PANCREATIC CANCER NEWS & UPDATES – NOVEMBER 2010

BIOLOGY OF CANCER

Virginia scientist studying pancreatic cancer

http://www.dailypress.com/news/virginia/dp-va--pancreaticcancerr1130nov30,0,6436593.story

The Daily Press published this article about 2010 Pancreatic Cancer Action Network – AACR Innovative Grant recipient Amy Tang, PhD. Congratulations, Dr. Tang!

Collagen regulation of let-7 involves TGF-β1-mediated membrane type 1-MMP expression

http://www.ncbi.nlm.nih.gov/pubmed/21057545

Paul Grippo, PhD, recipient of the 2007 Nancy Daly Riordan – Pancreatic Cancer Action Network – AACR Career Development Award, and colleagues at Northwestern University published this paper in *Oncogene*. It is known that pancreatic tumors are surrounded by a dense, collagen-rich desmoplastic reaction, but the role of the collagen is not fully understood. Results from this study suggest that pancreatic ductal adenocarcinoma cells in 3D collagen culture repress mature expression of the tumor suppressive miRNA family member let-7 via increase in MT1-MMP expression.

Cross-platform comparison of two pancreatic cancer phenotypes

http://www.ncbi.nlm.nih.gov/pubmed/21082040

This collaborative group of researchers out of Johns Hopkins, University of South Carolina, and Harvard includes 2007 Pancreatic Cancer Action Network Pilot Grant awardee, Christine Iacobuzio-Donahue. This study investigates three different high-throughput platforms as means to assess concordance of differential gene expression. Comparisons are made between technical platforms analyzing two primary pancreatic cancer cell lines, and two metastatic cell lines.

Aberrant overexpression of the Rgl2 Ral promotes pancreatic cancer growth

http://www.ncbi.nlm.nih.gov/pubmed/20801877

This *JBC* paper out of Channing Der's lab explores the role of the Rgl2 Ral small GTPase-specific guanine nucleotide exchange factor in pancreatic ductal adenocarcinoma (PDAC) cell lines. Rgl2 is studied as a potential targetable step in the K-Ras signaling cascade. Their studies suggest that Rgl2 has multiple, non-redundant roles in PDAC, including supporting Ras-mediated oncogenesis and affecting growth in both a Ral-dependent and -independent manner.

Identification of susceptibility loci in a mouse model of KRASG12D-driven pancreatic cancer

http://www.ncbi.nlm.nih.gov/pubmed/20959479

Here, University of Wisconsin researchers identified six susceptibility loci [pancreatic ras susceptibility quantitative trait loci 1-6 (Prsq1-6)] that affect the development and progression of K-Ras-driven pancreatic cancer. These loci are present on chromosomes 2, 4, and 12. Further analyses of these loci

will allow insight into the biological mechanisms of their potential role in pancreatic cancer development. The mouse studies should closely model human genetics.

The telomerase inhibitor imetelstat depletes cancer stem cells in pancreatic cancer cell lines
http://www.ncbi.nlm.nih.gov/pubmed/21062983
Joseph, *et al* explore the use of a telomerase inhibitor, imetelstat, in pancreatic and breast cancer models. Interestingly, their results suggest that cancer stem cells (CSCs) are particularly sensitive to the drug, indicative by disproportionate killing of CSCs in a PANC1 mouse engraftment model. The discrepancy between CSCs and bulk tumor cells' response is not explained by telomerase expression or activity, suggesting that a mechanism independent of telomerase is in play. Further studies need to be done to explore whether imetelstat has therapeutic potential in pancreatic cancer.

Nuclear receptor COUP-TFII controls pancreatic islet tumor angiogenesis
http://www.ncbi.nlm.nih.gov/pubmed/20978203
COUP-TFII is a steroid/thyroid nuclear hormone receptor that controls the balance of pro- and anti-angiogenic factors. A group from Baylor College report that COUP-TFII suppressed VEGF/VEGFR-2 signaling by transcriptionally repressing VEGFR-1 expression in a pancreatic cancer mouse model. These results suggest that COUP-TFII may play an important role in regulating angiogenesis in pancreatic cancer.

Pancreatic stellate cells promote epithelial-mesenchymal transition in pancreatic cancer cells
http://www.ncbi.nlm.nih.gov/pubmed/21081113
This study out of Japan explores the hypothesis that pancreatic stellate cells (PSCs) may induce epithelial-to-mesenchymal transition (EMT) in pancreatic cancer cells. To determine this, the researchers co-cultured PSCs with two pancreatic cancer cell lines. Looking at epithelial and mesenchymal markers, their data suggested that PSCs do stimulate EMT in the pancreatic cancer cells. Further, migration of the pancreatic cancer cells was also increased in the presence of PSCs, indicating that PSCs may play a role in the aggressiveness of pancreatic cancer cells.

Invasive three-dimensional organotypic neoplasia from multiple normal human epithelia
http://www.ncbi.nlm.nih.gov/pubmed/21102459
Researchers at Stanford University looked at differences between culturing cancer cells in two- or three-dimensional models. Their data suggest that 3D models are significantly more representative of human tumor behaviors, especially with invasive potential. In addition, oncogenic gene expression profiles of cells in 3D culture much better recapitulated the genetic changes of human tumors.

Fuel lines of tumors are new target
http://www.nytimes.com/2010/11/30/health/30cancer.html?_r=1&pagewanted=1&ref=general&src=me
This *NY Times* article describes cancer cell metabolism and how it may be useful for diagnostic tools (PET scans), treatment options, and a better understanding of cancer biology. The author describes the relationship between diabetes and cancer, which may be especially pertinent in the case of pancreatic cancer.

ETIOLOGY

Vitamin D, calcium, and retinol intake, and pancreatic cancer in a population-based case-control study
http://www.ncbi.nlm.nih.gov/pubmed/21072578
This study took place in the San Francisco Bay Area. Their results among men showing an increased risk of pancreatic cancer associated with dietary intake of vitamin D and of calcium require confirmation in further studies. Continued investigation is needed to clarify the complex role of vitamin D and calcium in pancreatic cancer risk and to determine their optimal intake level and preventive effects for pancreatic cancer.

Cigarette smoking and other lifestyle factors in relation to the risk of pancreatic cancer death
http://www.ncbi.nlm.nih.gov/pubmed/21075833
This prospective cohort study in Japan suggests that smoking increases the risk of death from pancreatic cancer in Japanese women.

PREVENTION

Synthetic triterpenoids prolong survival in a transgenic mouse model of pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/20959520
Comments: http://www.ncbi.nlm.nih.gov/pubmed/20978116
This publication represents a collaboration between researchers at Dartmouth and Johns Hopkins, including Anirban Maitra, MD (2004 Pancreatic Cancer Action Network – AACR Career Development Award recipient) and Ralph Hruban, MD (Scientific Advisory Board member). The authors tested two promising classes of noncytotoxic drugs, synthetic oleanane triterpenoids and rexinoids, for the prevention of carcinogenesis in the KPC transgenic mouse model of pancreatic cancer. Different combinations of triterpenoids and rexinoids extended the survival of the treated mice by three to four weeks, impacting the STAT3 and NFkB pathways. These data suggest that triterpenoids and rexinoids may have the potential to play a role in preventing pancreatic cancer.

The EGFR inhibitor gefitinib prevents the progression of pancreatic lesions to carcinoma
http://www.ncbi.nlm.nih.gov/pubmed/21084261
Comments: http://www.ncbi.nlm.nih.gov/pubmed/21084259
Using a conditional LSL-KrasG12D/+ transgenic mouse model, the authors from University of Oklahoma Health Sciences Center demonstrated whether the epidermal growth factor receptor (EGFR) inhibitor gefitinib affected the progression from pancreatic intraepithelial neoplasm (PanIN) to pancreatic ductal adenocarcinoma (PDAC). Dietary gefitinib significantly suppressed PDAC incidence and led to a dose-dependent inhibition of PanIN formation. This study highlights the promise of chemoprevention and potential usefulness of EGFR inhibitors in individuals at high risk for pancreatic cancer.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Early Detection/Diagnosis

Detection of early-stage pancreatic adenocarcinoma
http://www.ncbi.nlm.nih.gov/pubmed/20810605
Researchers at Garden State Cancer Center, Johns Hopkins, and NYU collaborated on this project, evaluating PAM4 antigen as an early-detection marker for pancreatic cancer. The monoclonal antibody PAM4 is reactive with a unique biomarker expressed by more than 85% of pancreatic adenocarcinomas.

A PAM4 immunoassay showed 82% specificity (false positive rate of about 5%) and sensitivity of 91, 86, and 62% for stage 3/4 advanced disease, stage 2, and stage 1, respectively. These data show promise that a PAM4 immunoassay may be useful in early detection of pancreatic cancer.

Prognosis

Jefferson researchers receive W.W. Smith Charitable Trust medical research grant

http://www.jeffersonhospital.org/News/2010-november-w-w-smith-charitable-trust-grant.aspx

Jonathan Brody, PhD, recipient of the 2010 Skip Viragh – Pancreatic Cancer Action Network – AACR – Career Development Award, and colleague Gregory Gonye, PhD received a prestigious W.W. Smith Charitable Trust grant. The Trust medical research grant is designed to fund "unique and meritorious" projects that, with this funding, may go on and receive larger federal grants in the future. Drs. Brody and Gonye's proposed project entails studying a polymorphism in the gene HuR that occurs frequently in African-American individuals, and is uncommon among Caucasians. Their hypothesis is that this HuR polymorphism may account for the poorer outcome of African-American patients diagnosed with pancreatic cancer and given the standard of care, gemcitabine. Congratulations, Dr. Brody!

Failure of normalization of CA19-9 following surgical resection is tantamount to metastatic disease

http://www.ncbi.nlm.nih.gov/pubmed/21042945

The authors, out of Ohio State University, looked at records of 93 pancreatectomy patients, with CA19-9 data before and after surgery. 38 patients' CA19-9 dropped to normal levels six months after surgery, whereas 55 patients' CA19-9 remained elevated. Those patients with persistently high CA19-9 levels showed overall survival rate of 10.8 months, compared to 23.8 months in patients whose CA19-9 normalized. The authors conclude that persistent CA19-9 elevation after pancreatectomy correlates with shorter survival analogous to unresected or metastatic disease and should be regarded as persistent disease regardless of radiographic findings.

Clinical and molecular determinants of survival in patients treated with second-line chemotherapy

http://www.ncbi.nlm.nih.gov/pubmed/21036754

This Italian/Swiss retrospective multicenter study was performed to evaluate the efficacy of salvage treatment with the hypothesis that levels of the DNA repair gene excision repair cross complementing 1 (ERCC1) could influence overall survival. In a population of 160 patients treated with fluoropyrimidine-based second-line chemotherapy, expression levels of ERCC1 were determined by immunohistochemistry and RT-PCR. Results suggested that patients with low ERCC1 levels showed significantly higher median survival and a trend towards longer time-to-progression.

Inhibition of renin-angiotensin system in advanced pancreatic cancer patients receiving gemcitabine

http://www.ncbi.nlm.nih.gov/pubmed/20978506

The authors retrospectively investigated the impact of angiotensin I-converting enzyme inhibitors (ACEIs) and angiotensin II type-1 receptor blockers (ARBs) in 155 patients with pancreatic cancer receiving gemcitabine monotherapy. Data indicated that receiving an ACEI or ARB for hypertension was a significant prognostic marker for improved progression-free-survival and overall survival with gemcitabine treatment. The authors conclude that prospective trials will be necessary to prove this hypothesis.

Predictive factors associated with malignancy of intraductal papillary mucinous pancreatic neoplasms
http://www.ncbi.nlm.nih.gov/pubmed/21072900
Between April 1995 and April 2010, 129 patients underwent surgery for IPMNs at Sungkyunkwan University in Seoul, South Korea. Their retrospective analyses revealed that main pancreatic duct size of >7 mm and preoperative lymph node enlargement were significantly associated with malignancy of IPMNs.

TREATMENT

Abstracts from the 52nd annual American Society for Radiation Oncology (ASTRO) meeting

Stereotactic radiotherapy for medically inoperable pancreatic cancer
http://www.redjournal.org/article/S0360-3016(10)01759-1/fulltext
Researchers at Henry Ford in Detroit studied the outcome of hypofractionated stereotactic body radiotherapy (SBRT) on locally advanced pancreatic cancer. Their results preliminarily suggested that SBRT may provide inoperable panceratic cancer patients a reasonable palliative care option with some local control and low toxicity.

Adjuvant radiotherapy and lymph node status: results of a study from SEER registry data
http://www.redjournal.org/article/S0360-3016(10)01238-1/fulltext
This study concludes that a greater number of positive lymph nodes and a higher lymph node ratio were indicators of worse cause-specific survival (CSS) and overall survival (OS) in pancreatic cancer patients, regardless of adjuvant radiation therapy (RT) treatment. Adjuvant RT was strongly associated with improved CSS and OS.

Low-dose upper-abdominal radiation potentiates gemcitabine in advanced pancreatic cancer
http://www.redjournal.org/article/S0360-3016(10)01242-3/fulltext
Due to promising laboratory and phase I clinical data suggesting limited toxicity and chemo-potentiation of gemcitabine using low-dose upper-abdominal radiation therapy (LD-UART), a phase II multi-institutional trial was undertaken. Conclusions were that LD-UART with full-dose gemcitabine offered a novel and effective paradigm for treating advanced pancreatic cancer patients. Further investigation is warranted.

Other Treatment Studies

CXCL12-CXCR4 signalling axis confers gemcitabine resistance to pancreatic cancer cells
http://www.ncbi.nlm.nih.gov/pubmed/21045835
Relatively little is known about the mechanisms of drug resistance that contribute to the deadliness of pancreatic cancer. Here, activation of CXCL12-CXCR4 signaling is hypothesized to confer drug resistance to pancreatic cancer cells by potentiating survival. The pancreatic cancer cells treated with gemcitabine exhibited reduced cytotoxicity in the presence of CXCL12, as compared with the cells treated with gemcitabine alone. Therefore, the CXCL12-CXCR4 pathway may serve as a novel therapeutic target, either alone or in combination with cytotoxic drugs.

Robotic-assisted major pancreatic resection and reconstruction
http://www.ncbi.nlm.nih.gov/pubmed/21079111
Thirty patients underwent completed robotic-assisted pancreatic resection and reconstruction at University of Pittsburgh Medical Center, between October 2008 and February 2010. Among the patients were six diagnosed with pancreatic adenocarcinoma. The study concludes that robotic-assisted pancreatic surgeries can be performed safely in a high-volume pancreatic tertiary care center, with peri-operative outcomes similar to open surgery, and that advances in robotic technology may improve long operative times.

A phase I, dose-escalation study of pomalidomide (CC-4047) in combination with gemcitabine
http://www.ncbi.nlm.nih.gov/pubmed/21051221
Pomalidomide is an investigational immunomodulating drug that also inhibits angiogenesis and has direct anti-tumor effects. This phase I trial of pomalidomide and gemcitabine determined that the dose-limiting toxicity was neutropenia, but it was brief and reversible. The investigators also observed that ten patients (about 50%) showed at least a 50% decrease in CA19-9 levels following this treatment regimen. Results suggest that future studies are warranted.

{Gamma}-tocotrienol inhibits pancreatic tumors and sensitizes them to gemcitabine treatment
http://www.ncbi.nlm.nih.gov/pubmed/20864511
This *Cancer Research* paper out of MD Anderson focuses on gamma-tocotrienol (gamma-T3), a novel, unsaturated form of vitamin E found in palm oil and rice bran oil. Looking at cell lines and mouse xenograft models, the authors found that gamma-T3 sensitizes pancreatic cancer cells to gemcitabine, by suppressing NFkB-mediated inflammatory pathways.

Curcumin and gemcitabine in patients with advanced pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21058202
Epelbaum *et al* discuss the activity and feasibility of gemcitabine in combination with curcumin in patients with advanced pancreatic cancer. Patients experienced severe abdominal problems, causing stoppage or decrease of curcumin treatment. Low compliance for curcumin at a dose of 8,000 mg/day, when taken together with systemic gemcitabine, may prevent the use of high doses of oral curcumin needed to achieve systemic effect. Further studies should be conducted to evaluate the ability of other formulations of curcumin to enhance the effect of chemotherapy in cancer patients.

XELIRI or FOLFIRI as salvage therapy in advanced pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21115942
Conclusion: Fluoropyrimidine and irinotecan combination does not seem to have any role in the treatment of gemcitabine-resistant pancreatic adenocarcinoma.

Current status of adjuvant therapy for pancreatic cancer
http://www.ncbi.nlm.nih.gov/pubmed/21045189
This review article published in *Oncologist* discusses neoadjuvant and adjuvant therapy options for patients with resectable and borderline resectable pancreatic cancer of the head and uncinate process. Well-defined prospective trials are needed to determine the ideal treatment strategy for these patients,

although retrospective data clearly suggest that systemic chemotherapy and/or chemoradiation should be offered to all pancreatic cancer patients who undergo potentially curative resection.

Pancreatic surgery – research of the past year

http://www.ncbi.nlm.nih.gov/pubmed/20651590

Drs. Tim Donahue and Howard Reber at UCLA published a review summarizing research on pancreatic surgery over the past year. Overall, they report that the morbidity and mortality from each type of pancreatic surgery continues to decrease with more accurate diagnosis, improved management techniques and standardized reporting systems.

Powerful online cancer drug discovery database unveiled

http://www.medicalnewstoday.com/articles/209473.php

Database: https://cansar.icr.ac.uk/

This Cancer Research UK-funded database, called "canSAR", brings together all the relevant biological, chemical, pharmacological, and eventually clinical data about genes and proteins critical to every type of cancer cell. These data will then aid in the discovery of new drugs. This freely available database contains information on the entire human proteome.

Phase III clinical trial development: a process of chutes and ladders

http://www.ncbi.nlm.nih.gov/pubmed/21062928

In response to Institute of Medicine and NCI reports, this article offers the first comprehensive review of all of the time and steps required to open a phase III oncology clinical trial, and discusses the effect of time to protocol activation on subject accrual. The authors conclude that the NCI clinical trials system needs to be reengineered in a collaborative manner.

SCIENTIFIC MODEL SYSTEMS

Deploying mouse models of pancreatic cancer for chemoprevention studies

http://www.ncbi.nlm.nih.gov/pubmed/21045161

Paul Grippo, PhD (2007 Nancy Daly Riordan – Pancreatic Cancer Action Network – AACR Career Development Award recipient) and Dave Tuveson, MD, PhD (2003 Pancreatic Cancer Action Network – AACR Career Development Award recipient, current Scientific Advisory Board chair) teamed up to write this review article. Drs. Grippo and Tuveson discuss molecular features of the currently available pancreatic cancer mouse models, and explore the process by which researchers should choose which model might be most relevant to address their research themes.