PANCREATIC CANCER NEWS & UPDATES – FEBRUARY 2011

PANCREATIC CANCER ACTION NETWORK NEWS

The vision of progress: Double the pancreatic cancer survival rate by 2020
http://www.pancan.org/section_about/vision_of_progress/index.php
The Pancreatic Cancer Action Network announced a bold initiative to double the five-year survival rate of pancreatic cancer by the year 2020. We will need all of your help in accomplishing this 2020 vision!

Press conference in Washington, DC to discuss pancreatic cancer federal funding
http://www.pancan.org/section_about/news_press_center/2011_press_releases/02_16_11_pr.php
On February 16, 2011, Pancreatic Cancer Action Network President and CEO Julie Fleshman, spokesperson Lisa Niemi Swayze, Senator Whitehouse (D-RI), and Representatives Eshoo (D-CA) and Lance (R-NJ) presented a press conference in Washington, DC to announce re-introduction of the Pancreatic Cancer Research and Education Act. In support of our bill, we also released the report, Pancreatic cancer: A trickle of federal funding for a river of need, to highlight the discrepancies in federal funding towards pancreatic cancer research, compared to the other top-five cancer killers in the US.

Pathway to Leadership grants awarded
http://www.pancan.org/section_about/news_press_center/2011_press_releases/03_08_11_pr.php
(This announcement technically came in March, but it's too exciting to wait!) The 2011 Pancreatic Cancer Action Network – AACR Pathway to Leadership grant recipients are Jennifer Bailey, PhD (Johns Hopkins University) and E. Scott Seeley, MD, PhD (Stanford University). Each will receive a grant for $600,000 over five years, funding them as they transition from a mentored, postdoctoral position to an independent laboratory. Very exciting! (All of the other grant recipients will be announced later this month, prior to the AACR Annual Meeting.)

BIOLOGY OF CANCER

Overexpression of receptor tyrosine kinase Axl promotes tumor cell invasion and survival in PDA
http://www.ncbi.nlm.nih.gov/pubmed/20922806
Research conducted in the laboratory of Huamin Wang, MD, PhD (2007 Skip Viragh – Pancreatic Cancer Action Network – AACR Career Development Award), in collaboration with others at MD Anderson, including Craig Logsdon, PhD (Scientific Advisory Board) and Jason Fleming, MD (Medical Advisory Board), analyzed the expression of the receptor tyrosine kinase Axl in pancreatic ductal adenocarcinoma (PDA). Axl was found to be over expressed in 70 percent of stage II PDA samples and 75% of PDA cell lines examined, and shown to promote invasion and survival. Moreover, Axl expression was found to be correlated with distant metastases and poor recurrence-free and overall survival rates.

Telomeres are shortened in ADM lesions associated with PanIN but not in isolated ADMs
http://www.ncbi.nlm.nih.gov/pubmed/20871595
This *Modern Pathology* publication, co-authored by Ralph Hruban, MD (Scientific Advisory Board), examines the changes in length of telomeres in acinar-to-ductal metaplasia (ADM) and pancreatic intraepithelial neoplasia (PanIN). Telomere length of human normal pancreas tissue, isolated ADMs, ADMs associated with PanIN lesions, and PanINs were measured. Telomeres were significantly shorter in PanIN-associated ADMs and in PanINs, than in normal cells or isolated ADMs. These results indicate

that isolated ADMs are not a precursor to PanINs, and support the hypothesis that PanIN-associated ADMs arise secondary to PanIN lesions.

Structural analysis of the cancer-specific promoter in mesothelin and in other genes overexpressed
http://www.ncbi.nlm.nih.gov/pubmed/21288909
Research out of Scott Kern's laboratory at Johns Hopkins led to this publication in *JBC*. The candidate biomarker mesothelin has previously been characterized as over-expressed in nearly one-third of human malignancies. Here, the authors' data suggest that the mechanism by which mesothelin is over-expressed in pancreatic cancer cells may also lead to over-expression of other tumor markers.

Pancreatic cancer cells respond to type I collagen by inducing Snail expression to promote MT1-MMP
http://www.ncbi.nlm.nih.gov/pubmed/21288898
Also published in *JBC*, explored the relationship between Snail (a well-known regulator of epithelial to mesenchymal transition) and the collagen-rich desmoplastic reaction surrounding pancreatic tumors. Culturing pancreatic cancer cells in a 3D collagen matrix led to an induction of Snail expression. Over-expression of Snail in PDAC cells resulted in a robust membrane type 1-matrix metalloproteinase (MT1-MMP, MMP-14)-dependent 2D collagen invasion. Overall, their data demonstrate that pancreatic cancer cells increase Snail on encountering collagen-rich milieu, and suggest that the desmoplastic reaction actively contributes to pancreatic ductal adenocarcinoma progression.

Spatial regulation of RhoA activity during pancreatic cancer cell invasion driven by mutant p53
http://www.ncbi.nlm.nih.gov/pubmed/21266354
Timpson, *et al* contributed this paper to *Cancer Research*, discussing the role of RhoA in invasion of pancreatic cancer cells. A mouse model of pancreatic cancer driven by mutant p53 was imaged using FLIM-FRET (fluorescence lifetime imaging microscopy-fluorescence resonance energy transfer). High RhoA activity was observed in the leading and rear ends of invasive pancreatic cancer cells, and absent from cells with poor invasive capacity. Treatment with the anti-invasive agent dasatinib specifically blocked RhoA activity in the poles of the invasive cells, independent on basal RhoA activity in the cell body.

DCAMKL-1 regulates EMT in human pancreatic cells through a miR-200a-dependent mechanism
http://www.ncbi.nlm.nih.gov/pubmed/21285251
Also published in *Cancer Research,* these findings illustrate direct regulatory links between the pancreatic stem cell marker DCAMKL-1, microRNAs, and epithelial-mesenchymal transition (EMT) in pancreatic cancer. Moreover, the authors demonstrate a functional role for DCAMKL-1.

PDX-1: Demonstration of oncogenic properties in pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/20886630
Please also see article about PDX-1 in the Early Detection, Diagnosis, and Prognosis section
PDX-1 (pancreatic-duodenal homeobox-1) is a transcription factor that regulates embryonic development of the pancreas and other organs. PDX-1 has been observed to be over-expressed in several cancer types, including pancreatic. Here, the authors perform experiments to over-express or repress PDX-1 in pancreatic cancer cell lines, and see an increase in proliferation, invasion, and colony formation in response to PDX-1 expression and activation. *In vivo*, cells expressing PDX-1 displayed larger subcutaneous tumor formation in mice. PDX-1 is a potential oncogene in pancreatic cancer.

CXCR2-dependent endothelial progenitor cell mobilization in pancreatic cancer growth
http://www.ncbi.nlm.nih.gov/pubmed/21286374
UCLA scientists showed that CXCR2-knockout mice with pancreatic cancer display reduced levels of bone marrow-derived circulating endothelial progenitor cells. CXCR2 gene knockout also reduced

proliferation, differentiation, and vasculogenesis of endothelial precursor cells *in vitro*, suggesting a role for CXCR2-mediated pancreatic tumor neovascularization.

ETIOLOGY

Patterns of pancreatic resection differ between patients with familial and sporadic pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21359597
Researchers at the Mayo Clinic, including Gloria Petersen, PhD (Scientific Advisory Board), investigated differences in outcome of pancreatic cancer patients with sporadic or familial disease, following resection. Their data suggest that patients with familial pancreatic cancer tended to develop tumors outside of the pancreas head more frequently than patients with sporadic disease. There was no difference in survival observed at two years between familial and sporadic pancreatic cancer patients.

Body mass index and obesity- and diabetes-associated genes and risk for pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21357378
MD Anderson researchers explored the hypothesis that obesity- and diabetes-related genes modify the risk of pancreatic cancer. Their findings revealed genetic factors that might impact the risk of pancreatic cancer, and therefore could help identify high-risk individuals for prevention.

Jewish ethnicity and pancreatic cancer mortality in a large United States cohort
http://www.ncbi.nlm.nih.gov/pubmed/21278327
Epidemiologists at Emory University conducted the Cancer Prevention Study II, involving one million participants. During follow-up from 1982 to 2006, there were 6,727 pancreatic cancer deaths, including 480 Jewish participants. After adjusting for age, sex, smoking, body mass index, and diabetes, pancreatic cancer mortality was higher among Jewish participants than among non-Jewish whites. Future studies are necessary to further understand this disparity.

Nutrients, food groups, dietary patterns and risk of pancreatic cancer in postmenopausal women
http://www.ncbi.nlm.nih.gov/pubmed/21278328
Conducted at the University of Minnesota, this group's findings do not support the hypothesis that fruits, vegetables, and red meat are associated with pancreatic cancer.

Intake of vegetables, fruits, carotenoids, and vitamins C and E and pancreatic cancer risk
http://www.ncbi.nlm.nih.gov/pubmed/21328344
Data from the Netherlands Cohort Study also yielded no association between a high consumption of fruit and vegetable consumption and pancreatic cancer risk. Furthermore, they observed no association between the intake of carotenoids, vitamins, and vitamin supplements and pancreatic cancer risk.

PREVENTION

Implications of cancer stem cell theory for cancer chemoprevention by natural dietary compounds
http://www.ncbi.nlm.nih.gov/pubmed/21295962
This *Journal of Nutritional Biochemistry* article reviews the current knowledge of the most common natural dietary compounds for their impact on self-renewal pathways and potential effect against cancer stem cells. The article summarizes three signaling pathways (Wnt/B-catenin, Hedgehog, and Notch) for their functions in self-renewal of cancer stem cells. The compound Sulforaphane has been specifically implicated in inhibiting pancreatic and breast tumor-initiating cells. (Another notable fact from this paper is that it represents a rare partnership/collaboration between University of Michigan [Go Blue!] and Ohio State University.)

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Pdx1 expression in pancreatic precursor lesions and neoplasms

http://www.ncbi.nlm.nih.gov/pubmed/21297446

Please also see article about Pdx1 in the Biology section

University of Texas, Memorial Sloan-Kettering, and Johns Hopkins researchers, including Anirban Maitra, MD (2004 Pancreatic Cancer Action Network – AACR Career Development Award) and Ralph Hruban, MD (Medical Advisory Board), examined expression of Pdx1 in pancreatic precursor lesions and neoplasms. Pdx1 (pancreatic and duodenal homeobox) is required for pancreatic embryonic development. The researchers found Pdx1 expression in many types of precursor lesions, in addition to pancreatic endocrine tumors and pancreatic ductal adenocarcinomas.

Serum biomarker panels for the detection of pancreatic cancer

http://www.ncbi.nlm.nih.gov/pubmed/21325298

Commentary: http://www.ncbi.nlm.nih.gov/pubmed/21304000

A multi-institutional collaborative team, including Selwyn Vickers, MD (Scientific Advisory Board), prepared this paper for *Clinical Cancer Research*. The researchers analyzed expression of 83 circulating proteins in the sera of patients with pancreatic ductal adenocarcinoma, benign pancreatic conditions, and healthy controls. The panels of CA19-9/ICAM-1/OPG and CA19-9/CEA/TIMP-1 showed promising sensitivity and specificity in differentiating pancreatic ductal adenocarcinoma samples from benign or healthy. Additional clinical validation is warranted to determine these marker panels' role in screening individuals at high risk for pancreatic cancer.

Poly(A) RT-PCR measurement of diagnostic genes in pancreatic juice in pancreatic cancer

http://www.ncbi.nlm.nih.gov/pubmed/21245863

The objectives of this study reported in the *British Journal of Cancer* were to utilize poly(A) RT-PCR to measure expression levels of diagnostic Indicator genes, selected from microarray studies, of RNA from intraoperatively sampled pancreatic ductal juice and to correlate these expression levels with those in matched pancreatic tissue resection samples. Of the 30 Indicator genes measured, just one, ANXA1, showed a significant correlation of expression level between pancreatic juice and tissue samples, whereas three genes, IGFBP3, PSCA, and SPINK1, showed significantly different expression between cancerous and benign pancreatic tissue samples. This study represents a proof of principle that pancreatic juice can be analyzed by poly(A) cDNA technique to correlate with gene expression in pancreatic tumor tissue samples.

L1CAM expression at the cancer invasive front is a novel prognostic marker of pancreatic cancer

http://www.ncbi.nlm.nih.gov/pubmed/21360711

L1 cell adhesion molecule (L1CAM) has been found to be a prognostic marker in other cancer types. Here, 107 surgical specimens of pancreatic ductal adenocarcinoma were examined, and 23 were positive for L1CAM. Of those, 21 showed expression specific to the invasive front of the cancer tissue. Moreover, L1CAM expression was significantly correlated with poor histological grade, lymph node involvement, and distant metastasis. These results suggest that L1CAM could serve as a poor prognostic marker for pancreatic cancer, associated with increased risk of invasion.

Pattern of lymph node involvement and prognosis in pancreatic adenocarcinoma

http://www.ncbi.nlm.nih.gov/pubmed/21263243

The purpose of this study was to retrospectively compare clinical outcome in patients with pancreatic ductal adenocarcinoma with direct invasion into peripancreatic lymph nodes, with patients with node-negative adenocarcinomas, and patients with true lymphatic lymph node metastasis. The authors' results indicate that patients with isolated direct lymph node invasion fare similarly to patients with node-negative disease, as opposed to patients with true lymph node metastases.

Distinguishing early-stage pancreatic cancer patients from disease-free people using serum profiling
http://www.ncbi.nlm.nih.gov/pubmed/21261478
Hocker and colleagues evaluated the usefulness of electrospray mass spectrometry to distinguish sera of early-stage pancreatic cancer patients from disease-free individuals. Predictive values for cancer stage I/II test efficiency, specificity, and sensitivity were 78%, 77%, and 79%, respectively, suggesting the usefulness of electrospray mass spectrometry.

Association of multi-drug resistance gene polymorphisms with pancreatic cancer outcome
http://www.ncbi.nlm.nih.gov/pubmed/20922799
The purpose of this study was to identify single nucleotide polymorphisms (SNPs) of multidrug resistance genes that are associated with clinical outcome in patients with potentially resectable pancreatic adenocarcinoma who were treated with preoperative gemcitabine-based chemoradiotherapy at MD Anderson Cancer Center. Genotypes of MRP5 A-2G AA and MRP2 G40A GG were associated with reduced overall survival, and the latter was associated with poor response to chemoradiotherapy.

Pancreatic cancer in 2010: New insights for early intervention and detection
http://www.ncbi.nlm.nih.gov/pubmed/21293504
Researchers at the University of Liverpool wrote this review article published in *Nature Reviews Gastroenterology and Hepatology*. The article discusses utilizing a better understanding of the biology of pancreatic cancer to discover biomarkers to aid in earlier detection and prognostic decisions.

TREATMENT

Everolimus for advanced pancreatic neuroendocrine tumors
http://www.ncbi.nlm.nih.gov/pubmed/21306238
MD Anderson press release: http://mdanderson.bm23.com/public/?q=preview_message
Published in the *New England Journal of Medicine*, this study reports that Everolimus, an inhibitor of mammalian target of rapamycin (mTor), significantly prolonged progression-free survival among patients with progressive pancreatic neuroendocrine tumors, with a low rate of adverse side effects.

Sunitinib malate for the treatment of pancreatic neuroendocrine tumors
http://www.ncbi.nlm.nih.gov/pubmed/21306237
Also published in the same edition of the *New England Journal of Medicine*, the multi-targeted tyrosine kinase inhibitor sunitinib was found to improve progression-free survival, overall survival, and the objective response rate in patients with advanced pancreatic neuroendocrine tumors.

3D collagen I promotes gemcitabine resistance through MT1-MMP-mediated expression of HMGA2
http://www.ncbi.nlm.nih.gov/pubmed/21148071
Among this research team at Northwestern University is Paul Grippo, PhD, recipient of the 2007 Nancy Daly Riordan – Pancreatic Cancer Action Network – AACR Career Development Award. The collagen-rich fibrotic reaction surrounding pancreatic tumors has been hypothesized to limit the efficacy of gemcitabine treatment. A 3D model of pancreatic cancer cells revealed that collagen from the microenvironment activates membrane-type 1 matrix metalloproteinase (MT1-MMP), leading to Erk1/2 phosphorylation and expression of HMGA2, overriding checkpoint arrest. The authors propose that targeting MT1-MMP may be a novel approach to sensitizing pancreatic tumors to gemcitabine.

Standardization of surgical and pathologic variables is needed in multicenter trials of adjuvant therapy
http://www.ncbi.nlm.nih.gov/pubmed/20811779
A collaborative group of researchers from across the country, including Vince Picozzi, MD (Medical Advisory Board), reports on results from the American College of Surgeons Oncology Group (ACOSOG) Z5031 trial. The Z5031 was a national trial of chemoradiation followed by pancreaticoduodenectomy

(PD). The authors discovered that trials of adjuvant therapy following PD suffer from a lack of standardization and quality control prior to patient enrollment. These data suggest areas for improvement in the design of multidisciplinary treatment protocols.

Multicenter phase II trial of adjuvant therapy for resected pancreatic cancer using cisplatin, 5-fluorouracil, and interferon-alfa-2b-based chemoradiation: ACOSOG Trial Z05031
http://www.ncbi.nlm.nih.gov/pubmed/20670978
Vince Picozzi, MD is joined by Eileen O'Reilly, MD (Medical Advisory Board) and other members of the American College of Surgeons Oncology Group for this *Annals of Oncology* report. Patients with resected (R0/R1) adenocarcinoma of the pancreatic head were treated with adjuvant interferon-alfa-2b, cisplatin, and continuous infusion 5-fluorouracil concurrently with external-beam radiation. The all-cause toxicity rate of at least grade 3 was 95% during therapy. Although the trial showed promising efficacy results, modifications to address the toxicity will be necessary before moving forward with this treatment regimen.

Axitinib plus gemcitabine in patients with advanced pancreatic adenocarcinoma
http://www.ncbi.nlm.nih.gov/pubmed/21306953
Axitinib, a potent anti-vascular endothelial growth factor (VEGF) receptor inhibitor, was tested in a randomized Phase 3 trial with gemcitabine, compared to gemcitabine alone, in advanced pancreatic adenocarcinoma. The trial showed that the addition of axitinib to gemcitabine does not improve overall survival in advanced pancreatic cancer. These results add to increasing evidence that targeting of VEGF signaling is an ineffective strategy in this disease.

Phase I trial of hedgehog pathway inhibitor GDC-0449 in patients with solid tumors
http://www.ncbi.nlm.nih.gov/pubmed/21300762
Researchers and clinicians in Detroit, Baltimore, South San Francisco, and Scottsdale came together to conduct a Phase I clinical trial of the hedgehog pathway inhibitor GDC-0449. Of the 68 enrolled patients, eight had pancreatic cancer. Tumor responses were observed in 20 patients: 19 with basal cell carcinoma and one unconfirmed response in a medulloblastoma patient. Only one pancreatic cancer patient achieved stable disease; the other seven pancreatic cancer patients experienced progressive disease while on the trial. The researchers hypothesized that pancreatic cancer patients on this trial had highly refractory, bulky disease, suggesting that the interplay between stromal (where hedgehog signaling is known to take place) and tumor cells may be less critical than observed in patients with less advanced disease.

Combined blockade of Src and EGFR with gemcitabine overcomes STAT3-mediated resistance
http://www.ncbi.nlm.nih.gov/pubmed/21266529
The authors combine Src inhibition (dasatinib), EGFR inhibition (erlotinib), and gemcitabine, and assess effects on growth of pancreatic cancer cells *in vitro* and *in vivo*. The triple combination proved more effective than any single agent, or combination of two agents. Further, triple treatment alleviated STAT3-mediated resistance of Src inhibition.

Context dependence of CHK1 as a therapeutic target for pancreatic cancers deficient in BRCA2
http://www.ncbi.nlm.nih.gov/pubmed/21289082
An RNA-interference screen identified that depletion of the checkpoint kinase CHK1 led to growth inhibition of pancreatic cancer cells lacking BRCA2. Further experiments showed that BRCA2-mutant cells with activated Kras and inhibited p53 were resistant to pharmacological inhibition of CHK1, but this resistance was overcome by combined treatment with gemcitabine.

Epeius Biotechnologies' REXIN-G gains Phase 3 product designation from the U.S. FDA
http://www.prnewswire.com/news-releases/epeius-biotechnologies-rexin-g-a-tumor-targeted-genetic-medicine-for-metastatic-cancer-gains-phase-3-product-designation-from-the-us-fda-117085613.html
REXIN-G is a targeted gene delivery system developed to seek out and destroy metastatic cancer. Since REXIN-G received Phase 3 status from the US FDA, Epeius will move forward with its diversified, strategic Phase 3 drug development program for pancreatic cancer, osteosarcoma, and soft tissue sarcoma.

Clavis Pharma's CP-4126 enters new Phase II clinical trial in pancreatic cancer patients
http://www.clavispharma.com/News+%26+Events/2011+Press+releases/776.cms
CP-4126 is a novel, patented, lipid-conjugated derivative of the anti-cancer drug gemcitabine, developed using Clavis' lipid vector technology. CP-4126 is designed to be absorbed by cancer cells independent of hENT1 levels, which would otherwise dictate the uptake of gemcitabine. This Phase II trial will investigate the use of CP-4126 as a second line treatment for advanced, metastatic pancreatic cancer in patients refractory to first line gemcitabine treatment, where the mechanism of resistance is likely to be due to impaired drug entry into tumor cells.

Treatment-related mortality with bevacizumab in cancer patients: a meta-analysis
http://www.ncbi.nlm.nih.gov/pubmed/21285426
Comment in: http://www.ncbi.nlm.nih.gov/pubmed/21285431
The February 2nd edition of *JAMA* included this article and editorial comments. Retrospective analyses of randomized controlled trials suggested that fatal adverse events have been reported in cancer patients treated with the widely used angiogenesis inhibitor bevacizumab in combination with chemotherapy. Currently, the role of bevacizumab in treatment-related mortality is not clear.

GI cancers in 2010: New standards and a predictive biomarker for adjuvant therapy
http://www.ncbi.nlm.nih.gov/pubmed/21278772
This *Nature Reviews Clinical Oncology* article discusses advancements in the treatment of poorer-prognosis GI cancers made over the past year.

SURVIVORSHIP
Suicide in patients with pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/20824626
Comment in: http://www.ncbi.nlm.nih.gov/pubmed/21254047
Researchers at the Moffitt Cancer Center, including Mokenge Malafa, MD (Medical Advisory Board), reviewed data from the SEER database for patients diagnosed with pancreatic cancer between 1995 and 2005. They found that male patients with pancreatic adenocarcinoma had an almost 11-times higher risk of committing suicide than age-matched controls. The risk of suicide is especially high in the first three months following diagnosis, suggesting that patients' psychosocial wellbeing should be carefully monitored during that period.

EUS visualization and direct celiac ganglia neurolysis predicts better pain relief
http://www.ncbi.nlm.nih.gov/pubmed/21295640
Endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) was found to improve pain control in patients with pancreatic cancer.

Global cancer facts & figures: 2nd edition
http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-027766.pdf
On February 4, 2011, World Cancer Day, the American Cancer Society released its second edition of global cancer facts & figures. According to estimates from the International Agency for Research on Cancer (IARC), there were approximately 12.7 million new cancer cases worldwide in 2008, 5.6 million of which occurred in economically developed countries and 7.1 million in economically developing countries. By 2030, the global cancer burden is expected to nearly double, growing to 21.4 million cases. While that increase is the result of demographic changes – a growing and aging population – it may be compounded by the adoption of unhealthy lifestyles and behaviors related to economic development, such as smoking, poor diet, and physical inactivity.

Cancer facts & figures for African Americans: 2011-2012
http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-027765.pdf
The American Cancer Society also published its newest data about cancer facts and figures for African Americans. This report reveals that even as overall cancer death rates continue a downward trend among black Americans, the community still bears the biggest brunt of cancer-related deaths in the United States.