PANCREATIC CANCER: NEWS & UPDATES May 2010

Inhibiting the Cyclin-Dependent Kinase CDK5 Blocks Pancreatic Cancer Formation and Progression through the Suppression of Ras-Ral Signaling
http://cancerres.aacrjournals.org/cgi/reprint/70/11/4460
This article is coauthored by Dr. Anirban Maitra, a recipient of a 2004 Pancreatic Cancer Action Network – AACR Career Development Award. Cyclin-dependent kinase CDK5 has a 60% structural homology with other CDK family members, although it does not functionally interact with cyclins or affect the mitotic process. CDK5 is activated in the presence of p35 and p39 proteins, which are shown to be expressed in normal and cancerous pancreatic cell lines. This study shows that blockade of CDK5, by expression of a dominant-negative version of the protein, leads to decreased motility, invasion, and anchorage-independent growth in pancreatic cancer cell lines. Also, xenograft studies suggest that expression of dominant-negative CDK5 reduces the size and metastatic potential of orthotopically engrafted pancreatic cancer cells. Further, results suggest that CDK5 functions through the K-ras pathway, via RalA and RalB. Strikingly, reactivation of the Ral molecules can "rescue" the activities inhibited by dominant-negative CDK5 expression.

Stereotactic Surgery Beneficial in Pancreatic Cancer
http://www.medpagetoday.com/MeetingCoverage/DDW/19942
Stereotactic radiosurgery may be an alternative for patients with locally advanced pancreatic cancer that is traditionally unresectable. It is usually limited to head and neck surgery, particularly brain tumors but is used in pancreatic cancer because it can deliver radiation to one location minimizing damage to surrounding tissue. In this study, patients treated with stereotactic surgery had a local tumor control rate of about 90%; researchers note this is a high value compared to conventional treatment.

High Intra-abdominal Fat Associated with Increased Pancreatic Cancer Mortality
http://www.hemonctoday.com/article.aspx?rid=63944
Although BMI was not a significant predictor for survival in patients with pancreatic cancer, researchers at Baylor College of Medicine found that elevated levels of intra-abdominal fat increased the risk for death as much as fourfold in some patients. BMI was postulated to be a poor predictor of prognosis because it does not show physicians where fat is distributed in obese patients. Fat inside the abdomen is hypothesized to be a better predictor of outcome in patients undergoing abdominal surgery. The researchers concluded that patients with more visceral fat are at greater risk for death.

People with Inflammatory Bowel Disease May be at Increased Risk for Pancreatic Cancer
http://www.webmd.com/ibd-crohns-disease/news/20100505/ibd-may-raise-risk-of-pancreatic-cancer?src=RSS_PUBLIC
University of Utah researchers noticed that pancreatic cancer seemed to be developing at higher-than-normal rates in inflammatory bowel disease (IBD) patients and their family members. Data were examined for 2,877 adults treated for IBD at the University of Utah Health System between 1996 and 2006, along with information from the Utah Cancer Registry and the Utah Population Database. People with IBD had a 3.36-fold higher risk of pancreatic cancer. Those with ulcerative colitis had a 4.85-fold greater risk of pancreatic cancer. Men with IBD had a 6.22-fold higher risk of pancreatic cancer, but women with IBD did not appear to be at increased risk for pancreatic cancer. This study does not prove cause and effect, and further research is needed to confirm and validate these findings.

Big Belly Raises a Woman's Pancreatic Cancer Risk
http://www.nlm.nih.gov/medlineplus/news/fullstory_98615.html
While a link between obesity and pancreatic cancer is suggested, studies looking at the association have yielded mixed results. New York University researchers report on results of a recent study that showed where a person carries their extra weight may influence their risk of pancreatic cancer. People -- especially women -- with more fat around their waistline are at increased risk of the disease. For all study

subjects, there was a positive link between increasing BMI and increasing risk for pancreatic cancer. Overall, the researchers found, people in the top fourth based on their BMI were at 33% higher risk of pancreatic cancer than those in the bottom fourth.

High Carbohydrate Diet and Pancreatic Cancer
http://www.reuters.com/article/idUSTRE64J60020100520
One of the first symptoms of pancreatic cancer -- often noticed even years before diagnosis -- is indigestion. A new study suggests that these timely tummy troubles may be enough to explain away previous links made between a high carbohydrate diet and an increased risk of the disease.

Heavy Alcohol Use, Binge Drinking, Might Increase Risk of Pancreatic Cancer
http://www.eurekalert.org/pub_releases/2010-05/usmc-hau051810.php
Research from UT Southwestern Medical Center suggests heavy alcohol use and binge drinking could increase the risk of pancreatic cancer in men. Researchers found that the more alcohol a man consumed, the higher his risk of pancreatic cancer. Men who consumed alcohol increased their risk of pancreatic cancer by 1.5 to 6 times compared with those who didn't consume alcohol or who had less than one drink per month. The increased risk depended on the amount and frequency of alcohol consumption. Researchers found that the risk was greater no matter when in the past heavy drinking occurred. They also found that men who engaged in binge drinking had a 3.5 times greater likelihood of developing pancreatic cancer. They did not find the association among women, possibly due to the lower proportion of women who reported heavy or binge drinking.

Quality-of-Life Testing May Predict Malignancy and Survival in Patients with Pancreatic Disease
http://www.sciencedaily.com/releases/2010/05/100503090143.htm
According to a study by Henry Ford Hospital, quality-of-life measures used routinely to assess treatment outcomes for patients with pancreatic disease may be used to predict both malignancy and survival for those patients. Researchers found that pre-treatment quality-of-life scores could predict malignancy in patients with pancreatic lesions and survival in those who are found to have malignancies. Their findings suggest that pretreatment quality-of-life scores may show which patients will have a poor survival and therefore could avoid aggressive, but futile, treatment.

Suicide Risk and Cancer: Treat the Mind and Body
http://www.hemonctoday.com/article.aspx?rid=64155
Among the psychological factors associated with a cancer diagnosis is an increased risk for suicide among cancer patients and survivors. Depression may be an important marker in identifying patients most likely to commit suicide. In addition to depression and feelings of hopelessness, there are other factors strongly associated with suicide ideation. Older white men, particularly those who are unmarried, are among the patients most likely to have suicidal thoughts.

Pancreatic Cancer Breakthrough
http://www.abc2news.com/mediacenter/local.aspx?videoId=22935&navCatId=14
This is a news story about Sinai Hospital's success using stereotactic radiosurgery (Cyberknife) in treating unresectable pancreatic cancer patients.

Effects of 5-FU and Heparin-Based Portal Infusion Chemotherapy Combined with Mitomycin C and Cisplatin After Curative Resection of Pancreatic Cancer
http://content.karger.com/produktedb/produkte.asp?typ=fulltext&file=000244265
Treatment with 5-fluorouracil (5-FU) and heparin-based portal infusion chemotherapy combined with systemic administration of mitomycin C and cisplatin following surgery is feasible and could become a promising adjuvant therapy in patients with potentially curative resection of pancreatic cancer.

President's Cancer Panel - Reducing Environmental Cancer Risk
http://deainfo.nci.nih.gov/advisory/pcp/pcp08-09rpt/PCP_Report_08-09_508.pdf
The President's Cancer Panel dedicated its 2008–2009 activities to examining the impact of environmental factors on cancer risk. The Panel considered industrial, occupational, and agricultural exposures as well as exposures related to medical practice, military activities, modern lifestyles, and natural sources. The Panel was particularly concerned to find that the true burden of environmentally induced cancer has been grossly underestimated. With nearly 80,000 chemicals on the market in the

United States, exposure to potential environmental carcinogens is widespread. Pancreatic cancer is referenced six times in the report with respect to its association with environmental contaminants.

Map Tracks Incidences of Cancer throughout New York State
http://www.nytimes.com/2010/05/11/nyregion/11map.html
New York unveiled what it billed as the nation's first comprehensive statewide cancer map, which became available Monday on the Web site of the State Department of Health. The interactive map allows users to see the count of incidences of various types of cancer in different census blocks. For instance, randomly highlighting a four-square-block area of Brooklyn shows 23 cases of cancer out of 1,195 residents, with pancreatic and uterine cancers the most prevalent.

How Cancer Cells Lose Their (Circadian) Rhythm
http://www.acor.org/news/display.html?id=9502
Immortality and uncontrolled cell division are the fundamental differences between cancer cells and normal cells. A widely held explanation for these differences is that the biological clocks in cancer cells are damaged and can't regulate cell division in the fashion that they do in normal cells. This assumption is challenged by the reported experiment that has continuously monitored variations in the rate of cell division for extended periods.

Insurance Coverage Expanding for Cancer Clinical Trials
http://www.cancer.gov/ncicancerbulletin/051810/page5
The movement to push for adopting laws or other formal agreements requiring coverage for the cost of "routine care" received in clinical trials culminated in March with the enactment of the Patient Protection and Affordable Care Act. This act requires health insurers to pay for routine costs of care delivered in phase I through phase IV clinical trials. The new requirement does not take effect until 2014, but once in effect, the new law will offer a baseline of coverage for clinical trial participants in all 50 states and the District of Columbia and help plug some gaps in existing state-level laws and agreements.

Taking Action to Diversify Clinical Cancer Research
http://www.cancer.gov/ncicancerbulletin/051810/page7
Only 3 to 5% of adults with cancer in the U.S. join clinical trials; close to 90% of those who do enroll in NCI-sponsored studies are white. Less than 6% are Hispanic/Latino. Minority, rural, elderly, and other underserved patient populations bear a heavy burden of cancer disease but remain underrepresented in clinical trials," says Dr. Jean Ford, from Johns Hopkins. This finding limits the benefits of clinical trials as a treatment option, and potentially compromises the ability to generalize trial results. The article shares several of the approaches the NCI is using to increase the enrollment of minority and underserved patients in clinical trials.

Why Don't More Medical Discoveries Become Cures?
http://www.newsweek.com/id/238078/
From 1996 to 1999, the U.S. food and Drug Administration approved 157 new drugs. In the comparable time frame a decade later (2006 to 2009), the agency approved 74. Not among them were any cures, or even meaningfully effective treatments, for Alzheimer's, lung or pancreatic cancer, or a host of other afflictions that destroy lives. More and more policymakers and patients are therefore asking, "Where are the cures?" The answer is that potential cures, or at least treatments, are stuck in the chasm between a scientific discovery and the doctor's office: what's been called the "valley of death". Private foundations like MMRF and the Michael J. Fox Foundation for Parkinson's Research are veering away from the NIH model of "here's some money, go discover something" to instead managing and directing researchers more closely, requiring data sharing and cooperation and related work that is required after a discovery is made.

Abstracts

Novel STAT3 Phosphorylation Inhibitors Exhibit Potent Growth-Suppressive Activity in Pancreatic and Breast Cancer Cells
http://www.ncbi.nlm.nih.gov/pubmed/20215512
The JAK/STAT pathway is frequently activated in human cancer, and is therefore an attractive therapeutic target. Dr. Lin (recipient of a 2009 Pancreatic Cancer Action Network – AACR Pilot Grant) and colleagues developed novel inhibitors of STAT3 dimerization (necessary for activity), which are derived from curcumin, the active ingredient in turmeric. Results suggest that the compounds FLLL31 and

FLLL32 are effective inhibitors of JAK2/STAT3 in pancreatic and breast cancer cell lines, leading to decreased growth, anchorage-independence, and invasion. Preliminary *in vivo* studies suggest that these drugs may have anti-angiogenic properties as well.

Primary Cilia Regulate Gli/Hedgehog Activation in Pancreas
http://www.ncbi.nlm.nih.gov/pubmed/20479231
This study was coauthored by Dr. Matthias Hebrok, the recipient of the 2008 Michael C. Sandler – Pancreatic Cancer Action Network – AACR Pilot Grant. The Hedgehog (Hh) pathway has been implicated in aiding pancreatic organogenesis and the development of pancreatic tumors. However, previous studies did not differentiate between epithelial and mesenchymal expression of Hh. In this study, the authors develop a mouse model with constitutively activated GLI (the transcriptional regulator of the Hh pathway), localized to the pancreatic epithelium. Surprisingly, they find a lack of Hh activity in the mouse pancreata. Hh activity in the presence of activated GLI can be stimulated by blocking the primary cilia in these cells, leading to enhanced exocrine and endocrine pancreatic function.

Notch1 Functions as a Tumor Suppressor in a Model of K-ras Induced Pancreatic Ductal Adenocarcinoma
http://www.ncbi.nlm.nih.gov/pubmed/20484026
This article was coauthored by Dr. Ben Stanger, recipient of the 2007 Ralph H. Hruban, MD – Pancreatic Cancer Action Network – AACR Career Development Award. Observations that Notch is expressed and active in some pancreatic ductal adenocarcinoma (PDAC) cases, whereas its expression is absent from normal adult pancreatic tissue, have suggested that Notch may behave as an oncogene. To test this, the authors created mice with mutant K-ras and the absence of Notch expression. Rather than observing decreased tumor formation, the K-ras-mutant, Notch-null mice exhibited a greater number of pancreatic lesions, that were also more aggressive than those observed in the K-ras-mutant, Notch-intact mice. Therefore, the conclusion from this report is that Notch behaves as a tumor suppressor, rather than an oncogene, in the context of mutated K-ras-induced PDAC.

Impact of Race, Age, and Socioeconomic Status on Participation in Pancreatic Cancer Clinical Trials
http://www.ncbi.nlm.nih.gov/pubmed/20467351
Patients enrolled on clinical trials were younger, had better socioeconomic status, and were less often African American. Patients with APC treated at academic institutions may have longer OS than patients treated in the community. Clinical trials seem to offer a survival advantage for patients with APC.

Long Term Follow-up of Resected Pancreatic Cancer Patients Following Vaccination Against Mutant K-Ras
http://www.ncbi.nlm.nih.gov/pubmed/20473937
K-ras mutations are frequently found in pancreatic adenocarcinoma and can elicit mutation-specific immune responses. Targeting the immune system against mutant Ras may influence the clinical course of the disease. Twenty-three patients who were vaccinated after surgical resection for pancreatic adenocarcinoma were followed for more than 10 years. Median survival for all patients was 27.5 months and 28 months for immune responders. The 5-year survival was 22% and 29%, respectively. Strikingly, 10-year survival was 20%, indicating that K-ras vaccination may consolidate the effect of surgery and represent an adjuvant treatment option for the future.

Prognostic Relevance of CA 19-9, CEA, CRP, and LDH Kinetics in Patients Treated with Palliative Second-Line Therapy for Advanced Pancreatic Cancer
http://www.ncbi.nlm.nih.gov/pubmed/20480409
The study examined serum biomarkers that could serve as surrogate survival endpoints during second-line treatment for advanced pancreatic cancer. A pretreatment value and one measurement during second-line treatment for CA 19-9, CEA, CRP, and LDH had to be available in order to evaluate the prognostic role on overall survival. Results indicate that an increase of >20% during treatment was significantly related to worse overall survival for CA 19-9, CEA, and CRP. Serum biomarker kinetics might serve as useful prognostic tools during second-line chemotherapy in advanced pancreatic cancer.

Surgical Resection and Multidisciplinary Care for Primary and Metastatic Pancreatic Islet Cell Carcinomas
http://www.ncbi.nlm.nih.gov/pubmed/20480251
Los Angeles County Cancer Surveillance Program was assessed for patients with islet cell cancers between 1982 to 2006. Two hundred thirty-six patients were identified; 86 patients underwent curative-intent surgery with median survival for local, regional, and distant disease of 17.3, 12.2, and 4.0 years, respectively. In comparison, 102 patients underwent medical management alone; survival was significantly shorter when compared to the surgical cohort. Although patients with metastatic disease had 3-year longer survival with adjuvant chemotherapy, these improvements were not statistically significant. Surgical resection was associated with improved survival compared to medical management for any extent of disease in patients with islet cell cancer, but adjuvant chemotherapy was not associated with survival.

New Drugs in Neuroendocrine Tumors: Rise of New Therapeutic Philosophies?
http://www.ncbi.nlm.nih.gov/pubmed/20473165
This review focuses on recent progress in the treatment of neuroendocrine tumors, new agents and the optimization/improvement of currently available therapies.

Pilot Study of Blood Biomarker Candidates for Detection of Pancreatic Cancer
http://www.ncbi.nlm.nih.gov/pubmed/20467349
The results suggest that biomarker candidates could fail in various steps of biomarker development. Earlier knowledge of candidate biomarker flaws could lead to strategies to overcome the flaw or alternatively lead to earlier termination of biomarkers that are prone to failure in the later phases of validation testing.

Phase II and Coagulation Cascade Biomarker Study of Bevacizumab With or Without Docetaxel `
http://www.ncbi.nlm.nih.gov/pubmed/20458210
Treatment options are limited for advanced pancreatic cancer progressive after gemcitabine therapy. The vascular endothelial growth factor pathway is biologically important in pancreatic cancer, and docetaxel has modest antitumor activity. Researchers evaluated the role of bevacizumab as second-line treatment for patients with metastatic pancreatic cancer. No confirmed objective responses were observed and the study was stopped. Bevacizumab with or without docetaxel does not have antitumor activity in gemcitabine-refractory metastatic pancreatic cancer.

Anthropometric Measures Body Mass Index, and Pancreatic Cancer
http://www.ncbi.nlm.nih.gov/pubmed/20458087
Obesity has been proposed as a risk factor for pancreatic cancer. Pooled data from the National Cancer Institute Pancreatic Cancer Cohort Consortium (PanScan) was analyzed to study the association between prediagnostic anthropometric measures and risk of pancreatic cancer. 2,170 cases and 2,209 control subjects were studied. A positive association between increasing BMI and risk of pancreatic cancer was observed. In men, the adjusted odds ratio for pancreatic cancer for the highest vs lowest quartile of BMI was 1.33 and in women it was 1.34. Increased waist to hip ratio was associated with increased risk of pancreatic cancer in women but less so in men. These findings provide strong support for a positive association between BMI and pancreatic cancer risk. In addition, centralized fat distribution may increase pancreatic cancer risk, especially in women.

Mistletoe Therapy: Friend or Foe in Established Anti-Tumor Protocols?
http://www.ncbi.nlm.nih.gov/pubmed/20455850
Mistletoe is often used as complementary therapy in oncology. The anti-tumor effects of mistletoe (Iscador) are well documented in-vitro. The clinical activity of mistletoe treatment remains still controversial. The researchers report on the results of a multicenter study of pancreatic cancer patients who following surgery were treated by adjuvant chemotherapy with gemcitabine supported by mistletoe, or with gemcitabine alone, or any other best of care, but not including mistletoe.

Phase II Study of Gemcitabine Plus Radiotherapy Versus Gemcitabine, 5-Fluorouracil, and CIsplatin followed by Radiotherapy and 5-Fluorouracil
http://www.ncbi.nlm.nih.gov/pubmed/20461765
A randomized phase II trial was conducted to assess toxicities and surgical resection rates in two neoadjuvant gemcitabine-based chemoradiation regimens in patients with borderline resectable

pancreatic cancer. While the trial was terminated early due to poor accrual, it showed that both regimens were tolerable, and respectability and survival were comparable to previous studies.

Available Carboydrates, Glycemic Load, and Pancreatic Cancer: Is There a Link?
http://www.ncbi.nlm.nih.gov/pubmed/20452999
High-carbohydrate diets have been linked to pancreatic cancer risk in case-control studies, but prospective studies have shown mostly null results. The authors investigated the associations of glycemic load, glycemic index, and carbohydrate intake with pancreatic cancer risk.

Phase II Study of PX-12 in Patients with Advanced Cancer of the Pancreas Following Progression After a Gemcitabine-Containing Combination
http://www.ncbi.nlm.nih.gov/pubmed/20461382
This study evaluated PX-12, a novel small molecule inhibitor of the proto-oncogene in patients with previously treated advanced pancreatic cancer. Due to the lack of significant antitumor activity, the study was terminated early. PX-12 does not appear to be active in unselected patients with previously treated advanced pancreatic cancer.

Phase I Study of the Biomodulation of Capecitabine, Docetaxel and Gemcitabine (mGTX)
http://www.ncbi.nlm.nih.gov/pubmed/20461379
Researchers studied the three drug combination of gemcitabine (G), docetaxel (T) and capecitabine (X) (mGTX) with schedule modification to maximize biomodulation of X. This results demonstrate acceptable tolerability with interesting activity in patients with pancreatic cancer.

Multicenter Phase I-II Trial of Capecitabine and Oxaliplatin in Combination with Radiotherapy
http://www.ncbi.nlm.nih.gov/pubmed/20451275
Researchers evaluated the feasibility and efficacy of capecitabine and oxaliplatin followed by the combination of these two drugs with radiotherapy in patients with locally advanced pancreatic or biliary tract cancer. Two cycles of XELOX (capecitabine + oxaliplatin) were followed by XELOX-RT (radiotherapy combined with capecitabine and oxaliplatin). XELOX-RT was well tolerated and effective for locally advanced pancreatic and biliary tract cancer.

Impact of S-1 in Patients with Gemcitabine-Refractory Pancreatic Cancer in Japan
http://www.ncbi.nlm.nih.gov/pubmed/20462979
Researchers investigated the impact of S-1 on the prognosis of patients with gemcitabine-refractory pancreatic cancer. Second-line chemotherapy was administered to 34 patients: 29 using S-1, four using 5-fluorouracil-based chemoradiation, and one using 5-fluorouracil. The introduction of S-1 might improve the prognosis of patients with gemcitabine-refractory pancreatic cancer.

Impact of Obesity on Perioperative Outcomes and Survival Following Pancreaticoduodenectomy
http://www.ncbi.nlm.nih.gov/pubmed/20431978
Obese patients had similar tumor-specific characteristics, as well as perioperative outcomes, compared with normal weight patients. However, obese patients undergoing pancreaticoduodenectomy for pancreatic cancer had an improved long-term survival independent of known clinicopathologic factors.

Ultraviolet B Irradiance and Vitamin D Status are Inversely Associated with Incidence Rates of Pancreatic Cancer Worldwide
http://www.ncbi.nlm.nih.gov/pubmed/20442683
Countries with lower ultraviolet B (UVB) irradiance had higher incidence rates of pancreatic cancer in both hemispheres, with occasional exceptions.

Adjuvant Therapy Outcomes for Resectable Pancreatic Adenocarcinoma
http://www.ncbi.nlm.nih.gov/pubmed/20446118
Curative-intent surgery for pancreatic cancer at large academic institutions can have very low mortality rates. Pathology findings are valuable prognostic markers in resected pancreatic cancer. Few studies have examined the prognostic value of preoperative LFTs or lymph node ratio, and the analysis indicates they may have prognostic value. This should be confirmed in other series. Patients who receive adjuvant therapy (chemo-XRT or chemotherapy) appear to live longer than patients who receive no adjuvant therapy in this retrospective analysis.

Intra-arterial Ultrasound in Pancreatic Cancer: Feasibility Study and Preliminary Results
http://www.ncbi.nlm.nih.gov/pubmed/20440500
Despite technological advances in computed tomography (CT) and magnetic resonance imaging, the involvement of the celiac or mesenteric artery in pancreatic cancer remains uncertain in many cases. Infiltration of these vessels is important in making decisions about therapy choices but often can only be definitively determined through laparotomy. Local (intraarterial) ultrasound may increase diagnostic accuracy.

Endoscopic Ultrasound in Solid Pancreatic Masses
http://www.ncbi.nlm.nih.gov/pubmed/20432768
Over two decades ago endoscopic ultrasound (EUS) was introduced into clinical practice for better visualization of the pancreas. At the time of introduction, EUS was superior to other methods of detection of pancreatic masses, allowing tissue diagnosis by later introduced EUS-guided fine needle aspiration (FNA). The aim of this review was to discuss the current evidence of clinical impact of EUS and EUS-FNA in evaluation of solid pancreatic masses, with special emphasis on differentiation between benign and malignant pancreatic lesions.