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PANCREAS CLUB

Summary of at the 45th Annual Pancreas Club Meeting Proceedings

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Abstract
Background The 45th meeting of the Pancreas Club was held on 5 and 6 May 2011 at the Robert H. Lurie Medical Research Center in Chicago, IL. An outstanding program of 47 oral presentations (Table 1) and 137 poster presentations was chosen from a record number of submitted abstracts. Ten posters each day were chosen for presentation as part of the Professor Rounds portion of the formal poster viewing program. Summaries of the oral presentations are provided; published work is referenced. Full abstracts are available on the Pancreas Club website: http://pancreasclub.com.

Keywords Pancreas Club

Session I: Cancer Clinical/IPMN/Steatosis

The first paper of this session (1) Pancreatic Cyst Fluid miRNA 21 and 221 Predict Invasive Cancer presented work from UCLA that endeavored to improve our ability to predict the biologic nature of incidentally discovered pancreatic cysts using micro RNA (miRNA) isolated from aspirates of the cysts. Based on experience reported in the literature and microarray performed on 44 resected pancreatic cancers, the authors identifie\d two miRNAs that had increased expression in adenocarcinoma: miRNA 21 and miRNA 221. They then assessed pancreatic fluid from aspirates of 22 resected pancreatic cysts and found increased expression of miRNA 21 in both premalignant and malignant cysts relative to that in serous cystadenomas. Two interesting questions raised in the discussion addressed the possibility of combining miRNA with cyst carcinoembryonic antigen (CEA) level measurement to enhance the ability to predict the potential of the tumor, and whether any trend differentiating dysplasia from carcinoma in situ was observed (the authors reported two samples of high grade dysplasia but no identifiable differences in miRNA levels relative to pancreatic cancers).

Paper (2) Should We Do EUS/FNA on Patients with Pancreatic Cysts? The Incremental Benefit of EUS over CT/MRI for Prediction of Cystic Neoplasms presented work from Johns Hopkins evaluating the benefit of endoscopic ultrasound (EUS) with fine needle aspiration (FNA) over CT or MRI axial imaging alone in the diagnosis of pancreatic cysts. The authors reviewed 130 pancreatic cysts that were evaluated with axial imaging and then EUS aspiration prior to resection. They found that CT and EUS had similar abilities to identify mural nodules but that EUS–FNA with assessment of cyst morphology, cyst fluid cytology, cyst fluid CEA, and amylase was more likely to identify a cyst as neoplastic than either CT (87% vs 56%) or MRI (87% vs 50%) alone. Patients with inadequate cellularity on aspiration cytology were included in the analysis; the authors used size and tumor markers to predict the presence of a neoplastic cyst. The relevance of mural nodules identified on CT and EUS was highlighted: 35% to 40% of the time these nodules represent cancer or dysplastic nodules in the authors' experience.

The third paper in this session (3) The Fate of the Pancreatic Remnant After Resection for Intraductal Pancreatic Mucinous NeoplasM (IPMN) presented work from the Virginia Mason Clinic in Seattle evaluating the pancreatic remnant following resection of a primary IPMN. The authors followed up 189 patients who had resections for IPMN with no lesions

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Table 1 Summary of the 45th Annual Pancreas Club Oral Program

Paper #	Title	Institution
Session I: Cancer Clinical/IPMN/Steatosis		
1	Pancreatic Cyst Fluid miRNA 21 and 221 Predict Invasive Cancer	UCLA
2	Should We Do EUS/FNA on Patients with Pancreatic Cysts? The Incremental Benefit of EUS over CT/MRI for Prediction of Cystic Neoplasms	Johns Hopkins University
3	Fate of the Pancreatic Remnant After Resection for Intraductal Papillary Mucinous Neoplasm	Virginia Mason Medical Center
4	Laparoscopic Versus Open Pancreaticoduodenectomy for Pancreatic Ductal Adenocarcinoma: Assessement of the Adequacy of Oncologic Resection	Mayo Clinic
5	Classifying the Severity of Acute Pancreatitis: the Way Forward	University of Auckland, New Zealand
6	Abdominal Fat Distribution Influences Survival Following Pancreatectomy for Pancreatic Ductal Adenocarcinoma (PDAC)	MD Anderson Cancer Center
7	Outcomes of Robotic-Assisted Minimally Invasive Pancreaticoduodenectomy: Multicenter Analysis of 103 Cases	University of Pittsburgh and other centers
8	Predicting Survival in Pancreatic Cancer: a Comparison of Lymph Node Ratio with Number of Metastatic Nodes	Massachusetts General Hospital
9	Method of Splenic Preservation During Distal Pancreatectomy Impacts Fistula Rates	University of Wisconsin and other centers
Session II: Cancer Basic and Translational		
10	Neoadjuvant Vaccine-Based Immunotherapy Inhibits Tumor Initiation of Pancreatic Cancer Stem Cells	Johns Hopkins University
11	CK20 Expression Affects the Prognosis of Patients with Cancer of the Ampulla of Vater After Surgical Excision: Results of the Analysis on 72 Cases Consecutively Observed	Bio-Medico University, Turin and Rome, Italy
12	Whole Genomic Exome Sequencing of Pancreatic Neuroendocrine Tumors Reveals Prognostic Markers and Potential Novel Therapies	Johns Hopkins University
13	Addition of Algenpantucel-L Immunotherapy to Standard Adjuvant Therapy May Improve Overall Survival (OS) and Disease-Free Survival (DFS) in Resected Pancreas Cancer Patients	Case Western University and other centers
14	Fluorophore-Conjugated Anti-CEA Antibodies for Rapid Staging of Metastatic Pancreatic Cancer Using Fluorescence Laparoscopy	University of California San Diego
15	Accuracy of the National Surgical Quality Improvement Project for Modeling Complex Pancreatic Operations	Henry Ford Hospital
16	Adding Days Spent in Readmission to the Initial Post Operative Length of Stay Limits the Perceived Benefit of Laparoscopic Distal Pancreatectomy When Compared to Open Distal Pancreatectomy	Evanston North Shore and University of Chicago
Session III: Cancer Basic		
17	A Synthetic Lethal Approach to Targeting Multipe Tumor Promoting-Pathways In Vivo: Nanotherapeutic Silencing of HuR	Thomas Jefferson University
18	HuR Regulates Death Receptor-5 (DR5)-Targeted Treatment of Pancreatic Cancer Cells	Thomas Jefferson University
19	MT1-MMP Cooperates with KRAS G12D to Promote Pancreatic Fibrosis Through TGF-β Activation of Pancreatic Stellate Cells	Northwestern University
20	Targeting ErbB Receptor-Mediated Stromal-Tumor Interaction in Pancreatic Ductal Adenocarcinoma (PDAC)	University of Alabama Birmingham
21	Hedgehog Signaling is Required for Tumor Stroma Maintenance and Tumor Angiogenesis in Pancreatic Cancer	Massachusetts General Hospital
22	Even Small Pancreatic Endocrine Neoplasms Have Lymph Node Metastasis	Johns Hopkins University
23	Serous Cystadenomas of the Pancreas: Study of Potential Factors Influencing Tumor Growth	University of Verona, Italy
24	Body Mass Index is Associated with Morbidity After Pancreatic Resection: Results from the ACS-NSQIP	University of Wisconsin
25	Preoperative CT Scan Can Predict Incidence and Severity of Pancreatic Fistula After Pancreaticoduodenectomy	University of Paris VII
Session IV: Pancreatitis		
26	Surgical Management of the Late Sequellae in Survivors of an Episode of Acute Necrotizing Pancreatitis (ANP)	Vanderbilt University
27	De Novo Expression of Urocortin1 in Pancreatic Acinar Cells During Acute Pancreatitis. Antagonism of Corticotropin-Releasing Factor Receptor 2 Exacerbates Inflammation	University of California San Francisco
28	Splenic Preserving Distal Pancreatectomy: Does Vessel Preservation Matter?	Indiana University
29	Pancreatic Cystic Lesions: Assessing Quality of Life	University of Massachusetts
30		

Table 1 (continued)

Paper #	Title	Institution
	Management of Pancreatic Fluid Collections (PFCS): a Changing of the Guard from Surgery to Endoscopy	University of Alabama, Birmingham
31	Pancreatic Surgery at the University Hospital of Rostock: Results of 265 Consecutive Pancreatic Resections	University of Rostock, Germany
Session V: Cancer Basic/Mechanisms of Tumorogenesis and Metastasis		
32	Identification of a Metastatic-Protective Stromal Factor in Pancreatic Cancer	MD Anderson Cancer Center
33	Direct Xenograft Models Recapitulate Molecular Features of Metastasis in Pancreatic Ductal Adenocarcinoma (PDAC)	MD Anderson Cancer Center
34	ALDH Activity Defines an Enhanced Tumor-Initiating Cell Population Relative to CD133 Expression in Human Pancreatic Adenocarcinoma	MD Anderson Cancer Center
35	Receptor For Advanced Glycation End-Products (RAGE) Knockout Delays the Progression of Pancreatic Intraepithelial Neoplasia (PANIN) in a Murine Model of KRAS Driven Pancreatic Carcinogenesis	University of Pittsburgh
36	GLI Activation Is Required for Pancreatic Tumor Formation In Vivo	University of Massachusetts
37	Nicotine Regulates DNA-Binding Protein Inhibitor (ID1) Through a SRC-Dependent Pathway Promoting Tumorigenic Properties and Chemoresistance in Pancreatic Adenocarcinoma	Moffitt Cancer Center
38	Identification of a Common Molecular Phenotype After Cytotoxic Therapy for Pancreatic Adenocarcinoma	MD Anderson Cancer Center
39	Casein Kinase-2 Downregulation: a Novel Therapeutic Strategy for Pancreatobiliary Tumors	University of Minnesota
Session VI: Cancer Clinical/Predictors of Outcomes and Technical Issues		
40	Clinical Predictors of Failure to Undergo Pancreatectomy Following Neoadjuvant Therapy in Patients with Potentially Resectable Pancreatic Cancer	MD Anderson Cancer Center
41	Prognostic Significance of Histologic and Precursor Epithelial Subtypes of Invasive Intraductal Papillary Mucinous Neoplasm: Improved Survival Compared to Pancreatic Ductal Adenocarcinoma are Limited to Indolent Colloid and Oncocytic Types	Massachusetts General Hospital
42	Human Equilibrative Nucleoside Transporter 1 Expression is a Strong Independent Prognostic Factor in T3/T4 Pancreatic Cancer Patients Treated with Preoperative Gemcitabine-Based Chemoradiotherapy	Mie University, Japan
43	Concurrent Analysis of Dihydropyrimidine Dehydrogenase and Human Equilibrative Nucleoside Transporter 1 Expression Predicts Survival Following Adjuvant Gemcitabine Plus S-1 Chemotherapy for Resected Pancreatic Adenocarcinoma	Hiroshima University, Japan
44	A Root Cause Analysis of Mortality Following Major Pancreatectomy	Beth Israel Deaconess and other centers
45	Postresection Diabetes after Distal Pancreatectomy: Incidence and Risk Factors	Mayo Clinic
46	Comprehensive Perioperative Geriatric Assessments May Predict Surgical Outcomes in a Prospective Study of Older Patients Undergoing Pancreaticoduodenectomy	University of Chicago
47	Is It Worth Looking? Abdominal Imaging After Pancreatic Cancer Resection: a National Study	University of Massachusetts

identifiable in the pancreatic remnant at the time of the initial procedure. Over 40 months of follow-up with annual axial imaging, 17 new lesions were identified. Twelve of these were side branch IPMN and were observed. Five underwent resection with pathologically proved two invasive cancers, one carcinoma in situ, and two benign adenomas. The overall rate of recurrence was 8% over 40 months of follow-up. There were no identifiable risk factors for recurrence in demographics, procedure type, duct location, histology, or original margin status. Two points were raised in discussion: the three patients who developed main duct IPMN on follow-up all had main duct IMPN resected primarily; and the fiscal responsibility of annual axial imaging in these patients was challenged.

The next paper (4) Laparoscopic Versus Open Pancreaticoduodenectomy (PD) for Pancreatic Ductal Adenocarcinoma: Assessment of the Adequacy of Oncologic Resection from the Mayo Clinic compared 52 laparoscopic PD to 129 open PD done for pancreatic cancer between 2007 and 2010. The laparoscopic group demonstrated a shorter postoperative length of stay (6 vs 10 days) and a lower estimated blood loss (400 vs 600 mL) than did the open PD group. Tumor size, incidence of vascular resection, operative time, rates of cancer recurrence, and 1- and 2-year survival rates were the same for laparoscopic and open PD. Points of discussion included the similar rates of delayed gastric emptying and fistula between the two groups, similarity of surgeons performing open PD, improvement in the rate at which patients return to normal activity (data in acquisition), clarification of the types of vascular resection (one segmental vein resection with an interposition with left renal vein graft and 11 were tangential vein resection), and inclusion of patients converted from laparoscopic to open procedure in the laparoscopic cohort as intention to treat.

The next paper (5) Classifying the Severity of Acute Pancreatitis: the Way Forward was identified as a seminal paper as selected by the members of the program committee. This work from the University of Auckland, New Zealand focused on improving methods for classifying severe acute pancreatitis.[1,2] The authors performed a meta-analysis of 14 studies including a total of 1,478 patients with severe acute pancreatitis and identified both multisystem organ failure and infected necrosis as individual contributors to risk of mortality. They also determined that the combination of multisystem organ failure and infected necrosis doubles the risk of mortality over those with one or the other risk factor. They then proposed a four-tiered risk stratification based on the presence or absence of multisystem organ failure and infected necrosis. The discussion highlighted in-progress work to validate this scoring system.

The sixth paper of the session (6) Abdominal Fat Distribution Influences Survival Following Pancreatectomy for Pancreatic Ductal Adenocarcinoma (PDAC) presented work from the MD Anderson Cancer Center and reviewed 215 patients undergoing pancreatectomy from 2001 to 2006. The investigators calculated visceral and subcutaneous adipose tissue areas based on axial imaging at the L3/L4 level. Patients with high levels of either visceral or subcutaneous fat were found to have decreased rates of overall survival. There were several interesting questions raised in the discussion. Several discussants asked for more of a comparison between the groups with regard to rates of postoperative complications, margins, and lymph node status; the authors found no notable differences in postoperative complication rates between patients with high and low visceral or subcutaneous fat compositions. The estimated operative blood loss was higher for patients with high levels of visceral fat but the percentage R0 resection and lymph node retrieval were similar. The fat distribution was determined using the first CT imaging (prior to any neoadjuvant therapy) and survival was disease specific.

The seventh paper in the session (7) Outcomes of Robotic-Assisted Minimally Invasive Pancreaticoduodenectomy: Multicenter Analysis of 103 Cases presented a multi-institutional review of 103 minimally invasive pancreaticoduodenectomies done with robotic assistance from the groups at the University of Pittsburg, the Mayo Clinic, The Cleveland Clinic, and University of Pisa. Seventy-six patients had a diagnosis of cancer. The mean operative time was 8.5 h. There were 11 conversions to open procedures. Eighteen patients developed pancreatic fistulas and 15 experienced delayed gastric emptying. The 90-day readmission rate was 22%. The conclusion of the authors was that this was a safe procedure that can replicate outcomes in large experiences with open pancreaticoduodenectomy. One interesting question raised in discussion was regarding the additional cost of the procedure. The authors answered that the exact marginal cost was not known but thought to be an additional $4,000 USD.

The eighth paper in the session (8) Predicting Survival in Pancreatic Cancer: a Comparison of Lymph Node Ratio with Number of Metastatic Nodes presented work from the Massachusetts General Hospital and used the SEER database and the MGH pancreatic data set to compare the value of lymph node ratio to the number of positive nodes identified in predicting outcome following pancreatectomy for pancreatic cancer. The authors found that among patients included in the SEER database, lymph node ratio was effective at predicting outcome even when relatively few (<5) nodes were analyzed. In contrast, the absolute number of positive nodes did not predict outcome when fewer than ten nodes were analyzed.

The final paper in the session (9) Method of Splenic Preservation During Distal Pancreatectomy Impacts Fistula Rates presented work from a multi-institutional consortium (eight institutions) and examined the impact of the method of splenic preservation on pancreatic fistula rates following distal pancreatectomy. There were 112 patients included in the analysis. Seventy-one had splenic-preserving distal pancreatectomy with preservation of the splenic vein and 41 had splenic-preserving distal pancreatectomy with excision of the splenic vein. Those undergoing vein preservation had statistically higher rates of pancreatic fistula compared to those with vein excision (36% vs 12%). This finding held for the rate of clinically significant fistulas and overall fistula rate. The authors performed a limited multivariate regression in effort to control for other variables that might influence fistula rate, and in their model, the treatment of the vein was a relevant predictor of fistula rate. There was a spirited discussion following this paper with several discussants identifying the methodology of the multi-insitutional retrospective review as making this determination of the relation between fistula rate and vein preservation almost impossible. Specific questions were whether an institutional subset analysis had been done, if there was not some other variable that might vary from one institution to another with vein preservation and also explain the observed differences in fistula rate. The authors reported limited ability to answer that question based on the data that they had. The rationale for splenic vein preservation was also questioned. The presenter identified their personal experience that patients with splenic vein excision develop splenic vein thromboses which may propagate into the portal vein/superior mesenteric vein.

Session II: Cancer Basic and Translational

The first paper of this session, (10) Neoadjuvant Vaccine-Based Immunotherapy Inhibits Tumor Initiation of Pancretic Cancer Stem Cells was presented by the Johns Hopkins group, extending their work on immunotherapy for pancreatic cancer. They specifically evaluated the effect of their granulocyte/macrophage colony-stimulating factor (GM-CSF) secreting

allogenic whole cell pancreatic tumor vaccine on pancreatic cancer stem cell markers (cd244/ALDH-expressing cells). These exciting data documented the fact that tumor cells retrieved from the surgical specimen of patients who have received preoperative vaccine therapy completely lost the ability to grow in soft agar, had decreased expression of ALDH, and failed to form tumors engrafted in immunosuppressed mice. These exciting translational studies provide further conceptual support for the efficacy of the GM-CSF tumor vaccine.

The second paper of the session, (11) CK20 Expression Affects the Prognosis of Patients with Cancer of the Ampulla of Vater After Surgical Excision Results of the Analysis on 72 Cases Consecutively Observed was presented by Italian investigators from Turin and focused on epithelial differences in cancers of the periampullary region. These authors described 72 patients with ampullary adenocarcinoma resected over a 20-year period. The authors divided these tumors based on immunohistochemical expression of ck7 and ck20; their data suggest that ck20 expression is an independent negative prognostic factor for long-term survival.

The third paper in this session, (12) Whole Genomic Exome Sequencing of Pancreatic Neuroedocrine Tumors Reveals Prognostic Markers and Potential Novel Therapies was presented by the Johns Hopkins group. This is an extension of their genomic analysis of pancreatic adenocarcinoma applied to pancreatic neuroendocrine tumors: specifically focused on defining the genetic landscape of 68 patients' pancreatic nonfunctional neuroendocrine tumors. Three "mountains" were identified: mTOR (16% of patients), DAXX/ATRX (44%), and MEN-1. Genetic mutations identified in a "discovery set" of ten patients were cross-referenced with mutations observed in an additional 58 resection specimens. The authors suggest that the genetic alterations found in pancreatic neuroendocrine tumors are dissimilar to those found in patients with pancreatic ductal adenocarcinoma. This work was recently published in *Science*.[3]

The next paper, (13) Additon of Algenpantucel-L Immunotherapy to Standard Adjuvant Therapy May Improve Overall Survival (OS) and Disease-Free Survival (DFS) in Resected Pancreas Cancer Patients was presented by Hardacre on behalf of co-investigators from multiple institutions. This open-armed phase II study evaluated efficacy and safety of hyperacute pancreatic cancer immunotherapy with Algenpantucel, an irradiated, live, allogenic human pancreatic cancer cells expressing the enzyme alpha-1,3 galactosyl transferase. Seventy patients were studied; the vaccine was found to be safe (no grade 4/5 adverse events). Sixty-three percent of patients achieved 1-year disease-free survival, with an 86% overall 1-year survival. As these data mature, long-term survival data will obviously be of interest. A randomized phase III trial was initiated in early 2010 with a goal of enrolling 733 patients.

Three short papers were then presented: the first, (14) Fluorophore-Conjugated Anti-CEA Antibodies for Rapid Staging of Metastatic Pancreatic Cancer Using Fluorescence Laparoscopy was from the University of California San Diego. This exciting technology highlighted the ability of fluorophore-labeled anti-CEA to localize small metastatic lesions in CEA expressing human pancreatic cancers. The authors suggest that this technology may be a useful tool in pancreatic cancer staging. Discussion questions highlighted the potential utility of this technology to (1) deliver chemotherapeutic agents or (2) assess operative margins intraoperatively.

The next paper, from Henry Ford Hospital was (15) Accuracy of the National Surgical Quality Improvement Project for Modeling Complex Pancreatic Operations. These authors analyzed National Surgical Quality Improvement Program (NSQIP) public use files from 2005 to 2008. Over this 4-year time period, the authors found 7,097 complex pancreatic procedures and compared these to 568,371 non-pancreatic procedures. Their data suggest that complex procedures such as pancreatectomy may not be adequately modeled by existing NSQIP methodology. The discussion pointed out that NSQIP was working at the national level to create focused subgroup analysis capturing important data points for specific operations, such as pancreatectomy.

The final paper of the first afternoon was (16) Adding Days Spent in Readmission to the Initial Post Operative Length of Stay Limits the Perceived Benefit of Laparoscopic Distal Pancreatectomy When Compared to Open Distal Pancreatectomy. This paper was presented by Baker and his colleagues from Evanston North Shore. Their hypothesis was that initial shorter lengths of stay achieved with laparoscopy may be mitigated somewhat by readmission. These authors compared 50 patients undergoing open distal pancreatectomy to 20 with attempted laparoscopic distal pancreatectomy over a 2-year period. More patients undergoing laparoscopic distal pancreatectomy were readmitted to the hospital compared to those undergoing open distal pancreatectomy and adding the length of these readmissions to the initial length of stay eliminated the perceived effect of laparoscopy in shortening postoperative stay. The authors conclude appropriately that overall perspective is critical in evaluating long-term outcomes.[4]

Session III: Cancer–Basic Science

The first of the Saturday sessions focused on basic cancer studies. The first two papers of this session represented work done in Dr. Jonathan Brody's lab at Thomas Jefferson Medical School to determine the role of an mRNA-binding protein (Human antigen R or HuR) in regulating pancreatic cancer cell growth.[5,6]

In the first paper, (17) A Synthetic Lethal Approach to Targeting Multiple Tumor Promoting-Pathways in Vivo: Nanotherapeutic Silencing of HuR, the authors from Thomas

Jefferson University employed HuR siRNA deployed by nanoparticle injection into pancreatic cancer cell xenografts to assess the ability of HuR siRNA to silence HuR activity and influence tumor progression. HuR protein expression and tumor growth were significantly impaired in the mice with HuR siRNA-treated pancreatic cancer xenografts.

In the second paper, (18) HuR Regulates Death Receptor-5 (DR5)-Targeted Treatment of Pancreatic Cancer Cells, the authors from Thomas Jefferson University investigated the effect of HuR on the extrinsic apoptotic pathway mediated by DR5. The authors found that silencing HuR using siRNA transfections in cancer cell lines resulted in an increased protein expression of DR5 and thus increased sensitivity to DR5-targeted chemotherapeutics (gemcitabine and PARP inhibitors). These two papers were discussed together. Relevant discussion questions were whether there were any known oncogenic mutations in HuR. The authors responded that they had examined the entire coding sequence and had found no mutations. Regulation of HuR is posttranscriptional. There is a micro RNA that seems to regulate HuR in cancer cells and there is a high level of this micro RNA in pancreatic cancer cells. Another question raised the possibility of giving the nanoparticles intravenously. The authors responded that they have been used in intraperitoneal injections in models of ovarian cancer but that an intravenous form had not yet been developed.

The subsequent three papers all involved investigations centered on understanding the relevance of the stromal environment to tumor progression. The third paper in the session, (19) MT1-MMP Cooperates with Kras ^{G12D} to Promote Pancreatic Fibrosis Through TGF-β Activation of Pancreatic Stellate Cells, presented work done at Northwestern University, Chicago, IL examining the role of membrane-type 1 matrix metalloproteinase (MT1-MMP) in the growth of pancreatic cancer cells. One of the hallmarks of pancreatic cancer is its dense desmoplastic reaction. This reaction is somewhat hostile to cells and cells that live in this environment must cleave the collagen in areas of fibrosis to continue dividing. MT1-MMP is the enzyme that does this and is essential to allowing cells to grow. This metalloproteinase is upregulated in human pancreatic cancer. In the work presented, the group created a mouse that overexpressed MT1-MMP and Kras ^{G12D} in the pancreas. These mice were found to develop a greater number of papillary lesions and a high degree of cellular atypia in the pancreas than a Kras ^{G12D}+/MT1-MMP mice. Subsequent in vitro studies suggested that this effect was dependent on TGF-beta signaling as inhibiting the expression or activity of TGF-beta receptor type I in stellate cells attenuated their response to MT1-MMP. In the discussion, the authors were asked if the MT1-MMP mice developed tumors that metastasize. They answered that their pathology was more akin to IPMN or large PanINs than pancreatic cancer. The tumors do not invade. Another question was regarding acinar to ductal cell metaplasia: is there evidence of this happening? The authors responded that they felt that their model was a model of early dysplasia but the relevance in human disease is unclear.

The fourth paper in the session (20) Targeting ErbB Receptor-Mediated Stromal–Tumor Interaction In Pancreatic Ductal Adenocarcinoma (PDAC) presented work done at the University of Alabama, Birmingham to target the interactions between stromal fibroblasts and pancreatic cancer cells in effort to improve response to chemotherapeutics. The authors developed a cultured cell line of cancer-associated fibroblasts from resected pancreatic cancer specimens. They then developed a cancer xenograft model that involved transplanting these cells with pancreatic cancer cell lines. They found that these xenografts were resistant to the EGFR inhibitor erlotinib, whereas xenografts without the fibroblasts were sensitive to erlotinib. They also demonstrated that co-treatment with erlotinib and an inhbitor of ERB3 MM-121 resulted in a dose-dependent inhibition of tumor growth in the xenografts. In discussion, the authors were asked if they had looked at EGFR downstream expression. The authors responded that they had examined downstream regulators but felt that downstream expression of EGFR was not a reliable predictor of response to treatment.

The fifth paper in this session (21) Hedgehog Signaling is Required for Tumor Stroma Maintenance and Tumor Angiogenesis in Pancreatic Cancer presented work examining the role of Hedgehog signaling in tumor stroma maintenance and angiogenesis in pancreatic cancer. Mice bearing three different pancreatic cancer cell line xenografts were treated with an antibody inhibiting the binding of Hedgehog ligand SHH. Two of these tumors demonstrated impaired tumor growth, stromal content, and tumor vacularity. Nanostring evaluation demonstrated upregulation of the antiangiogenic/proapoptotic thormbospondin-2 in the stroma around the tumors. In discussion, the question was asked if there were any detectable genetic differences between the tumors that responded to the antibody and that which did not. The authors answered that there were none detected.

The final three papers in the session were clinical. The sixth paper (22) Even Small Pancreatic Endocrine Neoplasms Have Lymph Node Metastasis presented a retrospective review of the resected neuroendocrine tumors in the pancreatic database at Johns Hopkins Hospital in effort to correlate the size of the tumor to lymph node status. There were 318 non-functioning tumors included in the study. Multivariate analysis demonstrated that lymph node status and size were independent predictors of survival. The authors identified positive nodes among all size ranges but increasing size was found to correlate with positive nodes. Tumors less than 1 cm in size had a 14% probability of positive nodes, whereas those greater than 3 cm had a 56% probability of positive nodes. There was a spirited

discussion of this paper. A description of the role of enucleation and specifically for clarification of the question of whether lymph node sampling should be done with enucleation of these neuroendocrine tumors was called for. The authors recommended an oncologic resection regardless of size. Another discussant commended the authors for excluding functional tumors from the study but raised doubts as to whether all small neuroendocrine tumors require resection. He asked if the nodes and size are predictive of survival in the small tumors. The authors responded that they could not answer the question with the available data. A third discussant described his institutional experience and bias that enucleation provides better outcomes than formal resection and stated that he felt sentinel lymph node biopsy may have a role in identifying those patients that would benefit from formal lymphadenectomy. The authors agreed with that comment. Finally, the authors were asked if Ki67 analysis was done and further if the survival data was disease specific. They responded that they could not answer the survival question with the data available and that they did not examine low grade (Ki67 >3) patients specifically.

The seventh paper in the session (23) Serous Cystadenomas of the Pancreas: Study of Potential Factors Influencing Tumor Growth was an observational study that reviewed 123 patients with a radiologic diagnosis of serous cystadenoma at a single institution, the University of Verona. These patients were followed up with annual MR imaging for 5 years to determine risk factors for tumor growth. The mean growth rate was found to be 1.3 mm/year. Tumors that were macrocystic appeared to grow more quickly. Their conclusions were that serous cystadenomas were very slow-growing tumors that needed infrequent follow-up surveillance. A discussant described his institutional experience with serous cystadenoma, stating that his study demonstrated faster growth for larger tumors. The problem for the unilocular cystic tumor is that we cannot make a definitive diagnosis by EUS. Those patients need to be followed up and the younger patients may need counseling to undergo surgery. The authors of the presented paper agreed with his observation.

The eighth paper (24) Body Mass Index Is Associated with Morbidity After Pancreatic Resection: Results from the ACS-NSQIP presented work from the University of Wiconsin, Madison investigating the effect of patient weight on morbidity following pancreatic resection using the ACS-NSQIP database. Six thousand seven hundred seventy-four patients undergoing pancreatic resection at NSQIP hospitals between 2005 and 2008 were studied. Both patients who were obese (BMI>40 kg/m^2) and those who were underweight were at increased risk for perioperative morbidity compared to patients of normal weight. Obese patients were found to be at high risk for wound infection, abscess, venous thromboembolism, and renal failure. Underweight patients were at risk for respiratory complications and venous thromboembolism. Preoperative weight loss in the obese patients was also identified as protective decreasing the risk of perioperative morbidity. Weight loss in normal weight individuals was not protective. One discussant asked how the weight loss was recorded. The authors responded that clinical nurses measured the weight of patients undergoing pancreatectomy prior to surgery and recorded weight loss. Another discussant reported that the NSQIP study group was in the process of developing a risk prediction model for patients undergoing pancreatic surgery.

The final paper of the session (25) Preoperative CT Scan Can Predict Incidence and Severity of Pancreatic Fistula After Pancreaticoduodenectomy presented work done at the Hopital Beaujon, University Paris VII investigating the ability of preoperative CT imaging to predict pancreatic fistula following pancreaticoduodenectomy. The authors reviewed 103 patients that underwent pancreaticoduodenectomy with pancreaticogastrostomy between 2006 and 2007. Preoperative CT images were used retrospectively to determine visceral fat area, subcutaneous fat area, global fat area, and hepatic and splenic density. Multivariate analysis demonstrated that high visceral fat area and a ratio of hepatic to splenic density less than 1 (liver steatosis) were associated with increased incidence of clinically significant pancreatic fistula. A discussant asked if there was any long-term outcome data suggesting that fat affected survival. The authors responded that there were no data. Another discussant asked for clarification regarding surgery, specifically was the procedure standardized from one patient to the next or did patients with soft glands receive a different reconstruction. The authors responded that the procedures were standardized.

Session IV: Pancreatitis

The second Saturday session was dedicated to acute pancreatitis. The first paper, (26) Surgical Management of the Late Sequellae in Survivors of an Episode of Acute Necrotizing Pancreatitis (ANP) was presented by Nealon and colleagues from Vanderbilt University. This analysis of 197 patients treated over a 17-year period provided critical and heretofore lacking long-term follow-up data for patients with this challenging disease process. An important feature in this analysis was categorization of these patients based on pancreatic ductal anatomy (integrity of the pancreatic duct—type 1/normal, type 2/stricture, and type 3/disconnected). Overall, 71 operations were performed more than 2 months after the initial insult; 59 were drainage operations and 12 were resections. The overall low morbidity and admirable mortality rate reflects a benchmark for severe pancreatitis

patients treated by an experienced pancreatic surgeon at a high volume center.

The next paper was from the University of California San Francisco, (27) De Novo Expression of Urocortin1 in Pancreatic Acinar Cells During Acute Pancreatitis. Antagonism of Corticotropin-Releasing Factor Receptor 2 Exacerbates Inflammation. These authors presented beautiful in vivo and in vitro data highlighting the importance of corticotrophin-releasing factor receptor 2 in the development of pancreatic inflammation. Discussion focused on the steps required to translate these findings to clinical utility.

The third paper was presented by Beane on behalf of his colleagues at Indiana University (28) Splenic Preserving Distal Pancreatectomy: Does Vessel Preservation Matter? This retrospective analysis compared 86 patients with spleen-preserving distal pancreatectomy, 45 with splenic artery and vein preservation, and 41 with splenic vessel ligation. Splenic vessel preservation was associated with significantly decreased blood loss, splenic infarct, pancreatic fistula rate, and overall morbidity. Short-term outcomes of vessel ligation were similar to those of patients undergoing distal pancreatectomy with splenectomy. This manuscript is published in the *Journal of the American College of Surgeons*.[7]

The next paper from the University of Massachusetts, (29) Pancreatic Cystic Lesions: Assessing Quality of Life evaluated serial quality of life measurements in eight patients with cystic pancreatic lesions: four who were resected, and four who were followed up. This small series suggested that the overall quality of life improved after surgical resection. The discussion highlighted the challenge, but importance of precise symptom definition relative to the pancreas, and the need for larger studies.

Paper (30) Management of Pancreatic Fluid Collections (PFCS): a Changing of the Guard from Surgery to Endoscopy was presented by Christein on behalf of his surgical and endoscopy colleagues from the University of Alabama at Birmingham. This report is important in that it included a very large number of patients (285) treated for symptomatic peripancreatic collections over a 6-year period. These expert endoscopists and GI surgeons highlighted a shift in the trend at their institution to the primary management of these collections by endoscopy. They push the envelope by performing endoscopy at the bedside in the intensive care unit. Discussion highlighted the fact that management of these patients mandates a multidisciplinary approach.

The final paper of this session (31) Pancreatic Surgery at the University Hospital of Rostock reviewed the outcomes of 265 patients undergoing pancreatic resection at this institution over a 7-year period. The majority of these operations (152) were performed for malignancy while 90 patients with chronic pancreatitis underwent operation. The authors' results highlight their experienced high volume German center.

How I Do It Session: Exocrine Enzyme Replacement—Why, When, and How

The How I Do It session was presented by Drs. Chris Forsmark of the University of Florida and Santhi Vege of Mayo Clinic. This scintillating presentation is available in video format on the Pancreas Club website: http://pancreasclub.com/video.htm.

John M. Howard, MD in Memoriam

Dr. Bill Traverso gave a short presentation honoring the life and contributions to pancreatology of John M. Howard, MD (1919–2011). Dr. Howard was a founding father of the Pancreas Club, and indeed a father of pancreatology.

Session V: Cancer Basic/Mechanisms of Tumorogenesis and Metastasis

The first paper of this session (32) Identification of a Metastatic-Protective Stromal Factor in Pancreatic Cancer presented work from the MD Anderson Cancer Center that aimed to identify a stromal factor protecting against metastases. The authors used dilutional subcloning to establish isolated clones of pancreatic cancer cell lines of increasing metastatic potential from a cell line that was not particularly aggressive. Two such pairs were developed and the low and high metastatic groups were compared using microarrays. Four genes were upregulated in both highly metastatic groups. One of these was lumican, a member of a family of small leucine-rich repeat proteoglycans (matrikines). The authors then looked at resected pancreatic cancer specimens and found four distinct patters of lumican expression. The group with a stroma-positive and tumor-negative pattern of staining had a significantly longer disease-free and overall survival (44% and 66%). This was born out as a predictor of outcome in univariate and multivariate studies. There was a lively discussion of this paper: one discussant asked for clarification of the distribution of pattern of lumican expression among resected patients. The authors reported equal distribution. He also asked for clarification of the function of lumican. The authors responded that it was known to be a fibrogenic molecule but otherwise not well understood. Another discussant asked if any of the patients resected

had neoadjuvant chemotherapy. The authors responded that none of the patients received neadjuvant treatment.

The second paper in this session (33) Direct Xenograft Models Recapitulate Molecular Features of Metastasis in Pancreatic Ductal Adenocarcinoma (PDAC) also highlighted work from MD Anderson, attempting to establish a xenograft model for metastatic lesions. The authors isolated pancreatic cancer tumor fragments from resected pancreatic cancer specimens including metastatic lesions from lymph nodes in the resected specimens. These were implanted in NOD/SCID mice. Xenografts from lymph node metastases demonstrated features of metastatic lesions including increased expression of matrix metaloproteinases and reduced expression of SMAD-4. A discussant raised a question about the mechanism of SMAD-4 loss in metastases. The authors responded that it was an unknown epigenetic mechanism.

The third paper in this session (34) Direct Xenograft Models Recapitulate Molecular Features of Metastasis in Pancreatic Ductal Adenocarcinoma (PDAC) was also from MD Anderson. This effort examined the human pancreatic cell line L3.6pl for surface expression of several known markers of cancer stem cells: ALDH, CD133, CD44, and CD24. The investigators noted variable expression of ALDH and CD133 and very rare expression of CD44 and CD24. They then employed sequential xenografting into NOD/SCID mice to assess the potency of these cells in tumorigenesis and demonstrated that increased ALDH expression alone was sufficient to result in efficient tumor initiation as ALDH-rich CD133+ tumor cells engrafted to the same degree as ALDH-rich CD133− tumor cells but ALDH-poor CD133+ tumor cells failed to engraft. In the discussion of this paper, the authors were asked if they had examined drug sensitivities in these variable tumor cell types. They responded that they had not done this. Another discussant asked if the authors were certain that they were examining initiation and not progression. There was no clear response to this question.

The fourth paper in the session (35) Receptor for Advanced Glycation End-Products (RAGE) Knockout Delays the Progression of Pancreatic Intraepithelial Neoplasia (PANIN) in a Murine Model of KRAS Driven Pancreatic Carcinogenesis made an effort to examine the effect of inhibiting at damage-associated molecular pattern molecule named RAGE (receptor for advanced glycation end-products) on the progression of PanIN to pancreatic cancer. This lab had previously shown that cells with increased levels of RAGE have increased autophagy (method of programmed cell survival in which organelles that are not functional are consumed by the cell) and decreased apoptosis. Immunohistochemistry has demonstrated increased RAGE staining in pancreatic cancer and murine models of pancreatic cancer. They generated a hypothesis that targeted inhibition of RAGE would result in impaired carcinogenesis in PanIN. To test this hypothesis, they crossed a RAGE knockout mouse with a PDX-Cre-KRAS (PanIN generating mouse model) knockout mouse. In these mice, the markers of apoptosis were expressed in increased levels in early life and the markers of autophagy were expressed at decreased levels later in life (42 weeks) relative to PDX-Cre-KRAS knock mice. The RAGE knockout animals also demonstrated 50% fewer high grade PanIN lesions. A discussant questioned the use of a small molecule inhibitor of RAGE in the PDX-Cre-KRAS knockout and also asked what is the relative impact of the RAGE signaling in the stroma and tumor. The authors responded that they had early results on the use of the RAGE inhibitor and these were similar to that seen in the RAGE PDX-Cre-KRAS double knockout. They also commented that they believed the microenvironment and not the tumor was dictating outcome in the RAGE PDX-Cre-KRAS double knockout.

The fifth paper in the session (36) Gli Activation Is Required for Pancreatic Tumor Formation in Vivo presented work from the University of Massachusetts Medical School examining the role of a family of transcription factors that are components of the Hedgehog signaling pathway (Gli transcription factors) in mediating pancreatic cancer tumorigenesis in vivo. The authors hypothesized that Gli activity is required during pancreatic cancer development in vivo. They employed an R26-Gli3T allele that expresses a dominant repressor form of GLI3 from the ubiquitous Rosa26 locus. They added this allele to a cohort of mice bearing Kras ^{G12D}, p48-cre, and a deleted TRP 53 Fl allele. They then compared KRAS-, TRP 53-, and p48 Cre Gli3T-positive mice to KRAS-, TRP- 53, p48-, and Gli3T-negative mice (these have normal Gli activity). The Gli3T-negative mice died faster than those who are Gli3T-positive. The Gli3t-negative mice had advanced PanIN and pancreatic ductal cancer. The Gli3t-positive mice (no GLI activity) demonstrated discrete PanIN lesions but had no cancers. The authors' conclusion was that inhibition of Gli transcriptional activation using the R26Gli3T allele delays the development and progression of pancreatic tumorigenesis.

The sixth paper in the session (37) Nicotine Regulates DNA-Binding Protein Inhibitor (ID1) Through a SRC-Dependent Pathway Promoting Tumorigenic Properties and Chemoresistance in Pancreatic Adenocarcinoma presented work from the H. Lee Moffitt Cancer Center in Tampa, FL examining the effect of nicotine on tumorigenesis and chemoresistance. The authors postulated that nicotine induces the expression of transcription factor Id1 (inhibitor of DNA binding/differentiation) in a Src-dependent manner and promotes tumorigenesis and impairs chemosensitivity. The authors treated several pancreatic cancer cell lines with nicotine and siRNA (small interfering RNA) for Id1. Nicotine resulted in increased expression of Id1 and cell proliferation and the siRNA against Id1 eliminated the increased cell proliferation. The authors also examined the cell lines treated with the

chemotherapeutic agent gemcitabine. They found impaired cell death when co-treated with gemcitabine and nicotine and also that the addition of siRNA for Id1 returned the efficacy of gemcitabine. A discussant asked for clarification of what the authors used for relevant levels of nicotine in these studies. The authors answered that they attempted to use levels thought to be comparable to those at physiologic levels seen in chronic smokers.

The seventh paper in the session (38) Identification of a Common Molecular Phenotype After Cytotoxic Therapy for Pancreatic Adenocarcinoma presented work from the MD Anderson Cancer Center attempting to clarify mechanisms of resistance to neoadjuvant chemoradiotherapy. The authors isolated samples from 24 resected pancreatic cancers and attempted to implant them into NOD/SCID mice to give a xenograft model. Nine of these engrafted to give usable models. Five of them had been treated with chemoradiotherapy prior to resection, four had been untreated. Subsequent microarray and RT-PCR were used to assess differential gene expression. These demonstrated impaired expression of TGF-beta receptor 2 and increased insulin-like growth factor-binding protein-3 in the specimens of the patients treated with neoadjuvant therapy. A discussant commented that this work seemed to indicate that the authors changed the biology of the tumor by neoadjuvant treatment and asked for more detail on what form of neoadjuvant therapy the patients received. The authors answered that there were a variety of regimens used most commonly gemcitabine was given plus/minus some other biologic agent and radiation. The authors also made the comment that in their study there was no discernable difference in gene expression from one treatment regimen to another. Another discussant asked the authors why they thought that some of the tumors did not engraft. The authors answered that they really had no indication as to the reason for that phenomenon.

The final paper of this session (39) Casein Kinase-2 Downregulation: a Novel Therapeutic Strategy for Pancreatobiliary Tumors presented work from the University of Minnesota investigating the inhibition of casein kinase-2 as a novel therapeutic strategy for pancreatic cancer. Heat shock factor-1 (HSF1) is upregulated in pancreatic cancer cells. Casein kinase 2 phosphorylates HSF1 and is believed to play a role in mediating cancer cell survival. Tetrabromobenzotriazole (TBB) is a pharmacologic inhibitor of CK2 and causes cell death in pancreatic cancer cell lines. The authors attempted to examine the mechanism for CK2 effect and looked at markers for both apoptosis and autophagy in cells treated with TBB. Apoptosis markers were not affected. Autophagy markers were detected in the media above cell lines tested. The authors concluded that the survival effect of CK2 was due to an effect on autophagy. In the discussion, one question raised from the audience was directed toward clarifying the role of autophagy in cell death. The authors were asked if they looked for markers of necrosis and the comment was made that autophagy may not be a cause of cell death, it may prevent cell death. The authors answered that they had not examined rates of necrotic cell death and stated that autophagy at high levels is associated with and thought to be a cause of cell death.

Session VI: Cancer Clinical/Predictors of Outcomes and Technical Issues

The first paper of the final session, (40) Clinical Predictors of Failure to Undergo Pancreatectomy Following Neoadjuvant Therapy in Patients with Potentially Resectable Pancreatic Cancer, from MD Anderson Cancer Center evaluated 226 patients initially deemed "potentially resectable" who underwent treatment with neoadjuvant chemotherapy/chemoradiation therapy. One hundred thirty-six patients ultimately proceeded to operative resection while 90 patients did not receive operation with curative intent. The authors highlighted the rapid development of metastases in a small subgroup of patients as the most common reason for failure of these patients to undergo resection. A notable finding was that local advancement was prohibitive in only 5% of patients.

The next paper, (41) Prognostic Significance of Histologic and Precursor Epithelial Subtypes of Invasive Intraductal Papillary Mucinous Neoplasm: Improved Survival Compared to Pancreatic Ductal Adenocarcinoma are Limited to Indolent Colloid and Oncocytic Types from the Massachusetts General Hospital evaluated outcomes of 61 patients with resected invasive IPMN. Their data confirmed previous observations that adenocarcinoma rising in the setting of IPMN have a more favorable 5-year survival; 47% vs 16% than those patients with "garden variety" pancreatic ductal adenocarcinoma. The authors feel that this survival advantage is principally due to the biology of indolent colloid and oncocytic types of invasive IPMN and highlights the phenotypic difference of the tubular type of IPMN which appears to have a clinical course more closely resembling pancreatic ductal adenocarcinoma.[8]

Paper (42) Human Equilibrative Nucleoside Transporter 1 Expression Is a Strong Independent Prognostic Factor in T3/T4 Pancreatic Cancer Patients Treated with Preoperative Gemcitabine-Based Chemoradiotherapy was presented by Murata et al. from Mie University in Japan and focused on biologic reasons for failure of chemotherapy. Human equilibrative nucleoside transporter 1 (hENT-1) is a gemcitabine transporter. The authors analyzed specimens from 55 pancreatic cancer patients who underwent resection. Patients with hENT-1-positive tumors had significantly increased overall survival. The discussion highlighted the question of which patients received adjuvant chemotherapy.

The fourth paper was from Hiroshima University, (43) Concurrent Analysis of Dihydropyrimidine Dehydrogenase and Human Equilibrative Nucleoside Transported 1 Expression Predicts Survival Following Adjuvant Gemcitabine Plus S-1 Chemotherapy for Resected Pancreatic Adenocarcinoma. These authors performed immunohistochemical analysis on 86 pancreatic cancer specimens from patients who had received adjuvant gemcitabine plus the drug S-1 (an oral fluoropryimindine dpd + oprt inhibitor). They found that patients who demonstrated high dpd and hENT-1 expression had significantly increased survival. This raised the discussion as to whether adjuvant gemcitabine therapy should be withheld from hENT-1-negative patients.

The next paper, (44) A Root Cause Analysis of Mortality Following Major Pancreatectomy, was presented by Vollmer on behalf of his colleagues from the multinational Pancreatic Mortality Study Group. This impressive work surveyed 32 pancreatic surgeons from 14 institutions in four countries, asking each surgeon to "deconstruct" clinical events preceding death to determine the clinical cause. This aggregate root cause analysis suggested that risk prediction should absolutely include if not emphasize *operative factors* related to pancreatectomy.

The next paper, (45) Postresection Diabetes After Distal Pancreatectomy: Incidence and Risk Factors, from the Mayo Clinic evaluated the outcome of 493 patients without preexisting diabetes who underwent distal (left-sided) pancreatectomy. They found that the short-term incidence of diabetes was 9%, and that elevated preoperative glucose, increased BMI, and extended resection were risk factors for developing diabetes. They appropriately acknowledge the short follow-up as a study limitation.

The next paper (46) Comprehensive Perioperative Geriatric Assessments May Predict Surgical Outcomes in a Prospective Study of Older Patients Undergoing Pancreaticoduodenectomy was from the University of Chicago. These authors studied 78 "older" patients (greater than 50 years old) who underwent pancreaticoduodenectomy. The authors highlight novel predictive scores including the vulnerable elder survey (VES 13) short physical performance battery and Freed criteria for frailty as potential predictors of poor postoperative outcomes.

The final paper of this year's meeting (47) Is It worth looking? Abdominal Imaging after Pancreatic Cancer Resection: a National Study was presented by the University of Massachusetts SOAR group. These authors evaluated patients undergoing pancreatectomy for pancreatic adenocarcinoma from the SEER-medicare database from 1991 to 2005. They analyzed claims for abdominal imaging within 5 years from resection. Overall, 94% of patients received at least one imaging study following resection. The vast majority of these imaging studies were computed tomography (93%), while magnetic residence imaging (6.2%) and positron emission tomography (0.9%) were used less liberally. The authors highlighted increased imaging usage over the recent years and extended their analysis to suggest that routine annual CT scanning does not confer a survival benefit.

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