICC, 2,432 ECC, and 1,107 GC cases) and 26,068 controls were identified for analysis. Factors associated (p < 0.05) with an increased risk of all three biliary tract cancers included cholangitis, cholelithiasis, diabetes, Crohn’s disease, and peptic ulcer. Factors associated with an increased risk for only ICC and ECC included non-specified cirrhosis of liver and hepatitis B. Chronic pancreatitis was positively associated with ICC and GC, but not ECC. Thyrotoxicosis was positively associated only with GC, whereas alcoholic liver disease and hepatitis C were only associated with an increased risk of ICC.

Conclusions
The current study shows risk factors that are common across and unique to different types of biliary tract cancer. The results of the current study may help devise effective prevention strategies for biliary tract cancer.

(This study was supported by the Establishment of Cancer Research System Excellence Program, Grant number: DOH99-TD-C-111-004)
**18F-FDG PET Predicts Tumor Response and Long-term Survival of Cholangiocarcinoma Rats after Target Therapy -- Validation with Histopathological Findings and Molecular Markers**

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**Objectives**

To elucidate whether 18F-FDG PET enables to precisely reflect the therapeutic response of cholangiocarcinoma treated by novel target therapy.

**Methods**

Cetuximab- and rad001-based combination regimens were employed to treat cholangiocarcinoma xenograft model and orthotopic cholangiocarcinoma rat model. Metabolic response of the experimental rats was determined by 18F-FDG PET before and at first and second cycle of chemo-target therapy, respectively. Histopathological examination was defined as final confirmation of therapeutic responses. Expression of Ki67, Glut-1, HK-II, VEGF, and HIF-1α was determined. Finally, the long-term survival of cholangiocarcinoma rats was analyzed.

**Results**

Gemcitabine plus rad001 was the most optimal regimen based on xenograft model, which was determined by directly measuring tumor size. Based on metabolic response detected by 18F-FDG PET, gemcitabine plus rad001 conferred the best therapeutic efficacy compared with that of either single agent. This observation was confirmed by histomorphological regression analysis, and was well correlated with protein and/or mRNA expression of Ki67, Glut-1, HK-II, VEGF, and HIF-1α. Of utmost significance, the trend of long-term survival of cholangiocarcinoma rats was coincided with the initial SUV changes of the subjects detected by 18F-FDG PET after 1-2 cycles of target therapy.

**Conclusions**

18F-FDG PET predicts therapeutic response and long-term outcome of cholangiocarcinoma rodent model treated by target therapy against receptor tyrosine kinase signaling.
Rad001 and Gemcitabine Combination Therapy Confers Synergistic Antitumor Effect on Cholangiocarcinoma

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Background
Effective modality for advanced or metastatic cholangiocarcinoma is eagerly lacking. Gemcitabine currently represents the standard chemotherapy, however, with a disappointing response rate around 20%. We herein tested the therapeutic efficacy of gemcitabine-based combination therapy on cholangiocarcinoma, as well its relevant mechanism.

Methods
The most optimal therapeutic regimen was surveyed upon six cholangiocarcinoma cell lines in vitro, based on which the in vivo therapeutic efficacy was tested using xenograft mouse model and a chemical-induced orthotopic cholangiocarcinoma rat model, respectively.

Results
Gemcitabine plus rad001 was the most optimal regimen based on in vitro drug cytotoxicity assay. The rationale of rad001 employed to treat Akt-bearing cholangiocarcinoma cells was verified by the attenuated expression of mTOR down-stream molecules after mTOR inhibition, including p70S6K, VEGF, eIF4E, and Ki-67. Gemcitabine plus rad001 exhibited a synergistic therapeutic benefit confirmed by combination index < 1, as well evidenced by stagnation of cell cycling, increased cellular apoptosis, tumor shrinkage and metabolic response as compared with either single agent. A surge of Fas, caspase 8, Bid, APAF1, XIAP and caspase 3 mRNA was observed in subjects treated with gemcitabine plus rad001 compared with those treated by either single agent. Finally, administration of rad001 alone induced release of feedback inhibition of Akt- mTOR axis, while gemcitabine plus rad001 avoided this undesirable phenomenon.

Conclusions
Gemcitabine plus rad001 conferred not only better therapeutic response but also avoided the potential target drug resistance. The synergistic antitumor effect of gemcitabine plus rad001 might involve reactivation of Fas signaling.
Clinicopathological and Prognostic Significances of EGFR, KRAS and BRAF Mutation in Biliary Tract Carcinomas

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Background
Biliary tract carcinomas (BTCs), which include cancers of the gallbladder and intra- and extrahepatic biliary trees, are notoriously difficult to diagnose and treat. Surgical resection is the only chance for cure. Conventional therapies are still unsuccessful in patients with BTCs. Novel effective therapeutic strategies are urgently required to improve the prognosis. Epidermal growth factor receptor (EGFR) represents a validated therapeutic target for the treatment of human cancer. Somatic mutations of the EGFR gene and the activation of its downstream pathways predict the sensitivity to anti-EGFR antibodies, such as cetuximab, as well as ATP-competitive tyrosine kinase inhibitors (TKIs), such as erlotinib or gefitinib in the non-small cell lung cancer and colon cancer. In addition, patients with KRAS mutations are unlikely to respond to EGFR TKIs. The aims of this study were to analyze the EGFR, KRAS and BRAF mutations simultaneously in BTCs as well as associations between these mutations and clinicopathological factors or clinical outcome.

Methods
Paraffin-embedded surgical specimens containing 137 BTCs, including 57 intrahepatic cholangiocarcinomas, 45 extrahepatic cholangiocarcinomas, and 35 gallbladder carcinomas resected at the National Taiwan University Hospital between 1995 and 2004 were used for this study. The clinicopathological features of the patients, including TNM staging, were recorded. The exons 18-21 of EGFR gene, the codon 12, 13 and 60 of KRAS gene and BRAF V600E mutation were analyzed by direct sequencing. We examined the correlation between these gene mutations and the clinicopathological factors, including overall survival, tumor location, tumor stage, and degree of tumor differentiation in patients with BTCs.

Results
In total, 11 out of the 137 (8%) BTCs, including 3 intrahepatic cholangiocarcinoma, 6 extrahepatic cholangiocarcinoma, and 2 gallbladder carcinoma, had EGFR mutations. None of these specimens had mutations in EGFR exon 18 and 19. Twenty-three patients (23/137, 16.8%), including 10 intrahepatic cholangiocarcinoma, 9 extrahepatic cholangiocarcinoma, and 4 gallbladder carcinoma, had KRAS mutations. Only one extrahepatic cholangiocarcinoma patient was found to have BRAF mutation. No patient had both EGFR and KRAS mutations. Factors influencing survival on univariate analysis were tumor stage (p < 0.00001), degree of tumor differentiation (p = 0.01), and EGFR mutation (p < 0.00001). On multivariate analysis using the Cox proportional hazard model, EGFR mutation, and tumor stage were independent predictors of survival.
prognostic factors in patients with BTCs. We failed to observe a correlation between KRAS or BRAF mutations and prognosis of patients.

Conclusions

EGFR and KRAS mutations are not uncommon in patients with BTCs. BRAF mutation is rare in BTCs. EGFR mutation was an independent prognostic marker in patients with BTCs in addition to tumor stage and tumor differentiation. No simultaneous EGFR and KRAS mutations in BTC were found in our study. EGFR and KRAS mutations should be evaluated when tailoring molecular targeted therapy to patients with BTCs.
Loss of Immunolabeling of Kruppel Like Factor 10 is Associated with Advanced Stage and Rapid Progression of Pancreatic Cancer

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Introduction

Pancreatic cancer is one of the most malignant tumors worldwide. With improved local-regional disease control by surgery and chemoradiation, liver metastases become the dominant form of tumor recurrence and occur in 25% to 53% of patients after potentially curative combined-modality treatment. On the other hand, rapid autopsy study reveals 8 to 15% of pancreatic cancer patients die from local destructive disease without distant metastasis. It is urgent to develop biomarkers to differentiate among patients with heterogeneous pattern of progression.

Deregulation of transforming growth factor-β (TGF-β) signaling pathways is one of the well recognized pathways reported to play significant role in pancreatic carcinogenesis. Kruppel Like Factor 10 (KLF10) is an early response gene that is turned on at the initial stage of the TGF-β signaling pathway. Previous studies have shown a close relationship between the transcription or translational level of KLF10 and various cancers, including breast, prostate, colorectal and pancreatic tumors. This study is conducted to determine patients’ outcome according to the expression of KLF10 of pancreatic cancer.

Patients And Methods

Detailed clinicopathologic and outcome data for a total of 95 patients with a diagnosis of pancreatic ductal adenocarcinoma were obtained from two teaching hospitals.

Immunohistochemical staining of KLF10 was done using methodology that has been previously described. Monoclonal antibody of KLF10 was kindly provided by Dr. HS Chang. Staining was assessed by two independent pathologists. Expression of KLF10 was quantified using a visual grading system based on the extent the intensity of staining. Correlation of KLF10 and clinicopathologic and outcome parameters was done using statistical software.

Results

Immunohistochemical study of KLF10 was done in 95 patients of pancreatic adenocarcinoma. Forty three were female. Median age was 62 ± 12 years. Sixty-six tumors were located
over pancreatic head. There were 8, 25, 32, 13 and 17 patients of stage I, IIa, IIb, III, IV respectively.

KLF10 expressed majorly within cytoplasm of normal pancreatic ductal, acinar cells and pancreatic cancer cells. Low expression of KLF10 correlated significantly with advanced stage (65.2% vs 89.7%, p = 0.01) and distant metastasis (67.9% vs 94.1%, p = 0.03). Univariate analysis revealed baseline CA19-9 level, stage, surgery and KLF10 predicted disease progression; while tumor location, stage, surgery and KLF10 correlated with overall survival. Multivariate analysis showed distant metastasis and loss of immunolabelling of KLF10 were two independent prognostic factors for rapid progression and shorter survival.

**Conclusions**

KLF10 in pancreatic cancer may represent a valuable prognostic factor as well as an attractive target for therapeutic purpose.

(The study was supported by grants of Department of Health (DOH99-TD-C-111-004, Taiwan, R.O.C.)
Identification and Characterization of Highly Selective Inhibitors of Cathepsin S Protease as Potential Therapeutic Agents Against the Migration and Invasion of Pancreatic Cancer Cells

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Background
Cathepsin S (CTSS) is a vital cellular protease required for tumor invasion and metastasis. This proteolytic enzyme is localized primarily in lysosomes but can be translocated to the cell surface or secreted into the extracellular milieu to degrade ECM (extracellular matrix) components. Unlike other members of the cathepsin family, CTSS is unique as it is highly active and stable at neutral pH, properties compatible with its distinct role in mediating ECM degradation and cell invasion. Consistent with these characteristics, an increase in CTSS expression is often found to be associated with tumor progression and adverse outcome. Here, we attempted to design and synthesize a variety of small molecules in hope to identify highly selective CTSS inhibitors as potential therapeutic agents against the invasion and metastasis of pancreatic cancer.

Methods
Compounds with inhibition higher than 95% against CTSS were characterized in details to determine their \( K_i \) values followed by a series of cytotoxicity assays, migration/invasion assays, and fibronectin/E-cadherin degradation assays. Compounds with or without any possible cross-inhibition against other cathepsin proteases were also clarified, and their suppressing effects on the survival and tumor metastasis were examined using the zebrafish model.

Results
Most of the synthetic compounds show no obvious cytotoxicity to any of the selected normal and cancerous pancreatic cell lines even at a concentration as high as 10 µM. Among these candidates, compound CCL-RJW-58 was identified to be a highly selective inhibitor against CTSS. Results from ECM degradation assay further revealed that CCL-RJW-58 can repress the cleavage of fibronectin and E-cadherin by CTSS in a dose-dependent manner, and therefore help to suppress the migration and invasion of pancreatic cancer cells.

Conclusions
We conclude that, by directly inhibiting cancer-related CTSS protease, these newly synthesized small molecules in particular compound CCL-RJW-58 can significantly suppress fibronectin/E-cadherin degradation and consequently reduce pancreatic tumor cell migration and invasion.

(The study was supported by grants of Department of Health (DOH99-TD-C-111-004, Taiwan, R.O.C.)
**Activation of Nrf2/AKR1C Axis Determine Chemoresistance in Gastric and Pancreatic Carcinomas**

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**Background**

We have previously established an oxaliplatin-resistant line, S3, from human gastric carcinoma TSGH cells, and found that overexpression of copper efflux transporter ATP7A and enhancement of DNA repair capacity response to oxaliplatin resistance in S3 cells ([British Journal of Cancer](97:334, 2007)). In this study, we applied global analysis using gene array technology to further elucidate the mechanisms and molecular targets of acquired oxaliplatin-resistance.

**Methods**

Gene array was used to screen the differential genes. Growth inhibition was determined using the methylene blue staining method and MTT assay. Western blot analysis, quantitative real-time PCR (qRT-PCR), and RNA interference method were used to reveal molecular events of drug resistance in this study.

**Results**

By microarray analysis, expression of 26 genes was found to be upregulated in oxaliplatin-resistant S3 cells. Among them, increment of mRNA level of the aldo-keto reductase (AKR) 1C subfamily form 9 – 16 fold was noted in the resistant line as compared to its parental cells. After validation process by qRT-PCR and Western blot analysis, the genes AKR1C1, AKR1C2 and AKR1C3 were positively validated. Since AKR1Cs are the target genes of NF-E2-related factor 2 (Nrf2), we therefore investigated the expression of Nrf2. The results demonstrated that the expression level of Nrf2 protein was significant increased in S3 as compared to TSGH. Knockdown Nrf2 not only reduces the mRNA and protein level of AKR1C1, 2, and 3, but also increases platinum sensitivity in S3 cells. In addition to oxaliplatin resistance, it is interesting to note that increased Nrf2/AKR1C axis also contributed to gemcitabine-driven drug resistance in pancreatic carcinomas.

**Conclusions**

Taken together, we demonstrated for the first time that oxaliplatin- and gemcitabine activate the Nrf2/ARE/AKR1C pathway which in turn induces cytoprotective effect and modulate chemosensitivity of gastric and pancreatic carcinoma, respectively. Therefore, we propose that targeting Nrf2 may be able to reverse chemoresistance in chemo-refractory gastrointestinal cancers.

(The study was supported by grants of Department of Health (DOH99-TD-C-111-004, Taiwan, R.O.C.)
A Core Transcriptional Program Associated with Structural Organization Predicts Prognosis of Pancreatic Cancer

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**Background**

The degree of structural organization is a key element of the pathologic grading systems of human glandular cancers such as pancreatic ductal adenocarcinoma (PDAC), and the associated molecular changes may associate with tumor behaviors whereby permit prediction of clinical outcome.

**Methods**

We used an *in vivo*-like organotypic culture model to mimic the tissue architectural transition of pancreatic ductal epithelial cells (HPDEs) or PDAC cells from unorganized cell monolayers, cell clusters to differentiated glandular units or tumor spheroids and profiled the associated transcriptomal changes.

**Results**

The transcriptomal changes associated with glandular morphogenesis strongly associate with overall survival of the patients with operable PDAC. In contrast, the DEGs related to the formation of unorganized tumor spheroids did not have prognostic significance. Using this strategy we identified a core structure-associated prognosis signature (SAPS) that strongly predicts recurrence-free or overall survival (*P* < 0.001). Importantly, the SAPS predicts pancreatic cancer survival independent of standard clinicopathological variables and performs excellently in the prognostic prediction of other glandular malignancies, including prostate and breast cancers.

**Conclusions**

By exploiting the distinct contribution of the structural differentiation program to tumor pathology we identified a novel, robust and biologically relevant genomic biomarker of PDAC.

(Supported by National Health Research Institutes (NHRI) Intramural Research Program CA-099-PP-19 and Department of Health (DOH) of Taiwan DOH99-TD-C-111-004 to K.K.T.)
High-resolution Synchrotron Radiological Profiling of Tumor Microangiogenesis in Pancreatic Cancer

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Background
Synchrotron x-ray imaging allows a high resolution (< 5 µm) and three dimensional profiling of the tissue microvasculature. The spatial patterns of early tumor neovascularization may correlate with subsequent tumor behaviors and malignant progression; however, this possibility has not been adequately addressed due to the lack of suitable and quantitative imaging methods.

Methods
We co-implanted pancreatic carcinoma PANC1 cells and ionizing radiation (IR)-activated pancreatic stromal stellate cells (aPSCs) or the mock-irradiated cells orthotopically into the pancreatic parenchyma of NOD-SCID mice. The images of microvessels were then taken at an early time point (3 days) following tumor transplantation.

Results
Numerous distorted and irregularly shaped microvessels formed surrounding the PANC1-PSC inoculation sites while the vascular pattern of the control tumors did not differ significantly from that of the normal pancreatic parenchyma. Image profiling algorithms identified that the aberrant microvasculature of the PANC1-aPSC xenografts underwent more frequent branching and looping per branch. Moreover, the tumor formed within the reactive stroma grew faster than the control tumors.

Conclusions
Our data suggest that synchrotron x-ray microangiography is a valid and sensitive tool for profiling early processes of tumor neovascularization and which may serve to predict subsequent tumor progression in pancreatic adenocarcinoma. Further studies are needed to more firmly establish the causality and the clinical relevance of this finding.

(Supported by Department of Health (DOH) of Taiwan DOH99-TD-C-111-004 to K.K.T.)
Anticancer Activities of Furanopyrimidine Aurora Kinase Inhibitors

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Background
Aurora kinases are serine/threonine protein kinases that regulate multiple processes in cell division, leading to high-fidelity progression through mitosis. They are essential regulators required for chromosome alignment, segregation, and cytokinesis. Up-regulated levels of aurora kinase RNA and proteins have been observed in human cancers. Targeted inhibition on aurora kinases has been an active anticancer drug discovery strategy. We discovered several novel furanopyrimidines with aurora kinase inhibitory activities and examined their in vitro cytotoxic activities and in vivo antitumor activities against pancreatic tumors in nude mice.

Methods
Novel furanopyrimidines were measured for inhibitory activities against aurora kinases A and B using an enzymatic reaction. Compounds mixed with GST-Aurora fusion protein, ATP and the enzyme substrate were allowed for reaction at 37°C for 90 min. Kinase-Glo® Plus was added in for an incubation at 25°C for 20 min and the remaining ATP in the reaction solution was quantified by measuring the luminescence using Ultra-Glo™ rLuciferase in the presence of luciferin. Human cancer cells were in vitro cultured and treated with furanopyrimidines in various concentrations. The cancer cell proliferative activity was measured by using the colorimetric MTS/PMS assay and the concentration (IC₅₀) inhibiting 50% of the cancer cell proliferation was estimated. In vivo antitumor activities of intravenously administered furanopyrimidines were evaluated in male nude mice subcutaneously bearing with human pancreatic and colorectal tumors.

Results
Newly synthesized novel furanopyrimidines showed either selective or non-selective inhibition profiles against aurora kinase A verses B. The compounds were in vitro cytotoxic against a panel of human cancer cells including pancreatic cancer MIA Paca-2 cells. Administered intravenously to the nude mice subcutaneously implanted with MIA Paca-2 tumors in a regimen of 50 mg/kg/day (5 days/week for 2 weeks), a furanopyrimidine lead suppressed 93% of the tumor growth compared to vehicle control. A dose-dependent manner of the tumor growth inhibition was observed. In addition, the drug lead also dose-dependently suppressed the growth of human colorectal HCT-116 tumors subcutaneously xenografted in nude mice.

Conclusions
Novel aurora kinase inhibitory furanopyrimidines were discovered. Selective compounds demonstrated in vitro and in vivo anticancer activities against human pancreatic and colorectal tumors.
Escalation the Radiation Dose for Inoperable Pancreatic Cancer by Tomotherapy -- Preliminary Study of One Institutional Experience

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Background
The mainstream treatment of pancreatic cancer is surgical intervention. But more than half pancreatic cancer patients are not suitable for operation. Combined chemotherapy and radiotherapy or radiotherapy alone is the alternative choice for inoperable patients. However, the radiation dose of previous literature reports is almost not more than 54 Gy because the traditional radiotherapy technique which related to adjacent organs damage limited the dose escalation. The newly radiotherapy technique, Tomotherapy, could deliver higher dose than before without more damage to adjacent organs. The higher radiation dose may result in effect of tumor control and over-all survival.

Methods
We conducted fourteen inoperable pancreatic patients who received radiotherapy by Tomotherapy from July, 2007 to July, 2010. The stages of these patients are IIA-IV. The radiation dose to pancreatic tumor bed is ranged from 64.8 Gy to 72 Gy.

Results
We estimate the over-all survival rate by Kaplan-Meier method. The average radiation dose to pancreatic tumor is 68.5 Gy. Nine of them received concurrent chemotherapy, mainly by single agent such as gemcitabine 600-800 mg per square meter. The median survival time is 16 months (4.8-27.2 months, 95% CI) and the average survival time is 20 months (11.6-28.5 months, 95% CI). One-year survival rate is 65.3%. Two-year and three-year survival rate is 39.2%, equally. Only two patients suffered from gastric or duodenal ulcers and got recovery after medication.

Conclusions
In our preliminary study, the newly radiotherapy technique, Tomotherapy, could result in promising over-all survival rate by escalation the tumor dose over than 64.8 Gy for inoperable pancreatic cancer patients without significant adjacent organ damage. Modern radiotherapy strategies to increase over-all survival in inoperable pancreatic cancer patients warrant further investigation.
Chemotherapy with Gemcitabine plus High-dose 5-Fluorouracil/Leucovorin Continuous Infusion for Patients with Metastatic or Unresectable Pancreatic Cancer -- Taipei TCGH Experience

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Background
To access the activity and toxicity of chemotherapy with gemcitabine plus high-dose 5-fluorouracil/leucovorin continuous infusion for patients with metastatic or unresectable pancreatic cancer.

Materials And Methods
In this retrospective analysis, patients treated with first-line gemcitabine plus high-dose 5-fluorouracil/leucovorin continuous infusion were included. Gemcitabine 1000 mg/m² was administered intravenously for 30 minutes on days 1 and 15 of each 28-day cycle. 5-Fluorouracil 3000 mg/m² and leucovorin 150 mg/m² continuous infusion for 48 hours were administered after gemcitabine. Patients were treated till disease progression or severe toxicity necessitated earlier discontinuation. Computed tomography was used to evaluate the response every 2-3 cycles of chemotherapy.

Results
From August 1, 2005 to June 30, 2010, 14 patients were enrolled. Five (35.7%) were female. Patient age ranged from 50-75 years (median age, 67 years). The location of primary tumor was over head/tail for 8/6 cases respectively. Five cases underwent previous Whipple’s operation. ECOG performance status for 0/1/2/3 was 1/8/4/1 cases respectively. The administered cycles ranged from 0.5-4 cycles (median 1.5 cycles). Due to rapid progression of disease, only 7 patients could be evaluated for response. Only one patient achieved a partial response and the other 6 patients disease progressed. The overall response rate was 14.3% (1/7). The median time to disease progression was 2.1 months (ranged from 1-8.4 months). The median survival was 4.1 months (ranged from 0.8-21.5 months). Grade 3 anemia and thrombocytopenia developed in only 1 patient (7.1%). Grade 2 leukopenia developed in 1 case (7.1%). Grade 3 infection and grade 2 vomiting developed in 2 cases (14.3%) and 1 case (7.1%). No grade 3-4 leukopenia, febrile neutropenia or treatment related death was observed. Most of the toxicities were easily manageable.

Conclusions
Gemcitabine and 5-fluorouracil have been demonstrated to possess proven activity in pancreatic cancer with a low toxicity profile. However, the outcome of treatment is still poor. Although some patients may benefit from the treatment, other dosing regimens and novel agents should be explored in this setting.
Robotic Pancreaticoduodenectomy for Pancreatic Head Cancer -- Preliminary Results

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Background
Despite the recent wide application of minimally invasive surgery in the GI malignancy, laparoscopic pancreaticoduodenectomy (PD) has been reported only rarely. To assess the safety, feasibility and clinical results of robotic PD, we reported our recent attempt of robotic PD with da Vinci Si robotic surgical system (Intuitive Surgical Corporation, Palo Alto, CA, USA).

Brief History
We presented a 48 y/o male patient who was admitted to the GI ward with chief complaint of tea colored urine. Further evaluation including abdominal sonography, computed tomography (CT) and ERCP revealed pancreatic head tumor with obstructive jaundice which was potential resectable. Then robotic pancreaticoduodenectomy was suggested.

Methods
Under general anesthesia, the patient was placed in reverse Trendelenberg position. Four arm technique was used. Another one assistant port was arranged in the LLQ of abdomen. After through intraperitoneal examination, the dissection began from the lymph node dissection along the common hepatic artery. Hepatic hilum was dissected and the common bile duct was divided. Pylorus and pancreatic neck were transected also during the next phase. The third arm of the robotic system was used for the medial traction of the pancreatic stump. The unciness process of the pancreas was freed from the SMA. The retroperitoneal soft tissue was cleared. After that, upper jejunum was divided through a 5 cm midline laparotomy and the specimen was removed. The pancreaticojejunostomy and the hepaticojejunostomy were done under the robotic system. Finally, the gastrojejunostomy was completed through the midline wound.

Results
The patient was sent back to the ordinary ward after surgery which last 870 min. All drain fluids remained serosanguinous during subsequent postOP course. Flatus passage occurred on POD 3 and the patient resumed oral intake on POD 6. After removing all drain tubes except the pancreatic duct stent, the patient was discharge home on POD 13 without postOP complication.

Conclusions
Our preliminary experience of robotic pancreaticoduodenectomy using da Vinci Si robotic surgical system showed potential clinical benefits. The physical activity recovery seemed also quicker than that in our open group. However, large control study is necessary to demonstrate the true benefits.
Triplet Induction Chemotherapy Followed by Concomitant Chemoradiotherapy in Patients with Locally Advanced Pancreatic Cancer: A Taiwan Cooperative Oncology Group Phase II Study

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Purpose
To evaluate the therapeutic efficacy of 3-months triplet induction chemotherapy (ICT) followed by concomitant chemoradiotherapy (CCRT) in patients with locally advanced pancreatic cancer (LAPC).

Methods
Chemo-naïve patients with measurable, histologically confirmed LAPC were eligible. The ICT consisted of biweekly 800 mg/m² gemcitabine at fixed-dose rate (10 mg/m²/min) infusion, followed by 85 mg/m² oxaliplatin and 48-hour infusion of 5-FU/leucovorin 3,000/150 mg/m² for 6 cycles. Patients without disease progression 4 weeks after ICT would receive weekly 400 mg/m² gemcitabine and 5,040 cGy radiation in 28 fractions. After CCRT, patients were subjected for surgical intervention and/or maintenance chemotherapy until progression or intolerable toxicity.

Results
Between December 2004 and August 2008, 50 patients were enrolled. The best response after ICT were partial response (PR) in 9, stable disease (SD) in 26 and progressive disease (PD) or not evaluable in 15. Among the former 35 patients, two had disease progression before CCRT and three declined to have CCRT. Of the 30 patients receiving CCRT, additional four and one patients achieved PR at the end of CCRT and during maintenance chemotherapy, respectively. On intent-to-treat (ITT) analysis, the overall best response was PR in 14 patients and SD in 21.
The overall response rate and disease control rate were 28% (95% confidence interval (CI), 16.2-42.5%) and 70% (95% CI, 44.4-99.2%), respectively. The median time-to-progression and overall survival of ITT population was 9.3 [95% CI, 5.8-12.8] and 14.5 (95% CI, 11.9-17.1) months, respectively. One- and two-year survival rates were 68% (95% CI, 55.1-80.9%) and 20.6% (95% CI, 8.7-32.5%), respectively. Neutropenia was the most common grade 3-4 toxicities of both ICT and CCRT with a frequency of 28% and 26.7%, respectively. Significant sensory neuropathy occurred in nine (18%) patients.

Conclusions

Three-months of triplet ICT followed by gemcitabine-based CCRT is feasible, moderate active and associated with encouraging survival in LAPC patients.

Hui-Ju Ch’ang and Yu-Lin Lin contributed equally to the manuscript. (The study was supported by grants of Department of Health (DOH99-TD-C-111-004, Taiwan, R.O.C.)
The Effectiveness of Oral Care Package on Increase Self-care Ability of Oral Care on Reducing Mucositis and Body Weight Loss of Nasopharyngeal Cancer (NPC) Patients Who were Receiving Chemotherapy and Radiotherapy

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Background

For achieving a better treatment outcome of NPC patients, concurrent chemo-radiotherapy (CCRT) has become the mainstay treatment. Many patients develop anxiety and depression due to side effects caused by CCRT. We aimed to minimize mucositis by providing patient an oral care packet (OCP) in which nursing guidance of oral lesions and diet instruction were contained.

Methods

A quasi-experimental design was adopted in this study. NPC patients who received CCRT were divided into two groups. The control group involved 112 patients who received conventional nursing care during CCRT in 2002. The experimental group included 91 patients who received a special nursing intervention, i.e. OCP. The major outcomes were the change of oral mucositis severity and body weight loss before and after CCRT. The necessity of other interventions for palliation was evaluated as well.

Results

In the control group 37.5% patients did not receive nasogastric intubation while it was 25% in the experimental group. None in the experimental group developed Grade 2 or more oral mucositis in the first week. The proportion of patients who did not have Grade III or more in the 3rd, 4th, and 5th weeks are 34.2%, 47.2%, 54.7% and 4.7%, 9.3%, 10.6%, in the control and experimental group, respectively. The mean body weight loss in the experimental and control group were 3.99 kg and 4.53 kg, respectively. All of these results indicated improvement of body weight loss and oral mucositis after intervention with the walking kit.

Conclusions

Our study demonstrated that an OCP can facilitate patients to keep good oral hygiene, have adequate water intake and maintain the wetness of mucosa. Aggressive and persistent nursing care is important for helping NPC patients to pass through the whole treatment course by providing associated information, education, psychological support, and care.
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