PANCREATIC CANCER NEWS & UPDATES – DECEMBER 2010

BIOLOGY OF CANCER

University of Michigan Cancer Center gets $10.7M grant to study colon, pancreas cancers
http://www2.med.umich.edu/prmc/media/newsroom/details.cfm?ID=1874
Researchers at the University of Michigan Comprehensive Cancer Center have received a five-year, $10.7 million SPORE (Specialized Program of Research Excellence) grant from the National Cancer Institute to study colorectal and pancreatic cancers. Three of the four major projects funded under the GI SPORE focus on pancreatic cancer. Diane Simeone, MD, recipient of the 2010 The Randy Pausch Family – Pancreatic Cancer Action Network – AACR Innovative Grant, is a co-Principal Investigator on the SPORE. Congratulations, Dr. Simeone, and Go Blue! (Michigan is my graduate school alma mater.)

Repression of the miR-143/145 cluster by Ras initiates a tumor-promoting feed-forward pathway
http://www.ncbi.nlm.nih.gov/pubmed/21159816
Johns Hopkins press release, includes video:
http://www.hopkinsmedicine.org/news/media/releases/missing_molecules_hold_promise_of_therapy_for_pancreatic_cancer
An all-star team of Johns Hopkins researchers determined that the microRNA cluster miR-143/145 is repressed in response to oncogenic KRAS activation. Down-regulation of miR-143/145 by KRAS is dependent on Ras-responsive element-binding protein (RREB1); both KRAS and RREB1 are themselves targets of repression by miR-143/145. Data suggested that restoration of miR143/145 could abrogate tumorigenesis in a mouse xenograft model.

Characterization of alternative spliceoforms and the RNA splicing machinery in pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21178653
A team of researchers, including Teri Brentnall, MD (Scientific Advisory Board), sought to evaluate the extent, pattern, and roles of alternative splicing in pancreatic cancer. Spliceoform-specific microarray and PCR analyses of near-normal pancreatic cells and two pancreatic cancer cell lines revealed that pancreatic cancer cells displayed fewer examples of alternatively spliced genes than normal cells. These results were validated in primary pancreatic cancer specimens.

Role for NQO1 and MnSOD in 17AAG-Induced Hsp90 inhibition in pancreatic cancer cells
http://www.ncbi.nlm.nih.gov/pubmed/21156818
Researchers at University of Colorado – Denver explored the role of the protein NQO1 in the metabolism and intercellular concentration of the Hsp90 inhibitor 17AAG. In the presence of NQO1, 17AAG is converted to 17AAGH2, a more potent Hsp90 inhibitor. Additionally, levels of both 17AAG and 17AAGH2 are higher in pancreatic cancer cells when NQO1 is present.

CpG island hypermethylation-associated silencing of non-coding RNAs in human cancer
http://www.ncbi.nlm.nih.gov/pubmed/20802525
This study published in *Oncogene* represents collaboration among researchers in Barcelona, Spain, Ohio State University, and MD Anderson (including 2009 Seena Magowitz – Pancreatic Cancer Action Network – AACR Pilot Grant awardee, George Calin, MD, PhD). The authors focused on transcribed ultra-conserved regions (T-UCRs) and analyzed their epigenetic regulation (specifically methylation). The study concludes that genetic changes leading to cell transformation include both genetic and epigenetic changes to both coding and non-coding RNA.

Identification of HLA-A2-restricted CTL epitopes over-expressed in pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21179034
This study aimed to identify a novel tumor-associated antigen (TAA) of pancreatic cancer, for immunotherapy. HLA-A2-restricted cytotoxic T lymphocytes (CTL) epitopes of KIF20A were discovered to be over-expressed in pancreatic cancer. The authors conclude that KIF20A is a novel promising candidate for anticancer immunotherapeutic target for pancreatic cancers.

Top science news stories of 2010
http://www.nature.com/news/2010/101222/full/4681014a.html
Just thought these were interesting!

ETIOLOGY

Prevalence of CDKN2A mutations in pancreatic cancer patients: implications for genetic counseling
http://www.ncbi.nlm.nih.gov/pubmed/21150883
Dr. Gloria Petersen and colleagues at the Mayo Clinic explored the prevalence of CDKN2A mutations among 1,537 pancreatic cancer patients. Mutations were detected in nine cases (0.6%), and mutation carriers were more likely to have a family history of pancreatic cancer or melanoma, compared to those who had wild-type CDKN2A. The risk of pancreatic cancer among carriers of CDKN2A mutations was higher for smokers than nonsmokers, suggesting that individuals with CDKN2A mutations should be counseled to avoid smoking.

The complexities of obesity, diabetes, and the development and progression of pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21129444
This review article by scientists at the Karmanos Cancer Institute in Detroit addresses the interconnectedness between obesity, diabetes, and risk of pancreatic cancer. Specifically, the authors discuss usage of diabetes medications as preventive or treatments for pancreatic cancer, as well as the possible roles of microRNAs in the pathogenesis of obesity, diabetes, and pancreatic cancer.

Salt, processed meat and the risk of cancer
http://www.ncbi.nlm.nih.gov/pubmed/21160428
Canadian and Italian researchers conducted a survey of nearly 20,000 cancer patients and about 5,000 normal controls, inquiring about food habits. Their results suggested that salt consumption was associated with increased risk of certain cancers, and eating processed meats was also significantly associated with increased risk of several cancer types, including pancreatic.

PALB2 germline mutations in familial breast cancer cases with history of pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21184274
The authors were unable to show that PALB2 mutations were preferentially associated with breast cancer families with cases of pancreatic cancer. However, this study was limited by small sample sizes. The authors conclude that screening for PALB2 mutations may be warranted in individuals or families affected by both breast and pancreatic cancer.

PREVENTION

Resveratrol suppresses pancreatic cancer by inhibiting leukotriene A_4 hydrolase
http://www.ncbi.nlm.nih.gov/pubmed/20952510
Resveratrol is a polyphenol found in red wine, and thought to be involved in cancer prevention and have other health-promoting benefits. Here, authors at the University of Minnesota determine that resveratrol's effects are mediated by leukotriene A_4 hydrolase to suppress anchorage-independent growth of pancreatic cancer cells, as well as delay or suppress pancreatic tumor growth in a xenograft mouse model.

Effect of daily aspirin on long-term risk of death due to cancer
http://www.ncbi.nlm.nih.gov/pubmed/21144578
Published in *The Lancet*, this report analyzes individual data from randomized clinical trials, exploring the relationship between daily aspirin and risk of cancer. Data suggest that daily aspirin reduces the risk of developing and dying from multiple types of cancer, including pancreatic.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Borderline resectable pancreatic cancer: what have we learned and where do we go from here?
http://www.ncbi.nlm.nih.gov/pubmed/21136179
Medical Advisory Board member Jason Fleming, MD and colleagues at MD Anderson prepared this editorial to discuss pancreatic cancer cases that are deemed borderline resectable. The editorial strives to define this categorization of tumors, recommend surgical and other treatment protocols, and discusses the potential of a multi-institutional trial to standardize this particular diagnosis.

CA 19-9 level as indicator of early distant metastasis and therapeutic selection
http://www.ncbi.nlm.nih.gov/pubmed/21129857
CA19-9 levels may be a useful predictor of whether patients will experience distant metastases within six months of diagnosis. Knowledge of this probability can inform the decision on whether to attempt surgery on certain pancreatic cancer patients.

TREATMENT

Pancreatic cancer: will incremental advances begin to make a difference?
http://jnci.oxfordjournals.org/content/102/24/1821.full.pdf
Chart: http://jnci.oxfordjournals.org/content/102/24/1822.full.pdf+html
This news article in *JNCI* discusses recent advances in pancreatic cancer treatments, and potential of future progress. Members of the Pancreatic Cancer Action Network's Scientific & Medical Advisory Boards are quoted throughout the article.

3D collagen I promotes gemcitabine resistance through MT1-MMP-mediated expression of HMGA2
http://www.ncbi.nlm.nih.gov/pubmed/21148071
Researchers at Northwestern University, including Paul Grippo, PhD (2007 Nancy Daly Riordan – Pancreatic Cancer Action Network – AACR Career Development Award), explore the role of the dense fibrotic reaction in chemoresistance of pancreatic cancer. They show that membrane type 1 matrix metalloproteinase (MT1-MMP) over-expression in the collagen microenvironment contributes to gemcitabine resistance *in vitro* and in a mouse pancreatic cancer xenograft model.

Tolerability and pharmacokinetics of adjuvant erlotinib and capecitabine with concurrent radiation
http://www.ncbi.nlm.nih.gov/pubmed/21151476
Joe Herman, MD (2008 Blum-Kovler – Pancreatic Cancer Action Network – AACR Career Development Award) and colleagues at Johns Hopkins conducted a prospective trial to determine a safety profile and recommended phase 2 dosage of erlotinib and capecitabine administered concurrently with intensity-modulated radiation therapy (IMRT) in resected pancreatic cancer patients.

Personalizing cancer treatment in the age of global genomic analyses
http://www.ncbi.nlm.nih.gov/pubmed/21135251
Prominent pancreatic cancer researchers at Johns Hopkins report on PALB2 gene mutations and the response to DNA damaging agents in pancreatic cancer. A personalized xenograft model was established from a patient's tumor sample with gemcitabine-resistant, advanced pancreatic cancer. Data from the mouse xenograft suggested responsiveness to mitomycin C, which then led to a long-lasting (36+ months) response in the patient. Sequencing revealed that the patient's tumor carried a PALB2 mutation, perhaps suggesting a predictor for response to DNA damaging agents.

Network and systems biology approaches aid in the discovery of potent anticancer drug combinations
http://www.ncbi.nlm.nih.gov/pubmed/21041384
This review article out of the Karmanos Cancer Institute in Detroit explores network and systems biology approaches to aid in selection of targeted therapeutics. In the last few years, novel and high throughput data acquisition technologies coupled with integrated network modeling and systems biology have emerged as key components of targeted-therapy research. The authors highlight an example of combining oxaliplatin and MDM2 inhibitor MI-219 in pancreatic adenocarcinoma as a proof of principle.

TRAIL-induced apoptosis is preferentially mediated via TRAIL receptor 1, enhanced by XIAP inhibitors
http://www.ncbi.nlm.nih.gov/pubmed/20940278
Pancreatic cancer cell lines, primary specimens, and a xenotransplant model in mice were analyzed for expression of TRAIL receptors 1 and 2 and response to inhibition of each. These authors' studies showed that pancreatic cancer samples were more susceptible to inhibition of TRAIL-R1 (via mapatumumab) than inhibitors of TRAIL-R2 (via lexatumumab). Further, the activity of mapatumumab was significantly enhanced in the presence of XIAP inhibitors, observed both *in vitro* and *in vivo*.

Noninvasive radiofrequency field destruction with targeted gold nanoparticles
http://www.ncbi.nlm.nih.gov/pubmed/21138869
Glazer, *et al* describe a xenograft model of mice injected with either Panc-1 or Capan-1 pancreatic cancer cell lines, and treated with targeted gold nanoparticles (AuNP) and nonionizing radiofrequency

(RF) radiation. The Panc-1 mice had AuNP targeted via cetuximab and the Capan-1 mice were targeted with PAM4 antibody. Results suggested that the heat generated by AuNP and RF induced apoptosis specifically in the pancreatic tumor cells, and not in normal cells throughout the mouse's body.

Agents targeting the Hedgehog pathway for pancreatic cancer treatment
http://www.ncbi.nlm.nih.gov/pubmed/21154121
This review provides a concise overview of translational studies assessing the use of Hedgehog inhibitors as novel therapeutic strategy for cancer, particularly pancreatic cancer.

Hedgehog signalling and therapeutics in pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21186299
This is also a review of hedgehog signaling in pancreatic cancer, conducted utilizing PubMed (2000-2010) and other literature-based references.

A CALGB phase II study of sunitinib malate in patients with metastatic pancreatic adenocarcinoma
http://www.ncbi.nlm.nih.gov/pubmed/21148613
Eileen O'Reilly, MD (Medical Advisory Board) and colleagues at Memorial Sloane-Kettering describe a Cancer and Leukemia Group B (CALGB) phase II study of sunitinib in previously gemcitabine-treated patients with metastatic pancreatic adenocarcinoma. Although the study met its endpoint, sunitinib displayed minimal activity and marginal toxicity. For future studies, it's recommended to enroll patients with ECOG performance scores of 0-1.

SUTENT® receives European approval for progressive pancreatic neuroendocrine tumors
http://pfizer.mediaroom.com/index.php?s=5149&item=20459SUTENT ® (sunitinib malate) becomes the first targeted therapy approved for pancreatic neuroendocrine tumors in Europe. A phase III trial demonstrated that patients treated with SUTENT showed double time-to-progression and overall survival, compared to placebo. SUTENT is an oral multi-kinase inhibitor.

Phase II study of nimotuzumab, a humanized monoclonal anti-EGFR antibody
http://www.ncbi.nlm.nih.gov/pubmed/21170759
Nimotuzumab, a humanized monoclonal antibody against epidermal growth factor receptor (EGFR), was tested in patients with locally advanced or metastatic pancreatic cancer. The compound proved safe and well-tolerated, and the investigators are therefore initiating a randomized, placebo-controlled trial combining nimotuzumab with gemcitabine to improve efficacy.

A phase I/II study of the Src inhibitor saracatinib (AZD0530) in combination with gemcitabine
http://www.ncbi.nlm.nih.gov/pubmed/21170669
This Canadian study aimed to define the recommended phase II dose saracatinib when combined with gemcitabine, and assess the efficacy of this combination in advanced, previously untreated, pancreatic cancer patients. Objective criteria for continuing were not met and the trial was closed. Saracatinib in combination with gemcitabine is well tolerated, but the combination did not improve efficacy over gemcitabine alone.

Phase 1 trial of Wilms tumor 1 (WT1) peptide vaccine and gemcitabine combination therapy
http://www.ncbi.nlm.nih.gov/pubmed/21150717
An open-labeled, dose-escalation phase 1 trial of Wilms tumor 1 (WT1) vaccine and gemcitabine (GEM) combination therapy for patients with advanced pancreatic cancer or biliary tract cancer was performed. Although objective clinical efficacy was not apparent, the safety of WT1 vaccine and GEM combination therapy was confirmed in this study.

Novel postoperative adjuvant strategy prevents early hepatic recurrence after resection of PC
http://www.ncbi.nlm.nih.gov/pubmed/21165654
The authors evaluated the efficacy of postoperative combination therapy of high-dose 5-fluorouracil (5-FU) arterial infusion with systemic gemcitabine. This novel adjuvant strategy had a significant beneficial effect on early hepatic recurrence, and may have the potential to prolong the overall survival of pancreatic cancer patients.

Drug cocktails for cancer get streamlined U.S. review
http://www.bloomberg.com/news/2010-12-14/drug-cocktails-for-cancer-heart-disease-get-streamlined-review.html
Drug cocktails for cancer, heart disease and other conditions may reach the U.S. market sooner under new guidelines that let companies seek approval for a combination of two or more medicines at the same time. The path will be reserved for serious illnesses where a combination therapy is needed to overcome resistance or weak response to only one medicine, per draft guidelines released by the FDA. Previously, the merit of each compound had to be first proven on its own.

SURVIVORSHIP

Explaining marginal benefits to patients, when "marginal" means additional but not necessarily small
http://www.ncbi.nlm.nih.gov/pubmed/21169251
This *Clinical Cancer Research* article discusses patient/physician communications surrounding prognosis and treatment options. The authors use the administration of gemcitabine and erlotinib to pancreatic cancer patients as an example. Patients should be presented with honest, realistic, and caring descriptions of the pros and cons of every treatment option.

The attitudes of 1066 patients with cancer towards participation in randomised clinical trials
http://www.ncbi.nlm.nih.gov/pubmed/21119659
This article in *British Journal of Cancer* explores barriers to recruiting patients in randomized clinical trials. Clearly communicating with and informing patients are necessary to achieve improved participation in clinical trials.