PANCREATIC CANCER NEWS & UPDATES – APRIL 2011

BIOLOGY OF CANCER

Stat3 and MMP7 contribute to pancreatic ductal adenocarcinoma initiation and progression
http://www.ncbi.nlm.nih.gov/pubmed/21481787
UCSF press release: http://www.ucsf.edu/news/2011/04/9694/ucsf-scientists-discover-link-between-inflammation-and-pancreatic-cancer
The senior author of this study is two-time grant recipient Matthias Hebrok, PhD (2008 Michael C. Sandler – Pancreatic Cancer Action Network – AACR Pilot Grant and 2011 Abby Sobrato – Pancreatic Cancer Action Network – AACR Innovative Grant). This collaborative project investigated the link between chronic inflammation of the pancreas and pancreatic adenocarcinoma. The researchers determined that two proteins, Stat3 and MMP7, contribute directly to inflammation-related pancreatic cancer initiation and metastasis, respectively.

Cyclooxygenase-2 confers growth advantage to syngeneic pancreatic cancer cells
http://www.ncbi.nlm.nih.gov/pubmed/21343834
Researchers at UCLA, including Dave Dawson, MD, PhD (2008 Seena Magowitz – Pancreatic Cancer Action Network – AACR Career Development Award), sought to characterize the phenotype of cyclooxygenase-2 (COX-2) expressing syngeneic pancreatic cancer cells. Stable expression of COX-2 led to enhanced anchorage-dependent and -independent growth, and these cells grew faster in a mouse xenograft model.

Notch-1 induces epithelial-mesenchymal transition consistent with cancer stem cell phenotype
http://www.ncbi.nlm.nih.gov/pubmed/21463919
Notch activation is known to occur in pancreatic cancer, and contribute to the development and progression of the disease. Here, Wayne State University investigators show that Notch-1 leads to changes in expression of several miRNAs, contributing to epithelial to mesenchymal transition, and the acquisition of stem cell like characteristics. This can be reversed by treatment with genistein.

Over-expression of FoxM1 leads to epithelial-mesenchymal transition and cancer stem cell phenotype
http://www.ncbi.nlm.nih.gov/pubmed/21503965
The same group of Wayne State researchers presents data here suggesting that FoxM1 also contributes to the acquisition of the epithelial to mesenchymal transition as well as stem cell like behavior, also by manipulating expression of important miRNAs. Genistein is also inhibitory of this mechanism.

Pancreatic tumor suppression by benzyl isothiocyanate is associated with PI3K/AKT/FOXO pathway
http://www.ncbi.nlm.nih.gov/pubmed/21350002
These researchers at Texas Tech University had previously shown that benzyl isothiocyanate suppressed pancreatic cancer growth by inducing apoptosis. To further understand the mechanism, they studied

the PI3K/AKT/FOXO pathway. Their findings suggested that pancreatic tumor suppression by benzyl isothiocyanate was associated with inhibition of the PI3K/AKT/FOXO pathway.

Histone modification enhances the effectiveness of IL-13 receptor targeted immunotoxin
http://www.ncbi.nlm.nih.gov/pubmed/21477288
This *Journal of Translational Medicine* paper reports a novel function of histone modification in the regulation of interleukin-13 receptor alpha2 in pancreatic cancer cell lines. Inhibition of histone deacetylases, in combination with immunotoxins, synergistically blocked growth of pancreatic cancer cell lines.

Identification of RegIV as a novel GLI1 target gene in human pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21494603
Published in *PLoS One*, this article describes the relationship between GLI1, key transcription factor involved in the Hedgehog pathway, and RegIV, a protein associated with regeneration, cell growth, survival, adhesion, and apoptosis resistance. These investigators from Shanghai find that expression of GLI1 and RegIV was higher in pancreatic cancer tissue, than normal tissue of the pancreas. RegIV expression was directly regulated by GLI1 expression and activity.

Nrf2 is overexpressed in pancreatic cancer: implications for cell proliferation and therapy
http://www.ncbi.nlm.nih.gov/pubmed/21489257
Lister and colleagues looked at Nrf2, a key transcription factor that regulates the expression of genes involved in drug metabolism and defense against oxidative stress. Keap1 functions to control Nrf2 expression, targeting the protein for degradation. The Keap1/Nrf2 system has been found to be altered in other solid tumor types, so the authors decided to look at pancreatic cancer. Their experiments showed that Nrf2 expression is elevated in pancreatic cancer cell lines. Based on these results, perhaps manipulation of Nrf2 may enhance pancreatic tumors' responsiveness to therapeutics.

The homeobox gene MSX2 determines chemosensitivity via the regulation of transporter gene ABCG2
http://www.ncbi.nlm.nih.gov/pubmed/21465479
Published in *Journal of Cellular Physiology*, this study evaluated the expression and activity of the homeobox gene MSX2 and how it regulates ABCG2. Manipulation of MSX2 up or down led to parallel changes in ABCG2, and MSX2/ABCG2 were found to correlate with epithelial to mesenchymal transition, maintenance of a stem cell phenotype, and chemoresistance.

Abstracts of the 9th Congress of the European-African Hepato-Pancreato-Biliary Association
http://onlinelibrary.wiley.com/doi/10.1111/hpb.2011.13.issue-s2/issuetoc
This issue of the *HPB*, official journal of the Hepato-Biliary Association, includes abstracts from the E-AHPBA meeting in Cape Town, South Africa, April 12-16.

ETIOLOGY

Inflammation-related gene variants as risk factors for pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21467233
Gloria Petersen, PhD (Scientific Advisory Board) is the senior author for this study. The research team at the Mayo Clinic sought to investigate the link between chronic inflammation and progression to

pancreatic cancer. They examined small nucleotide polymorphisms (SNPs) in genes known to be involved in inflammatory pathways. Single SNP analysis revealed an association between four SNPs in NOS1 and one in CD101, and risk of developing pancreatic cancer.

Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies
http://www.ncbi.nlm.nih.gov/pubmed/21458985
A total of 35 cohort studies were included in this meta-analysis. The authors' data strongly support that diabetes mellitus is associated with an increased risk of pancreatic cancer in both males and females, and that diabetes is both an early manifestation and an etiologic factor of pancreatic cancer.

Cigarette, cigar and pipe smoking, passive smoke exposure, and risk of pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21496267
Tranah *et al* published this study in *BMC Cancer*, conducting a population-based study in the San Francisco Bay Area of the association between cigarette, cigar, and pipe smoking, cessation of smoking, or passive smoke exposure, and risk of pancreatic cancer. Both men and women displayed increased risk of pancreatic cancer with increased intensity and duration of cigarette smoking. Previous smokers' risk was reduced to that of nonsmokers after at least ten years smoke-free. Pipe and cigar smokers and those exposed to passive smoke were not at increased risk of pancreatic cancer.

Nutrients, food groups, dietary patterns, and risk of pancreatic cancer in postmenopausal women
http://www.ncbi.nlm.nih.gov/pubmed/21278328
This *Cancer Epidemiology, Biomarkers & Prevention* publication looked at the Iowa Women's Health Study, and determined that there was no significant association between the intake of nutrients and food groups or dietary patterns and pancreatic cancer.

Jewish ethnicity and pancreatic cancer mortality in a large U.S. cohort
http://www.ncbi.nlm.nih.gov/pubmed/21278327
This study, also published in *Cancer Epidemiology, Biomarkers & Prevention*, used data from the Cancer Prevention Study II to examine the link between pancreatic cancer and Jewish ethnicity. After adjusting for variables such as obesity, smoking, and age, the authors saw a statistically significant increased rate of, and death from, pancreatic cancer among those of Jewish ethnicity in the United States.

Fiber intake and pancreatic cancer risk: a case-control study
http://www.ncbi.nlm.nih.gov/pubmed/21460379
Bidoli *et al* explored the role of various types of dietary fiber in the etiology of pancreatic cancer. The results of this case-control study suggested that certain types of fiber were inversely associated with the risk of pancreatic cancer.

PREVENTION

Aspirin may lower the risk of pancreatic cancer
http://www.aacr.org/home/public--media/aacr-in-the-news.aspx?d=2322
This abstract was presented at the AACR 102nd Annual Meeting, reporting research from the Mayo Clinic suggesting that aspirin may lower the risk of pancreatic cancer. Data were collected from 2004 to 2010, generated from self-reported questionnaires of pancreatic cancer patients and healthy age-matched

controls. After adjusting for variables, individuals who took at least one dosage of aspirin per month were at a lower risk for developing pancreatic cancer. This association was not observed with NSAIDs or acetaminophen.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Feasibility and yield of screening in relatives from familial pancreatic cancer families
http://www.ncbi.nlm.nih.gov/pubmed/21468009
This study out of Memorial Sloan-Kettering received considerable media attention. The Family Pancreatic Tumor Registry included 309 asymptomatic at-risk family members. Participants were offered screening by various methods. Individuals with suspicious findings were referred for surgical evaluation. Their data suggested that screening at-risk relatives from familial pancreatic cancer families had a significant diagnostic yield, particularly in relatives >65 years of age.

Tumour epithelial vimentin expression and outcome of pancreatic ductal adenocarcinomas
http://www.ncbi.nlm.nih.gov/pubmed/21448168
The authors of this *British Journal of Cancer* article include Ralph Hruban, MD (Scientific Advisory Board). Here, researchers investigated the extent and prognostic significance of vimentin expression in pancreatic ductal adenocarcinoma. Overall, the data suggest that the presence of vimentin-expressing tumor epithelial cells in surgically resected pancreatic adenocarcinomas independently predicted a shorter postsurgical survival.

Tumor size and location correlate with behavior of pancreatic serous cystic neoplasms
http://www.ncbi.nlm.nih.gov/pubmed/21468008
This team of Johns Hopkins researchers also included Ralph Hruban, MD (Scientific Advisory Board). Although the majority of serous cystic neoplasms (SCNs) are benign, some can be aggressive. The authors sought to determine predictors of aggressiveness in SCNs. Data suggested that large tumor size and location of the tumor in the head of the pancreas were independently associated with aggressive behavior in SCNs.

Pancreas-protocol imaging at a high-volume center leads to improved preoperative staging
http://www.ncbi.nlm.nih.gov/pubmed/21484522
This study out of the University of Virginia confirmed the value of re-imaging pancreatic cancer patients at a high-volume center, as opposed to relying on pre-referral imaging.

The clinical utility and limitations of serum CA19-9 as a diagnostic tool for pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21516323
Stanford University researchers looked at serum levels of carbohydrate antigen (CA19-9) as a diagnostic marker for pancreatic cancer and cholangiocarcinoma. Overall, serum CA19-9 had poor clinical utility for diagnosing pancreatic cancer or cholangiocarcinoma, and did not change patient management.

Identification and validation of SRC and phospho-SRC family proteins in circulating mononuclear cells
http://www.ncbi.nlm.nih.gov/pubmed/21461171
Tumor associated macrophages (TAMs) originate from circulating mononuclear cells (MNCs) and are heavily present in the stroma surrounding pancreatic tumors. MD Anderson investigators searched for

differential protein expression or protein modifications that could make these MNCs or TAMs serve as much-needed biomarkers for pancreatic cancer. They found that Src and phospho-Src expression were elevated in MNCs and TAMs of mice with pancreatic tumors. However, increased Src expression and activity were also evident in mice with chronic pancreatitis. Further work is necessary to determine whether MNCs or TAMs can play a role in the detection or diagnosis of pancreatic cancer.

Hypoxia predicts aggressive growth and spontaneous metastasis formation
http://www.ncbi.nlm.nih.gov/pubmed/21343390
This *Cancer Research* study looked at hypoxia in orthotopically grown primary xenografts of human pancreatic cancer. The results suggest that hypoxia is a major adverse prognostic factor in pancreatic cancer patients and support the introduction of techniques to measure hypoxia directly in patients and the development of treatment protocols to target hypoxia.

TREATMENT

Two drugs recommended for approval to treat pancreatic neuroendocrine tumors
http://www.pancan.org/section_research/scientific_strategy/topic_two_drugs_approved_april_2011.php
Two *New England Journal of Medicine* articles published in February reported data on clinical trials of the Pfizer drug sunitinib malate (Sutent®) and the Novartis drug everolimus (Afinitor®) in the treatment of pancreatic neuroendocrine tumors. Based on these clinical trial data, the Oncologic Drugs Advisory Committee (ODAC) recommended that the FDA approve both compounds for the treatment of pancreatic neuroendocrine tumors. The ODAC voted 8-2 in favor of approving Sutent®, and 10-0 to approve Afinitor®. The final decision from the FDA is still pending.
**Update: on May 6, 2011, the FDA approved Afinitor® for the treatment of advanced pancreatic neuroendocrine tumors.*

A review of systemic and liver-directed therapies for metastatic neuroendocrine tumors
http://www.ncbi.nlm.nih.gov/pubmed/21451455
Researchers from the Moffitt Cancer Center prepared this review of systemic and liver-directed therapies for metastatic neuroendocrine tumors of the gastroenteropancreatic tract. The authors conclude that treatment options are expanding rapidly for patients with metastatic gastroenteropancreatic NETs, driven largely by randomized, collaborative clinical trials, and believe that future clinical trials should compare the efficacy of emerging therapies administered in combination or sequential approaches.

Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy
http://www.ncbi.nlm.nih.gov/pubmed/21460848
Authors of this collaborative study include Andrew Ko, MD (2003 Pancreatic Cancer Action Network – ASCO Career Development Award), Douglas Hanahan, PhD (2007 Pancreatic Cancer Action Network Pilot Grant), and Margaret Tempero, MD (Scientific Advisory Board). This *Nature Medicine* publication reports the search for intrinsically variable genes in microarray data sets of pancreatic adenocarcinoma. Based on these data, the authors define three subtypes of pancreatic adenocarcinoma: classical, quasimesenchymal, and exocrine-like. Further, they observe differential response to treatment based

on genetic classifications of pancreatic tumors, potentially influencing future efforts towards individualizing therapy to be most effective for each patient.

Potential targets for pancreatic cancer immunotherapeutics
http://www.ncbi.nlm.nih.gov/pubmed/21463193
Co-authored by William Hawkins, MD (2005 Skip Viragh – Pancreatic Cancer Action Network – AACR Career Development Award), this article describes progress in tumor antigen vaccination and mechanisms by which immune suppression affects pancreatic cancer.

Aptamers: potential applications to pancreatic cancer therapy
http://www.ncbi.nlm.nih.gov/pubmed/21492073
This review article is authored by Rebekah White, MD (2007 Seena Magowitz – Pancreatic Cancer Action Network – AACR Career Development Award) and her research fellow, Kristy Rialon, MD. The article summarizes recent advances in the field of aptamers and discusses aptamer targets that have relevance to pancreatic cancer.

Current treatment options for pancreatic carcinoma
http://www.ncbi.nlm.nih.gov/pubmed/21491194
This *Current Oncology Reports* review article features Jordan Berlin, MD (Chair, Medical Advisory Board), and discusses current strategies in the diagnosis and treatment of resectable and advanced pancreas cancer.

Neoadjuvant GTX chemotherapy & IMRT chemoradiation for borderline resectable pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21520097
A team of researchers at the Moffitt Cancer Center, including Mokenge Malafa, MD (Medical Advisory Board), looked at neoadjuvant treatment with gemcitabine, docetaxel, and capecitabine (GTX) followed by 5-FU intensity modulated radiation therapy (IMRT) in borderline resectable patients. The authors conclude that neoadjuvant GTX induction chemotherapy followed by 5-FU-IMRT shows promise in improving the likelihood of resectability with negative margins in borderline resectable pancreatic cancer.

TeloVac pancreatic cancer vaccine in final stage of accrual in UK
http://www.bbc.co.uk/news/health-13088819
The TeloVac trial involves a vaccine targeting the protein telomerase present on the surface of pancreatic cancer cells. The goal is to make the tumor susceptible to attack by the patient's immune system. This trial is funded by the Cancer Research UK. Trial info can be found here.

Robotic techniques show promise for pancreatic procedures
http://www.internalmedicinenews.com/news/oncology-hematology/single-article/robotic-techniques-show-promise-for-pancreatic-procedures/1b50297d18.html
University of Pittsburgh clinicians are using the da Vinci Surgical System by Intuitive Surgical to perform pancreatic surgeries with robotic assistance. Surgeons at the Cleveland Clinic, Mayo Clinic, and University of Pisa also participated in these trials. Data have previously been published here, and new data have been submitted for publication.

Treatment of advanced pancreatic carcinoma with ^{90}Y-clivatuzumab tetraxetan
http://www.ncbi.nlm.nih.gov/pubmed/21527562
This *Clinical Cancer Research* article describes a phase I single dose escalation trial of ^{90}Y-clivatuzumab tetraxetan in patients with advanced pancreatic cancer. This agent, based on the humanized version of the PAM4 monoclonal antibody that binds a mucin produced very specifically by pancreatic carcinoma, was very effective as a single agent in arresting the growth, and even curing, human pancreatic carcinoma xenografts in animal models. In this human trial, toxicity was manageable and drug delivery to the tumor was accomplished. Additional studies of this agent in combination with gemcitabine are warranted.

Context dependence of CHK 1 as a therapeutic target for pancreatic cancers deficient in BRCA2
http://www.ncbi.nlm.nih.gov/pubmed/21289082
Published in *Molecular Cancer Therapeutics*, this study employed an RNAi screen to identify genes whose repression inhibited pancreatic cancer cell growth in the absence of BRCA2. The authors found that blocking the expression of checkpoint kinase 1 (CHK1) reduced cell growth. However, pancreatic cancer cells with the common alterations of K-Ras activating mutation and p53 inactivation were resistant to CHK1 small molecule inhibitors. This resistance could be overcome by co-administration of gemcitabine.

Role of heparanase in radiation-enhanced invasiveness of pancreatic carcinoma
http://www.ncbi.nlm.nih.gov/pubmed/21447736
Israeli and Italian scientists came together to study whether heparanase could modulate the effectiveness of radiotherapy in the treatment of pancreatic cancer. Their results suggested that combining heparanase inhibition with ionizing radiation (IR) is an effective strategy to prevent pancreatic tumor resistance and dissemination, compared with IR alone.

Paclitaxel as second-line chemotherapy in patients with gemcitabine-refractory pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21455624
In a retrospective study, researchers at Tohoku University Graduate School of Medicine in Japan found that weekly administration of paclitaxel in patients with gemcitabine-refractory pancreatic cancer seems to be well tolerated and can be effective. They include that paclitaxel treatment should be considered as salvage chemotherapy after gemcitabine failure in patients with good performance status.

Salvage therapy with mitomycin and ifosfamide in gemcitabine-resistant metastatic pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21454973
This Phase II Italian study was prematurely stopped based on poor outcome and a high level of grade 3-4 toxicity, and the authors concluded that the mitomycin and ifosfamide regimen was insufficiently active in gemcitabine-pretreated advanced pancreatic cancer.

Bevacizumab plus gemcitabine & oxaliplatin as first-line therapy for pancreatic cancer: a phase II trial
http://www.ncbi.nlm.nih.gov/pubmed/21479635
Because combined treatment with gemcitabine and oxaliplatin has yielded positive results, these MD Anderson researchers evaluated the addition of bevacizumab to that regimen. A phase II trial

investigated this combination in locally advanced or metastatic pancreatic cancer patients. The results did not meet the researchers' expected outcome, and yielded significant toxicity, leading to the conclusion that further evaluation of this regimen is not recommended.

Neoadjuvant therapy is associated with improved survival in resectable pancreatic adenocarcinoma
http://www.ncbi.nlm.nih.gov/pubmed/21523715
Published in *Cancer*, this study utilizes the California Cancer Surveillance Program for Los Angeles County to compare neoadjuvant versus adjuvant treatment strategies in resectable pancreatic cancer. The authors found that neoadjuvant therapy is associated with a decreased rate of lymph node positivity and improved overall survival.

NeoGemTax: gemcitabine & docetaxel neoadjuvant treatment for locally advanced pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21523499
Researchers from the Medical University of Vienna looked at preoperative administration of gemcitabine and docetaxel for patients with locally advanced, non-metastatic pancreatic cancer. Although NeoGemTax was safe and resection was feasible in a number of patients after systemic neoadjuvant treatment, further studies need to be done to increase the probability that treated patients will be able to undergo potentially curative surgical resection.

Combined treatment of pancreatic cancer with mithramycin A and tolfenamic acid promotes SP1 degradation and synergistic antitumor activity—letter/response/rebuttals
http://cancerres.aacrjournals.org/content/71/7.toc *(Scroll to Letters to the Editor at bottom of page)*
Dr. Chou from Memorial Sloan-Kettering expresses concern about a publication by Drs. Lee and Kong at MD Anderson. Here is the abstract for the original study. The authors disagree about the mathematical presentation of clinical data.

SURVIVORSHIP

Resection benefits older adults with locoregional pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21453378
University of Texas researchers conducted a retrospective cohort study utilizing SEER data and linked Medicare claims database. Despite greater short-term morbidity and mortality, surgical resection in older adults was associated with significantly lower hazard of death, compared to individuals of any age who did not undergo surgery.

Wait times for cancer surgery in the United States: trends and predictors of delays
http://www.ncbi.nlm.nih.gov/pubmed/21475020
Mark Talamonti, MD (Medical Advisory Board) is among the authors on this study, looking to identify changes in patients' wait times prior to surgery over the past decade, and factors associated with long wait times. The authors conclude that wait times for cancer treatment have increased over the last decade. As case-loads increase, wait times for treatment are likely to continue increasing, potentially resulting in additional treatment delay. Additional resources and strategies are needed to reduce wait times for cancer treatment in the United States.

Body mass index and outcomes from pancreatic resection: a review and meta-analysis
http://www.ncbi.nlm.nih.gov/pubmed/21484490
This study took place at the University of Louisville, evaluating MEDLINE data of the association between body mass index (BMI) and pancreatic cancer surgery. The authors report that BMI increases the operative complexity of pancreatectomy, but aggressive peri- and post-operative care can help minimize these enhanced risks.

Palliative chemo: When is enough too much?
http://www.clinicaloncology.com/ViewArticle.aspx?d_id=148&a_id=16929&ses=ogst
This *Clinical Oncology News* article discusses the difficult decisions of whether, when, and how much palliative chemotherapy to administer to patients at the end of their lives.