PANCREATIC CANCER ACTION NETWORK AND COMMUNITY NEWS

AACR Special Conference – Pancreatic Cancer: Progress and Challenges – registration is open

The first AACR special conference on pancreatic cancer will take place June 18-21, 2012 at the Hyatt Regency Lake Tahoe. Registration is now open. The deadline for abstract submission and award application is Wednesday, April 11, and advance registration closes on Monday, May 7.

Be a Hero: Volunteer for Progress
http://www.knowitfightitendit.org/

The campaign for this year’s November Awareness Month was “Volunteer for Progress”. Check out the site to see all the videos, including Kimberly Kelly, PhD (2007 Laurie and Paul MacCaskill – Pancreatic Cancer Action Network – AACR Career Development Award). There are also opportunities to sign up to volunteer and inspirational stories of heroism.

Abstracts of papers submitted to the 42nd Annual Meeting of the American Pancreatic Association
http://journals.lww.com/pancreasjournal/Citation/2011/11000/Abstracts_of_Papers_Submitted_to_the_42nd_Annual.26.aspx

The APA Annual Meeting took place in Chicago, November 2-5, 2011. Please also see the Presidential Address by immediate past-president Diane Simeone, MD (2010 The Randy Pausch – Pancreatic Cancer Action Network – AACR Innovative Grant):
2011 American Pancreatic Association Presidential Address: Demystifying the Pancreas

NPR This American Life podcast: So Crazy It Just Might Work
http://www.thisamericanlife.org/radio-archives/episode/450/so-crazy-it-just-might-work
Jonathan Brody, PhD (2010 Skip Viragh – Pancreatic Cancer Action Network – AACR Career Development Award) is featured in this edition of the NPR radio show, This American Life. The story discusses an unlikely collaboration between Dr. Brody and one of his music professors from his undergraduate studies at Skidmore College, whereby they try to kill pancreatic cancer cells with sound waves.

Caring for Carcinoid Foundation-AACR Grants for Pancreatic Neuroendocrine Tumor Research
http://www.aacr.org/home/scientists/aacr-research-funding/current-funding-opportunities-for-independent-researchers.aspx

“The Caring for Carcinoid Foundation-AACR Grants for Carcinoid Tumor and Pancreatic Neuroendocrine Tumor Research represent a joint effort to promote and support innovative cancer research. These
grants are available to independent junior and senior investigators to develop and study new ideas and approaches that have direct application and relevance to carcinoid tumors or pancreatic neuroendocrine tumors.” Applications are due January 17, 2012.

**Researchers make discoveries in fight against pancreatic cancer**

The American Cancer Society website posted this piece in their News and Features, describing recent progress in pancreatic cancer research.

**BIOLOGY OF CANCER**

**Pancreatic cancer stem cell biology and its therapeutic implications**

This review in the *Journal of Gastroenterology* is coauthored by Diane Simeone, MD (2010 The Randy Pausch Family – Pancreatic Cancer Action Network – AACR Innovative Grant and Scientific Advisory Board). Drs. Bednar and Simeone discuss the role and importance of pancreatic cancer stem cells in the development and progression of the disease, as well as resistance to therapy.

**GLI1 inhibition promotes epithelial-to-mesenchymal transition in pancreatic cancer cells**

This *Cancer Research* paper is coauthored by Martin Fernandez-Zapico, MD (2007 Carole and Bob Daly – Pancreatic Cancer Action Network – AACR Career Development Award). The investigators observe that the Hedgehog signaling pathway is active in the stroma surrounding pancreatic tumors, but inactive in the tumors themselves. Here, they show that inhibition of the transcription factor GLI1 (normally activated by Hedgehog signaling) leads to increased epithelial-to-mesenchymal transition. Therefore, the low levels of Hedgehog/GLI in the tumor promote aggressive and metastatic behavior of pancreatic cancer cells.

**Restricted heterochromatin formation links NFATc2 repressor activity with growth promotion**

Martin Fernandez-Zapico, MD (2007 Carole and Bob Daly – Pancreatic Cancer Action Network – AACR Career Development Award) is also an author on this article. The oncogenic transcription factor nuclear factor of activated T cells (NFAT) c2 was found to transcriptionally silence the p15(INK4b) tumor suppressor pathway in pancreatic cancer cells. Inactivation of NFATc2 resulted in restoration of p15(INK4b) activity and inhibited tumor growth, suggesting a novel treatment strategy.

**Crosstalk between the canonical NF-kB and Notch signaling pathways inhibits Ppar-g expression**

An author on this paper is Dave Tuveson, MD, PhD (2003 Pancreatic Cancer Action Network – AACR Career Development Award and Chair, Scientific Advisory Board). The investigators examined crosstalk between Kras, Notch, and the NFkB pathway in pancreatic cancer initiation and progression. In the mouse model of pancreatic cancer driven by mutant Kras, expression of a mutated form of Ikk2, a component of the NFkB family, led to a marked delay in the progression of pancreatic cancer. Absence
of Ikk2 also led to down-regulation of Notch-target genes, which stimulate an inflammatory response. These data suggest significant crosstalk and interdependence of these three major signaling pathways.

**Use of multifunctional sigma-2 receptor ligand conjugates to trigger cancer-selective cell death**


This study came out of the lab of William Hawkins, MD (2005 Skip Viragh – Pancreatic Cancer Action Network – AACR Career Development Award) and also features Hiroyuki Kashiwagi, MD (2007 Samuel Stroom – Pancreatic Cancer Action Network – AACR Young Investigator Award). The authors found that the SV119 ligand of the sigma-2 receptor (present on the surface of pancreatic cancer cells) was able to induce a selective cell killing. Additionally, small molecules that target cell survival pathways can be effectively conjugated to SV119.

**Targeting Notch pathway enhances rapamycin antitumor activity through PTEN phosphorylation**


Jordan Berlin, MD (Chair, Medical Advisory Board) contributed to this *Molecular Cancer* publication. A crosstalk between the Notch and Akt signaling pathways was discovered, whereby Notch activation in pancreatic cancer cells led to Akt activation via PTEN phosphorylation. Interestingly, combined treatment with a gamma-secretase inhibitor (blocks Notch signaling) and rapamycin (blocks mTor, part of Akt pathway) showed promising effects in suppressing activation of Akt and leading to greater cell killing than either drug alone.

**Proteomics portrait of archival lesions of chronic pancreatitis**


This study took place in the lab of Teri Brentnall, MD (Emeritus Scientific Advisory Board). Proteomic analyses of tissue samples of normal pancreas, mild pancreatitis, severe pancreatitis, and pancreatic ductal adenocarcinoma were compared, and it was discovered that there is a substantial increase in the number of differentially expressed proteins consistent as the disease advances. The differently expressed proteins and pathways involved could shed light on the biology of disease progression.

**Metformin inhibits cell proliferation, migration and invasion by attenuating CSC function**


The AACR journal *Cancer Prevention Research* published this article discussing the diabetes drug metformin and its effects on pancreatic cancer stem cells (CSCs). The authors’ data suggest that treatment with metformin decreased cell survival and other CSC-like phenotypes, including a decrease in protein markers of CSCs, and an increase in otherwise repressed microRNAs.

** Targeting FGFR/PDGFR/VEGFR impairs tumor growth, angiogenesis, and metastasis**


Published in *Molecular Cancer Therapeutics*, this article describes treating pancreatic cancer cells with TKI258, an inhibitor of the receptor tyrosine kinases fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR). The investigators’ data suggested that TKI258 affected the growth and motility of the pancreatic cancer cells as well as endothelial and vascular smooth muscle cells.
MiR-126 acts as a tumor suppressor in pancreatic cancer cells via the regulation of ADAM9
Hamada and colleagues report that miR-126 levels are lower in pancreatic cancer cells. MiR-126 was found to regulate levels of disintegrin and metalloproteinase domain-containing protein 9 (ADAM9), allowing its high expression in pancreatic cancer. Disruption of the miR-126/ADAM9 axis led to inhibition of invasion of pancreatic cancer cells.

Hedgehog signaling antagonist GDC-0449 inhibits pancreatic cancer stem cell characteristics
Scientists at the University of Kansas Cancer Center sought to examine the molecular mechanisms by which GDC-0449 (Vismodegib), an inhibitor of Smoothened, regulates human pancreatic cancer stem cells characteristics in vitro. Treatment with GDC-0449 led to decreased cell viability and increased death by apoptosis in both pancreatic cancer cell lines and cancer stem cell populations.

Expression of DNMT1 and DNMT3a are regulated by GLI1 in human pancreatic cancer
Scientists from Tongji University in Shanghai, China investigated the relationship between GLI1 transcription factor and DNA methyltransferases (DNMTs) in pancreatic cancer. Their data suggest that DNMT1 and DNMT3a are target genes of GLI1 in human pancreatic cancer tissue samples.

Two distinct sites in sonic hedgehog combine for heparan sulfate interactions, cell signaling functions
This JBC paper looks at the heparin and heparan sulfate proteoglycan binding sites on sonic hedgehog, and how that interaction affects pathway activation. Using a pancreatic cancer cell line as a model, the authors determined that mutating some or all of the lysine residues responsible for heparin and heparan sulfate binding led to a reduction in proliferation and invasive capacity of the cells.

Metscape 2 bioinformatics tool for the analysis and visualization of metabolomics, gene expression
Metscape, part of the NIH-supported National Center for Integrative Biomedical Informatics suite of tools, has been redesigned and can be used to link metabolite data with other types of high-throughput molecular data. The authors use gene expression and metabolite data from pancreatic ductal adenocarcinoma as a demonstration of the Metscape tool.

2-triazenoazaindoles: Novel class of triazenes inducing transcriptional down-regulation of EGFR, HER-2
Researchers at University of Southern Denmark evaluated AS104, a novel compound of the triazene class, for its effectiveness at blocking activity of epidermal growth factor receptor family members EGFR and HER-2 in pancreatic cancer cell lines. They found that AS104 regulates EGFR and HER-2 at the transcriptional level, and treatment induces decreased cell growth and metabolic activity.
Long noncoding intronic RNAs are differentially expressed in primary and metastatic pancreatic cancer
Tahira et al explored the expression and relevance of long non-coding RNA (lncRNA) in pancreatic cancer cells. Their data suggest that several sets of lncRNAs are preferentially expressed in pancreatic cancer cells, and their presence correlates with more malignant and/or metastatic cells.

Proteome of formalin-fixed paraffin-embedded pancreatic ductal adenocarcinoma and LN metastases
Published in The Journal of Pathology, this study describes the use of laser capture microdissection to obtain matched tumor and lymph node metastasis samples from formalin-fixed paraffin-embedded tissue from pancreatic cancer patients. Proteomic analyses revealed a significant overlap between altered protein levels in each type of sample, providing a proof of principle for this technique. Further, 14-3-3 sigma and S100P were identified as potential targets for therapeutic intervention.

Beta2-adrenoceptor blockage induces G1/S phase arrest and apoptosis in pancreatic cancer cells
This Molecular Cancer paper explores response of pancreatic cancer cells to ligands that activate or block the beta-adrenoceptors. The beta2-adrenergic antagonist ICI118,551 was found to induce G1/S arrest and apoptosis via Ras/Akt/NFkappaB signaling.

Curcumin analog CDF inhibits pancreatic tumor growth by switching on microRNAs, attenuating EZH2
Bao et al looked at effects of CDF, a novel analog of the turmeric spice component curcumin that has anti-oxidant properties, in the treatment of pancreatic cancer cells. CDF led to decreased cell growth, survival, formation of pancreatospheres, invasion, and cancer stem cell function. These effects were thought to be mediated by increased expression of tumor suppressor microRNAs which led to decreased expression of the histone methyltransferase EZH2.

Role of MUC4-NIDO domain in the MUC4-mediated metastasis of pancreatic cancer cells
University of Nebraska Medical Center researchers report that the nidogen-like (NIDO) domain of MUC4 (a large glycoprotein that is over-expressed in pancreatic cancer and associated with disease progression and metastasis) contributes to the protein-protein interaction property of MUC4 in pancreatic cancer cells. In in vitro experiments, expression of a mutant form of MUC4 lacking the NIDO domain led to decreased invasiveness of a pancreatic cancer cell line, but did not affect cell growth or motility. In vivo, implantation of cells expressing NIDO-mutant MUC4 led to significantly decreased metastasis as compared to cells expression wild-type MUC4.

Inactivation of Mirk/dyrk1b kinase targets quiescent pancreatic cancer cells
Researchers at SUNY Upstate Medical University published this Molecular Cancer Therapeutics paper. Their experiments showed that expression of the serine/theronine kinase Mirk/dyrk1B is elevated in quiescent pancreatic cancer cells. Furthermore, a small molecule inhibitor of Mirk kinase blocked cell arrest, and led to increased cell-killing by gemcitabine.
3,5-bis(2,4-difluorobenzylidene)-4-piperidone, a novel compound that affects growth & angiogenesis
The authors describe a novel compound: 3,5-bis(2,4-difluorobenzylidene)-4-piperidone (DiFiD). DiFiD blocked activation of Notch-1 in pancreatic cancer cells, due to reduction of Jagged-1 and gamma-secretase complex proteins presenilin-1 and nicastrin. Overall, their data suggest that DiFiD has potential as a therapeutic agent by blocking several components of the Notch signaling pathway.

Targeting interleukin-4 receptor alpha with hybrid peptide for effective cancer therapy
Molecular Cancer Therapeutics published this article describing an alpha-lytic peptide targeting interleukin-4 receptor (IL4R) in cancer cells. The authors’ model was a xenograft of pancreatic cancer cells, and the results suggested that their alpha-lytic IL4R peptide has potential in the treatment of IL4R-positive tumors.

Long noncoding intronic RNAs are differentially expressed in primary and metastatic pancreatic cancer
Tahira and colleagues looked at long noncoding intronic RNAs (lncRNAs) and found their expression/abundance correlated with stage of pancreatic cancer disease.

EpCAM/CD3-bispecific T cell engaging antibody M110 eliminates primary pancreatic cancer stem cells
Since a known feature of pancreatic cancer stem cells (CSCs) is expression of EpCAM, researchers from Spanish National Cancer Research Centre investigated the use of a targeted immunotherapy to EpCAM using the bispecific T cell engaging antibody MT110 in pancreatic cancer cell lines and primary patient samples. Although more pronounced in the cell lines than primary tumors, treatment with MT110 showed effectiveness targeting pancreatic CSCs.

Primary cilium depletion typifies cutaneous melanoma in situ and malignant melanoma
This work was conducted by Scott Seeley, MD, PhD (2011 Pancreatic Cancer Action Network – AACR Pathway to Leadership Grant). Although this PloS One article is focused on Dr. Seeley and colleagues’ studies in melanoma, their findings related to the roles of primary cilium can be considered directly relevant to pancreatic cancer. Overall, their data suggest that the loss of primary cilium can differentiate early melanocytic lesions from nevi, or moles. Similarly, the primary cilium has been shown to be lost from pancreatic cancer.

ETIOLOGY
Cigarette smoking and pancreatic cancer
Gloria Petersen, PhD (Scientific Advisory Board) contributed to this study reporting results from the International Pancreatic Cancer Case-Control Consortium (PanC4). PanC4 included over 6,500 pancreatic cancer cases, and this large pooled analysis confirmed that cigarette smoking is associated with an increased risk of pancreatic cancer. The risk increases in association with more cigarettes.
smoked and longer duration of smoking. It takes 20 years after quitting for a past smokers’ risk to equal the never-smoking population.

**Pancreatic cancer susceptibility loci and their role in survival**
Researchers at the German Cancer Research Center sought to replicate results from the PanScan project, a genome-wide association study, to identify susceptibility loci as well as determine whether expression of observed SNPs might impact patient survival. The authors were able to replicate several associations between SNPs and pancreatic cancer risk and found that expression of one particular SNP was weakly associated with a better overall survival.

**High glucose promotes cell proliferation via the induction of EGF expression, transactivation of EGFR**
The authors of this *PLoS One* article investigated the mechanism by which high glucose levels (frequently observed in pancreatic cancer patients) are connected to pancreatic cancer development. In cell line experiments, they determined that high glucose stimulates the expression and secretion of the epidermal growth factor (EGF) ligand, and the transactivation of its receptor, EGFR.

**Plasma 25-hydroxyvitamin D and risk of pancreatic cancer**
Wolpin et al report that prediagnostic levels of plasma 25-hydroxyvitamin D were inversely associated with risk of pancreatic cancer.

**EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS**

**Outcome of the pancreatic remnant following segmental pancreatectomy for non-invasive IPMN**
This study primarily took place in the laboratory of Max Schmidt, MD, PhD (2003 Pancreatic Cancer Action Network – AACR Career Development Award) at Indiana University. Dr. Schmidt and colleagues analyzed data on patients who were diagnosed with intraductal papillary mucinous neoplasms (IPMNs) and who underwent segmental pancreatectomy, rather than total pancreatectomy. Their data suggest that patients who still had remnant IPMN growth following surgery were not at a higher risk for development of invasive pancreatic cancer, nor did they show a difference in survival.

**Outcomes of primary surveillance for intraductal papillary mucinous neoplasm**
This paper is also out of the lab of Max Schmidt, MD, PhD (2003 Pancreatic Cancer Action Network – AACR Career Development Award). Patients who were monitored for intraductal papillary mucinous neoplasm (IPMN) were retrospectively stratified as low- or high-risk, and the data collected demonstrated that low-risk patients had a lower likelihood of progressing to invasive pancreatic cancer. Not unexpectedly, patients who were deemed high-risk were more likely to develop pancreatic cancer, however the majority of these patients ultimately died of other causes.
The proteome of normal pancreatic juice
Max Schmidt had yet another paper published in November. Here, Dr. Schmidt and his team endeavored to compare the proteome of normal pancreatic juice to data published describing the protein profile of samples from pancreatic cancer patients. Of 285 proteins found in normal pancreatic juice and 170 proteins published as detected in pancreatic cancer juice, only 42 proteins overlapped.

EGFR and IGF-1R expression predict poor survival in pancreatic ductal adenocarcinoma
Jonathan Brody, PhD (2010 Skip Viragh – Pancreatic Cancer Action Network – AACR Career Development Award) coauthored this Cancer paper. Dr. Brody and colleagues at Thomas Jefferson University evaluated protein expression and gene copy levels of epidermal growth factor receptor (EGFR) and insulin-like growth factor 1 receptor (IGF-1R) in pancreatic cancer cells, and determined their relationship to patient prognosis. The expression patterns of both receptors seem to be correlated with pancreatic cancer patient outcome.

Vascular invasion in infiltrating ductal adenocarcinoma of the pancreas can mimic PanIN
This Johns Hopkins research team includes Joe Herman, MD (2008 Blum-Kovler – Pancreatic Cancer Action Network – AACR Career Development Award) and Ralph Hruban, MD (Emeritus Scientific Advisory Board). The authors performed histopathologic evaluation of resected infiltrating pancreatic cancer samples, and found that nearly 70 percent of cases displayed vascular invasion mimicking pancreatic intraepithelial neoplasia (PanIN-like invasion). This microscopic vascular invasion proved to be a poor prognostic indicator.

Detection of pancreatic cancer tumours and precursor lesions by cathepsin E activity in mouse models
This study came out of the lab of Craig Logsdon, PhD (Scientific Advisory Board) and also features Huamin Wang, MD, PhD (2007 Skip Viragh – Pancreatic Cancer Action Network – AACR Career Development Award). The authors explored the potential of cathepsin E to serve as a biomarker for pancreatic cancer. Indeed, patient samples of precancerous pancreatic intraepithelial neoplasm and invasive pancreatic ductal adenocarcinoma showed strong and specific expression of cathepsin E. Moreover, a fluorescently-labeled tag specific for cathepsin E allowed imaging of genetically engineered and human xenograft mice at different stages of pancreatic tumor development.

MicroRNA alterations of pancreatic intraepithelial neoplasms (PanINs)
Ralph Hruban, MD (Emeritus Scientific Advisory Board) is an author on this Clinical Cancer Research paper. The authors compared expression levels of 735 microRNAs in pancreatic intraepithelial neoplasms (PanINs) compared to normal pancreatic duct samples. Over 100 miRNAs were found to be aberrantly expressed in PanIN lesions vs. normal ducts, and several were found to specifically be expressed only in PanIN-3. These findings could have implications as diagnostic markers.
MicroRNA molecular profiles associated with diagnosis, clinicopathological criteria, overall survival
Published in the same issue of Clinical Cancer Research as the article above, this paper describes global miRNA microarray expression profiling of surgically collected pancreatic ductal adenocarcinoma samples. Their data suggested that expression patterns of microRNAs were significantly altered in pancreatic cancer, and aberrant expression of a number of miRNAs were independently associated with reduced survival.

Novel diagnostic value of circulating miR-18a in plasma of patients with pancreatic cancer
Published in the British Journal of Cancer, this article describes the detection of the microRNA miR-18a in the plasma of patients with pancreatic cancer. Levels of miR-18a were significantly higher in patients with pancreatic cancer compared to healthy controls, and the authors also observed that miR-18a levels were greater in patients before surgery, than after.

Large duct type invasive adenocarcinoma of the pancreas with microcystic and papillary patterns
Researchers at Rize University in Turkey described an unusual type of invasive pancreatic adenocarcinoma with a large duct pattern that represent a potential mimic of non-invasive ductal neoplasia. Based on a high degree of differentiation, these lesions tend to display better clinical outcomes than conventional ductal adenocarcinoma.

Results show microRNA-based pancreatic cancer assay improves diagnostic accuracy of FNA cytology
Asuragen, Inc. reported findings at the annual American Pancreatic Association (APA) meeting. Their data demonstrate that the addition of a miRNA-based molecular test may enhance the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspirate (EUS-FNA) cytology on indeterminate and suspicious pancreatic masses. Asuragen's miRInform™ Pancreas evaluates expression of seven proprietary miRNAs, and improves upon both the sensitivity and specificity of EUS-FNA cytology analyses alone.

Molecular predictors of gemcitabine response in pancreatic cancer
This review describes the lack of clinically applicable methods to predict which pancreatic cancer patients will respond best to gemcitabine, and discusses recently proposed markers such as drug uptake, activation, and catabolism, or proteins that define the ability of the cell to undergo apoptosis in response to the drug, as well as the presence of cancer stem cells.

Pathologic complete response to neoadjuvant therapy is associated with a better prognosis
Among the authors on this paper is Jason Fleming, MD (Medical Advisory Board). This study suggested that patients who achieve a pathologic complete response following neoadjuvant therapy and
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Pancreatectomy showed a better survival than patients who had residual disease post-therapy. Although this type of response is rare, it is associated with a better prognosis.

**Loss of 18q22.3 involving the carboxypeptidase of glutamate-like gene associated with poor prognosis**


A research team at NCI looked at recurrent copy number alterations of cytobands and genes by array comparative genomic hybridization in resected pancreatic cancer specimens. They discovered that loss of 18q22.3 was associated with poor prognosis, likely due to the presence of a potential growth suppressor, carboxypeptidase of glutamate-like, within that chromosomal region.

**HER3 overexpression as an indicator of poor prognosis for curatively resected pancreatic cancer**


This *Oncology* paper presents evidence that human epidermal growth factor receptor 3 (HER3) is a poor prognostic marker in pancreatic cancer. The authors’ results suggest that high expression of HER3, lymph node metastasis, and elevated levels of serum CA19-9 each independently predicted for worse survival in pancreatic cancer patients who underwent curative resection.

**Impact of microvessel density on lymph node metastasis and survival after curative resection**


Benckert and colleagues found that microvessel density was higher in pancreatic cancer patients’ samples than chronic pancreatitis. They further found that high microvessel density served as a prognostic marker for poor outcome among pancreatic cancer patients.

**Diagnostic intervals in breast, colorectal, lung, pancreatic, oesophageal and gastric cancers**

http://www.ncri.org.uk/ncriconference/2011abstracts/abstracts/A91.html


Presented at the National Cancer Research Institute (NCRI) Cancer Conference in Liverpool, England, this database study looked at the interval of time between presentation of symptoms and diagnosis of various types of cancer. Specifically, the authors evaluated this time interval before and after implementation of the 2005 NICE (National Institute for Health and Clinical Excellence) urgent cancer referral guidelines. The diagnosis interval improved for pancreatic cancer in the timeframe evaluated, although the data did not reach statistical significance.

**Alliance targets pancreatic cancer**

http://www.businessweekly.co.uk/biomedtech-/13035-alliance-targets-pancreatic-cancer

A UK partnership between Abcodia in Cambridge and Oxford Gene Technology is striving to discover and validate potential biomarkers for pancreatic cancer. Abcodia maintains a large prospective serum biobank, with samples from patients up to seven years prior to a pancreatic cancer diagnosis. Working together, these two companies will employ bioinformatics approaches to identify biomarkers to predict for the development of pancreatic cancer.
**TREATMENT**

Nodal/Activin signaling drives self-renewal and tumorigenicity and a target for combined drug therapy


This Cell Stem Cell paper generated some media attention last month. Lonardo et al explored the activity and expression of Nodal and Activin in pancreatic cancer cells, and found their expression upregulated in the cancer stem cell population. When cancer stem cells were implanted into mice, a combination of gemcitabine with an Alk4/7 (Nodal/Activin receptor) inhibitor led to decreased self-renewal and tumorigenicity. When whole tumor tissue was implanted instead, the stromal component negated the response. Therefore, the authors also included a hedgehog inhibitor into the regimen, and saw significant increase in progression-free survival. Please see preview to this article below.

Nodal/Activin signaling: a novel target for pancreatic cancer stem cell therapy


Tim Donahue, MD and Dave Dawson, MD, PhD (2008 Seena Magowitz – Pancreatic Cancer Action Network – AACR Career Development Award) coauthored this preview to the above article.

Imaging guided trials of the angiogenesis inhibitor sunitinib in mouse models predict efficacy


This study took place in the lab of Doug Hanahan, PhD (2007 Pancreatic Cancer Action Network Pilot Grant) at UCSF. Dr. Hanahan and colleagues utilized genetically engineered mouse models of pancreatic ductal adenocarcinoma (PDAC) and pancreatic neuroendocrine tumors (PNET) to decipher the response to the angiogenesis inhibitor sunitinib. Consistent with previous studies, sunitinib was effective in the treatment of mouse PNET (the drug has been approved by the US FDA and in Europe for this setting). Although sunitinib led to decreased blood vessel density in PDAC also, the drug had no effect on tumor growth or survival. These latter results are consistent with other studies showing that anti-angiogenic drugs have minimal effect in the treatment of PDAC. Overall, the results underline the potential predictive value of experiments conducted preclinically in appropriate mouse models.

Effect of neoadjuvant chemoradiation, surgical technique on recurrence of localized pancreatic cancer


This paper includes two members of the Pancreatic Cancer Action Network Medical Advisory Board: Chris Crane, MD and Jason Fleming, MD. The researchers retrospectively evaluated pancreatic adenocarcinoma patients who underwent pancreaticoduodenectomy. The superior mesenteric artery (SMA) margin distance was measured, and data suggested that patients who received neoadjuvant chemoradiation and had SMA margins >1mm showed the best clinical outcomes. SMA margins could be improved by careful dissection of the superior mesenteric artery.

Early data promising in SU2C pancreatic cancer trial

http://journals.lww.com/oncology-times/blog/onlinefirst/pages/post.aspx?PostID=319

Preliminary Stand Up To Cancer data were presented at the AACR Translation of the Cancer Genome meeting. The Phase II data presented by Michael Barrett, PhD of T-Gen described molecular profiling of advanced pancreatic cancer patients, and using that information to guide treatment decisions. Three core needle biopsies from each patient (often from liver metastases) were evaluated for protein
expression, copy number, and gene expression. The molecular results were then compared to xenograft samples, drawing comparisons of which drugs worked best in those tumor models.

**Radiosensitization of pancreatic cancer cells by MLN4924, an NEDD8-activating enzyme inhibitor**
Researchers in the Radiation Oncology department at the University of Michigan looked at MLN4924, an investigational drug currently being tested in Phase I clinical trials, as a radiosensitizer for pancreatic cancer cells. MLN4924 is an inhibitor of NAE (NEDD8 Activating Enzyme), a protein involved in the DNA repair pathway.

**Radiotherapy: The importance of local control in pancreatic cancer**
This review was published in *Nature Reviews Clinical Oncology* and discusses radiotherapy as a treatment option for pancreatic cancer patients.

**Shining the light on Aurora-A kinase as a drug target in pancreatic cancer**
*Commentary on: The mitotic serine threonine kinase, Aurora-2, is a potential target for drug development in human pancreatic cancer*  
The original 2004 article by Rojanala *et al* was selected by *Molecular Cancer Therapeutics* as one of “The Best of MCT – 10 Years”. In response to that honor, David Bearss, PhD wrote this commentary to describe his lab and the field’s progress on targeting Aurora kinases in pancreatic cancer.

**Kinome-wide siRNA screening identifies targets mediating sensitivity to Aurora kinase inhibitors**
Researchers at TGen performed an RNAi screen targeting kinases in pancreatic cancer cells, to determine which down-regulation would improve cell-killing of Aurora kinase inhibitors. Further experiments suggested that inhibiting PDGFRA sensitized pancreatic cancer cells to Aurora inhibition.

**Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer**
This article in the *European Journal of Cancer* describes a clinical trial of advanced pancreatic cancer patients randomized to receive either gemcitabine or gemcitabine with weight-adjusted dalteparin (intended to prevent vascular thromboembolism). Results suggested that dalteparin led to a highly significant reduction in the risk of vascular thromboembolism.

**Neuroendocrine tumors of the pancreas**
Drs. Milan and Yeo at Thomas Jefferson University wrote this review highlighting current treatment options for pancreatic neuroendocrine tumors.
Promising procedure for pancreatic cancer

This tells the story of the first pancreatic cancer patient in Florida to have a NanoKnife procedure, which took place at the University of Miami Sylvester Comprehensive Cancer Center. The procedure involves four needles inserted to bracket the tumor, and then high voltage electrical currents run between the needles. This patient was able to have successful surgery five months later, and her scans remain clear a year after receiving NanoKnife.

CureFAKtor Pharmaceuticals demonstrates novel FAK inhibitor C4 analogs inhibited pancreatic cancer

This article describes data presented at the 2011 AACR-EORTC-NCI Molecular Targets and Cancer Therapeutics Conference. CureFAKtor Pharmaceuticals, LLC reported that analogs of novel focal adhesion kinase (FAK) inhibitor CFAK-C4 disrupted FAK-vascular endothelial growth factor receptor 3 interaction and inhibited pancreatic cancer tumor growth at low concentrations as single agents.

ZIOPHARM Oncology presents new darinaparsin preclinical prostate and pancreatic cancer data

Also at the AACR-EORTC-NCI meeting, ZIOPHARM Oncology, Inc presented two separate studies of darinaparsin (Zinapar® or ZIO-101), a novel organic arsenic, in combination with x-ray irradiation. Preclinical data in mouse models of pancreatic and prostate cancer suggest an increase in time to tumor doubling without systemic toxicity.

Neogenix Oncology’s novel antibody NEO-101 named one of Windhover’s Top 10 Projects to Watch

http://www.digitaljournal.com/pr/505685
The criteria for Windhover’s annual Top 10 Projects to Watch list include: unmet medical need, market potential, diversity of indications, strong science, and multi-level partnering opportunities. Neogenix Oncology’s NEO-101 antibody was selected this year for its potential against pancreatic and colon cancers. NEO-101 targets a variant of MUC5AC that is thought to be specifically expressed on pancreatic and colon cancer cells.

University of Iowa study tests ketogenic diet for lung, pancreatic cancers

http://fyi.uiowa.edu/11/08/ui-study-diet-cancers/
Researchers with UI Health Care have received a two-year, $340,023 grant from the National Cancer Institute to investigate whether a ketogenic diet (high fat, low carbohydrate) can increase the effectiveness of radiation and chemotherapy for lung and pancreatic cancer. The researchers hope that the ketogenic diet will deprive cancer cells of glucose and force them to rely on their flawed mitochondrial metabolism, causing oxidative stress and making the cancer cells more susceptible to chemotherapy and radiation.
New pancreatic cancer treatment shows promise in NJ clinical trial
This article describes a Phase I clinical trial conducted at the Cancer Institute of New Jersey in New Brunswick. Six patients with inoperable pancreatic cancer were treated with a vaccine-based therapy, designed to trick the patient’s immune system into responding to the tumor.

Immunomedics announces FDA allows resumption of clivatuzumab tetraxetan clinical trial
The FDA put a partial hold on the Phase Ib/II clinical trial of clivatuzumab tetraxetan in patients with advanced pancreatic cancer in September, due to a patient receiving too high of a dose of yttrium-90. Now, the FDA has removed the partial hold on this trial, and the company is hoping to begin Phase III of this trial in 2012.

Infinity reports third quarter 2011 financial results
Infinity Pharmaceuticals, Inc announced its third quarter 2011 financial results, and also highlighted accomplishments including full enrollment of their Phase 2 trial of the hedgehog inhibitor, IPI-926, in patients with pancreatic cancer. Preliminary data of IPI-926 in combination with nab-paclitaxel were presented at the AACR Tumor Microenvironment Complexity meeting.

Research and Markets: GV1001 (Pancreatic Cancer) - Analysis and Forecasts to 2020 for the UK
This report describes the GV1001 pancreatic cancer vaccine and analyzes data to date, as well as making predictions up until the year 2020 related to the drug’s activity in the UK.

The shortage of essential chemotherapy drugs in the United States
Drug shortages – a critical challenge for the generic-drug market
These New England Journal of Medicine perspective articles discuss rising concerns about drug shortages in the US.

Cancer drug 'scalpers' corner US market
http://www.google.com/hostednews/afp/article/ALeqM5ivMEIZKOXp23d9PaCGSvtsUfZA?docId=CNG_d98e4dcabe814b504fd30d7f2c0d09c.161
This article describes a “gray market” phenomenon whereby companies buy up critical cancer drugs in short supply and attempt to resell them at huge markups. The article further discusses strategies by the Obama administration and suggests ways to combat this problem.
**CANCER CONTROL, SURVIVORSHIP, AND OUTCOMES RESEARCH**

Who receives their complex cancer surgery at low-volume hospitals?


Selwyn Vickers, MD (Emeritus Scientific Advisory Board) contributed to this study examining patient-related factors that contribute to having complex surgeries at low-volume hospitals. Using the 2003-2008 National Inpatient Sample, the authors found that non-white race and increased comorbidities contributed to receipt of cancer surgery at low-volume hospitals. About 38 percent of pancreatectomies were performed at low-volume hospitals. Future policy and research will be necessary to improve the numbers of patients getting complex surgeries at higher-volume hospitals.

**Does quality of life improve for advanced pancreatic cancer patients who respond to gemcitabine?**


This team of researchers evaluated health-related quality of life (HRQOL) in patients with advanced pancreatic cancer who participated in a Cancer and Leukemia Group B trial comparing gemcitabine with bevacizumab or gemcitabine with placebo. There were not significant HRQOL differences between the treatment arms, so results were pooled. Overall, the data suggest that response to gemcitabine treatment in advanced pancreatic cancer is not associated with appreciable improvement of global HRQOL.

**Determinants of outcomes in pancreatic surgery and use of hospital resources**


This *Journal of Surgical Oncology* paper reports on high levels of morbidity following pancreatic cancer surgeries, and subsequent increased usage of hospital resources for these patients.

**Survival in population-based pancreatic cancer patients: San Francisco Bay Area, 1995-1999**


Gong et al used multiple active and passive follow-up methods to determine vital status and date of death for nearly 2,000 pancreatic cancer patients diagnosed from 1995 to 1999 in a large population-based study in the San Francisco Bay Area, California. The authors found associations between better survival and factors such as younger age and earlier stage of disease, while worse survival was linked to male gender and poorer differentiated tumors, for example.

**Tackling the conundrum of cachexia in cancer**


The *NCI Cancer Bulletin* takes “A Closer Look” at the wasting syndrome cachexia. Pancreatic cancer patients see one of the highest levels of cachexia, which can factor directly into mortality. The article discusses the onset of cachexia in cancer patients, and possible treatment options.

**Medical oncologists' attitudes and practice in cancer pain management: a national survey**


*Media attention: Oncologists still not great with patients' pain*


Published in *JCO*, this article describes a survey of oncologists across the country, discussing their capacity to manage cancer patients’ pain, in the form of a vignette about a hypothetical patient. The
study suggests that, over the past 20 years, little progress has been made in medical oncologists’ ability to manage patients’ pain, which can (and perhaps should) include referrals to specialists in the field of pain medicine and/or palliative care.

**SCIENTIFIC MODEL SYSTEMS**

Disruption of p16, activation of Kras in pancreas increase adenocarcinoma formation, metastasis


This study was conducted in the laboratory of Gloria Su, PhD (2010 Pancreatic Cancer Action Network – AACR Innovative Grant and 2007 Pancreatic Cancer Action Network Pilot Grant), with collaboration from Christine Iacobuzio-Donahue, MD, PhD (2007 Pancreatic Cancer Action Network Pilot Grant and Scientific Advisory Board member) and Ralph Hruban, MD (Emeritus Scientific Advisory Board). Dr. Su and colleagues created a conditional p16/INK4A knockout mouse with expression specific to pancreas tissue, in combination with mutant activated Kras. Expression of p19/ARF was not affected. These mice developed the full spectrum of PanIN lesions, followed by pancreatic ductal adenocarcinoma and metastasis. Interestingly, they also observed that wild type Kras expression was progressively lost in this mouse model, suggesting that drugs targeting Kras should be specific to the oncogenic mutant.