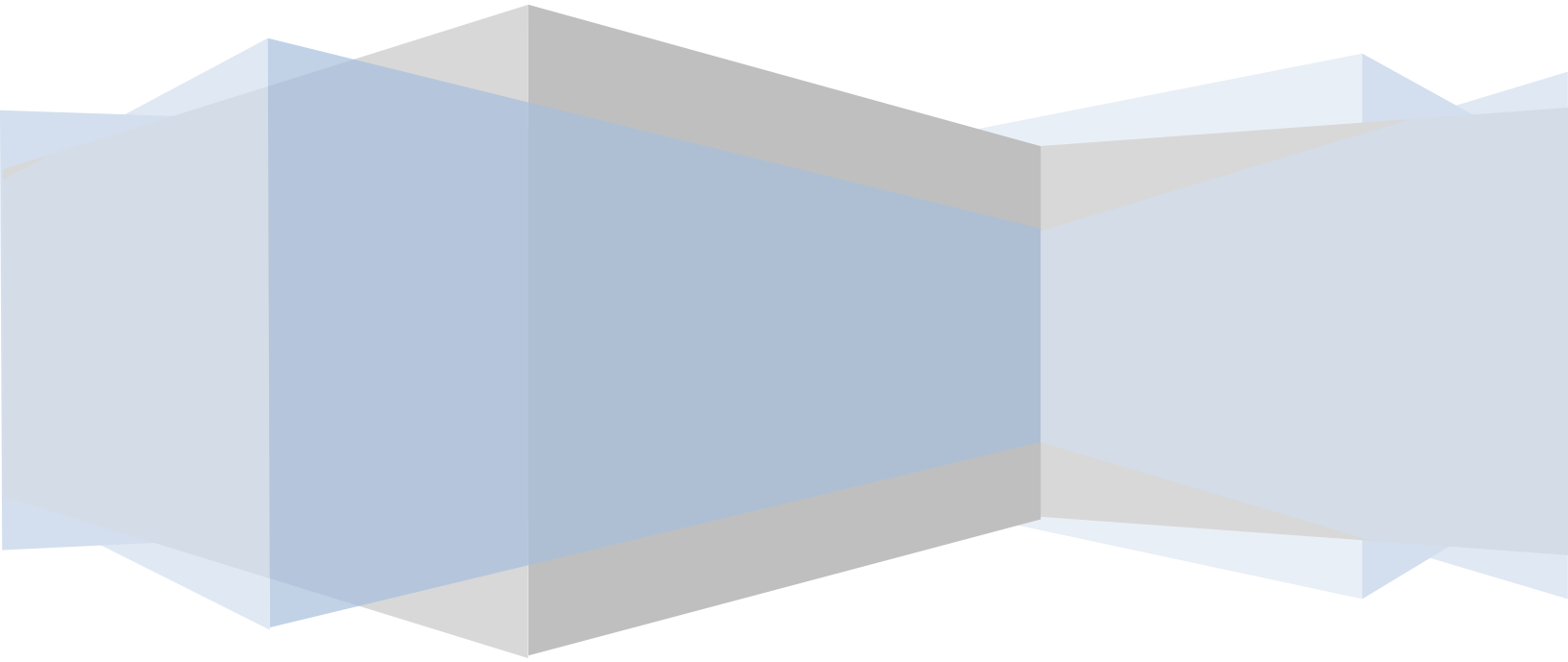
SPORE Advances

April 1 – June 30, 2009

Translational Research Program, DCTD, NCI



University of California, San Francisco
Berger, Mitchel S., M.D.

(***Crane***... *et al*)

Honokiol-mediated inhibition of PI3K/mTOR pathway: a potential strategy to overcome immunoresistance in glioma, breast, and prostate carcinoma without impacting T cell function

PI3Kinase mediated immunoresistance is an obstacle to effective T-cell mediated immunotherapy. Systemic inhibition of PI3Kinase with conventional inhibitors in patients is feasible, but negatively impacts T-cell activity, undermining the impact of any effective vaccine strategy. Here we show that a novel inhibitor of PI3kinase (Honokiol) impacts tumor cells, but not T-cells, suggesting that this clinical agent would be ideal to augment our current HSP vaccine strategy being tested in recurrent and primary glioma. (J Immunother)

http://journals.lww.com/immunotherapy-journal/Abstract/2009/07000/Honokiol_mediated_Inhibition_of_PI3K_mTOR_Pathway_.5.aspx

(***Drummond***... *et al*)

Development of a highly stable and targetable nanoliposomal formulation of topotecan

This report (in press) describes the development of a new lipidic nanoparticle drug in which topotecan is delivered via a nanoliposome carrier, including mAb-targeted and non-targeted constructs. This advance is an extension of the technology used to develop nanoliposomal CPT-11, a previous construct currently in Phase II clinical trials. The new nanoliposomal and immunoliposomal topotecan constructs are also potential candidates for clinical testing, based on encouraging preclinical results. (J Control Release)

http://www.ncbi.nlm.nih.gov/pubmed/19686789?log$=activity

(***Fan***... *et al*)

EGFR signals to mTOR through PKC and independently of Akt in glioma

In glioblastomas, an Akt-independent, PTEN (phosphatase and tensin homolog deleted on chromosome ten) regulated signaling pathway links EGFR (epidermal growth factor receptor) to the phosphorylation of mTOR (mammalian target of rapamycin) and of the ribosomal protein S6 and to the control of cell replication. PKCα (protein kinase Cα) is an essential component of this pathway. Inhibitors of PKC showed activity in glioma cells irrespective of PTEN status. (Sci Signal).

http://stke.sciencemag.org/cgi/reprint/sigtrans;2/55/ra4.pdf

(***Prados***... *et al*)

Phase II study of Erlotinib plus Temodar during and following radiation therapy in patients with newly diagnosed Glioblastoma Multiforme or Gliosarcoma

We previously reported on a phase I trial of erlotinib alone or in combination with temozolomide that suggested that amplification of EGFR and presence of intact phosphatase and tensin homolog (PTEN) are correlated with response. After the phase I trial, we designed an open-label, single-arm, phase II trial that adds erlotinib to the standard therapy of radiation and temozolomide for treating GBM. Patients treated with the combination of erlotinib and temozolomide during and following radiotherapy had better survival than historical controls. There was a strong positive correlation between MGMT promoter methylation and survival, as well as an association between MGMT promotor-methylated tumors and PTEN positivity shown by immunohistochemistry with improved survival. (J Clin Oncol)

http://jco.ascopubs.org/cgi/reprint/27/4/579

(***Wrensch**... et al*)

Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility

The causes of glioma have eluded researchers for decades, as very few risk factors have been consistently observed across studies. We have now conclusively shown that common inherited variants in regions of chromosome 9p21 near CDKN2B and chromosome 20 intronic to RTEL1 predict risk of high grade glioma and we also identified a variant in chromosome 5 intronic to TERT as a promising glioma risk predictor. Having established biologic predictors of glioma risk opens unique and novel research opportunities for more complete understanding of the etiology of this devastating disease. (Nat Genet)

http://www.nature.com/ng/journal/v41/n8/abs/ng.408.html

http://www.ucsf.edu/science-cafe/articles/genetic-risk-for-brain-cancer-a-glioma-called-glioblastoma/

Mayo Clinic, Rochester

O'Neill, Brian, M.D.

(***Loftus**... et al*)

The Pyk2 FERM domain as a target to inhibit glioma migration

The invasion of malignant glioma cells into the surrounding normal brain precludes effective clinical treatment. In this report, we investigated the role of the NH(2)-terminal FERM domain in the regulation of the promigratory function of Pyk2. We report that the substitution of residues that constitute a small cleft on the surface of the F3 module of the FERM domain do not significantly alter Pyk2 expression but result in the loss of Pyk2 phosphorylation. A monoclonal antibody, designated 12A10, specifically targeting the Pyk2 FERM domain was generated and recognizes an epitope located on the beta5C-alpha1C surface of the F3 module of the FERM domain. Amino acid substitutions in the F3 module that resulted in the loss of Pyk2 phosphorylation also inhibited the binding of 12A10, suggesting that the 12A10 epitope overlaps a site that plays a role in Pyk2 activity. Conjugation of 12A10 to a membrane transport peptide led to intracellular accumulation

and inhibition of glioma cell migration in a concentration-dependent manner. A single chain Fv fragment of 12A10 was stable when expressed in the intracellular environment, interacted directly with Pyk2, reduced Pyk2 phosphorylation, and inhibited glioma cell migration in vitro. Stable intracellular expression of the 12A10 scFv significantly extended survival in a glioma xenograft model. Together, these data substantiate a central role for the FERM domain in regulation of Pyk2 activity and identify the F3 module as a novel target to inhibit Pyk2 activity and inhibit glioma progression. (Mol Cancer Ther)

http://mct.aacrjournals.org/content/8/6/1505.long

(***Pulido**... et al*)

Racial differences in primary central nervous system lymphoma incidence and survival rates

To determine racial and ethnic differences in incidence and survival in patients with primary central nervous system lymphoma (PCNSL), NCI Surveillance, Epidemiology, and End Results (SEER) program data from 1992 to 2002 were queried. Data were substratified by age (20-49 years vs. 50 or above) and race (White, Black, Asian/Pacific Islander [A/PI], American Indian/Alaskan Native [AI/AN]). Incidence of PCNSL and survival were calculated by SEER(*)Stat software. The incidence rates were 0.94 per 100,000 per year (95% confidence interval [CI] 0.90-0.98) for Whites, 1.10 (95% CI 0.98-1.22) for Blacks, 0.51 (95% CI 0.28-0.74) for AI/AN, and 0.64 (95% CI 0.56-0.72) for A/PI. In patients aged 20-49 years the rates were 0.72 (95% CI 0.68-0.76) for Whites, 1.43 (95% CI 1.27-1.59) for Blacks, 0.58 (95% CI 0.30-0.86) for AI/AN, and 0.21 (CI 0.15-0.27) for A/PI. In patients over 49 years, the rates were 1.30 (95% CI 1.22-1.38) for Whites, 0.56 (95% CI 0.40-0.72) for Blacks, 0.34 (95% CI 0-0.70) for AI/AN, and 1.31 (95% CI 1.00-1.53) for A/PI. PCNSL incidence for ages 20-49 years for Black patients was twice that for Whites. Incidence for ages over 49 years for Whites was twice that for Blacks. Survival at 12 months, 24 months, and 60 months was higher among Whites than Blacks. Research is needed to determine the origin of these differences. (Neuro Oncol)

http://neuro-oncology.dukejournals.org/cgi/content/full/11/3/318?ck=nck

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(***Wrensch**... et al*)

Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility

The causes of glioblastoma and other gliomas remain obscure. To discover new candidate genes influencing glioma susceptibility, we conducted a principal component-adjusted genome-wide association study (GWAS) of 275,895 autosomal variants among 692 adult high-grade glioma cases (622 from the San Francisco Adult Glioma Study (AGS) and 70 from the Cancer Genome Atlas (TCGA)) and 3,992 controls (602 from AGS and 3,390 from Illumina iControlDB (iControls)). For replication, we analyzed the 13 SNPs with P < 10(-6) using independent data from 176 high-grade glioma cases and 174 controls from the Mayo Clinic.

On 9p21, rs1412829 near CDKN2B had discovery P = 3.4 x 10(-8), replication P = 0.0038 and combined P = 1.85 x 10(-10). On 20q13.3, rs6010620 intronic to RTEL1 had discovery P = 1.5 x 10(-7), replication P = 0.00035 and combined P = 3.40 x 10(-9). For both SNPs, the direction of association was the same in discovery and replication phases. (Nat Genet)

http://www.nature.com/ng/journal/v41/n8/full/ng.408.html

Breast

Vanderbilt University
Arteaga, Carlos, M.D.

(***Miller***... *et al*)

Loss of PTEN engages ErbB3 and IGF-I receptor signaling to promote antiestrogen resistance in breast cancer

This paper highlights signaling pathways that become preferentially upregulated in hormone receptor-positive breast cancers upon loss of the tumor suppressor phosphatase PTEN and concordant upregulation of PI-3 kinase signaling. In doing so, the authors propose signaling inhibitors that are worth testing in ER+, PTEN-negative breast cancers. (Cancer Res)

http://cancerres.aacrjournals.org/cgi/content/full/69/10/4192

(***Shah***... *et al*)

Imaging Biomarkers Predict Response to Anti-HER2 (ErbB2) Therapy in Preclinical Models of Breast Cancer

This paper highlights preclinical noninvasive methods that can be used in clinical trials as predictive biomarkers of response to inhibitors of the HER2 oncogene. (Clin Cancer Res)

http://clincancerres.aacrjournals.org/cgi/content/full/15/14/4712

University of North Carolina
Earp, H. Shelton, M.D.

(***Courtwright***... *et al*)

Secreted Frizzle-Related Protein 2 Stimulates Angiogenesis via a Calcineurin/NFAT Signaling Pathway

Angiogenesis is the growth of new capillary blood vessels and is a critical component of solid tumor growth. We discovered a novel protein, SFRP2, that is expressed in the tumor vessels of the following cancers: breast, colon, lung, prostate, ovarian, pancreas, angiosarcoma, and hepatocellur cancer. We found that SFRP2 stimulates angiogenesis in animal models, and therefore is a new therapeutic target to develop a monoclonal antibody gainst for the treatment of a wide variety of cancers. (Cancer Res)

http://cancerres.aacrjournals.org/cgi/reprint/69/11/4621
http://www.unchealthcare.org/site/newsroom/news/2009/June/demore/

University of California, San Francisco

Gray, Joe W., Ph.D.

(***Hennessy***... *et al*)

Characterization of a Naturally Occurring Breast Cancer Subset Enriched in Epithelial-to-Mesenchymal Transition and Stem Cell Characteristics

This project identified an important subset of breast cancers and breast cancer cell lines that has many characteristics of stem cells. It may be a form of cancer that originates in an early progenitor cell line the breast. (Cancer Res)

http://cancerres.aacrjournals.org/cgi/content/abstract/69/10/4116

(***Suzuki***... *et al*)

Protein Acetylation and Histone Deacetylase Expression Associated with Malignant Breast Cancer Progression

Baseline levels of candidate markers for assessment of tumor response to HDAC inhibitor treatment are evaluated in invasive and in situ breast cancer. This is the first study to show significant changes in histone acetylation levels in the course of tumor progression from normal breast epithelium to in situ and invasive ductal carcinoma. Based on our findings, HDAC inhibitors will be expected to reverse hypoacetylation levels observed even in early stages of breast cancer progression. (Clin Cancer Res)

http://clincancerres.aacrjournals.org/cgi/content/full/15/9/3163

Mayo Clinic, Rochester

Ingle, James N., M.D.

(***Milne***... *et al*)

Newly discovered breast cancer susceptibility loci on 2q35

This large collaborative study involving the Breast Cancer Association Consortium (BCAC) identified a new commonly inherited risk factor for breast cancer. The identification of this variant is expected to provide further nsight into the etiology of breast tumors. The variant may also prove useful as a target of prevention and therapeutic agents. (J Natl Cancer Inst)

http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&term=%22Journal%20of%20the%20National%20Cancer%20Institute%22%5BJour%5D%20AND%201012%5Bpage%5D%20AND%202009%5Bpdat%5D

University of Chicago
Olopade, Olufunmilayo, M.D.

(***Drukker**... et al*)

Automated method for improving system performance of computer-aided diagnosis in breast ultrasound

The feasibility of a computerized auto-assessment method in which the computer system itself provides a level of confidence for its estimate for the probability of malignancy for each radiologist-identified lesion is demonstrated. The computer performance was assessed within a leave-one-case-out protocol using a database of sonographic images from 542 patients (19% cancer prevalence). The use of this auto-assessment method resulted in the modest but statistically significant increase in the area under the receiver operating characteristic (ROC) curve (AUC value) of 0.01 with respect to the performance obtained using the "traditional" CADx approach, increasing the AUC value from 0.89 to 0.90 (p-value 0.03). (IEEE Trans Med Imaging)

http://ieeexplore.ieee.org/Xplore/login.jsp?url=http%3A%2F%2Fieeexplore.ieee.org%2Fstamp%2Fstamp.jsp%3Ftp%3D%26arnumber%3D4563674%26isnumber%3D4729788&authDecision=-203

(***Li, H**... et al*)

Computerized breast parenchymal analysis on DCE-MRI for use in the assessment of breast cancer risk

Breast density has been shown to be associated with the risk of developing breast cancer, and MRI has been recommended for high-risk women screening, however, it is still unknown how the breast parenchymal enhancement on DCE-MRI is associated with breast density and breast cancer risk. We analyzed ninety-two DCE-MRI exams of asymptomatic women in which the computer extracted and analyzed the 3D breast volume, the fibrogandular regions, and the parenchymal kinetic curve dynamics. From kinetic analyses, we found that women with dense breast (BIRADS 3 and 4) were found to have more parenchymal enhancement at their peak time point (Ep) with an average Ep of 116.5% while those women with fatty breasts (BIRADS 1 and 2) demonstrated an average Ep of 62.0%. (SPIE)

http://spiedl.aip.org/getabs/servlet/GetabsServlet?prog=normal&id=PSISDG00726000000172600N000001&idtype=cvips&gifs=yes

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Baylor College of Medicine
Osborne, C. Kent., M.D.

(***De Amicis**... et al*)

Androgen receptor overexpression induces tamoxifen resistance in human breast cancer cells

Resistance to tamoxifen is a major problem in treating women with breast cancer. By gene expression profiling, we found elevated AR, and reduced estrogen receptor (ER) α mRNA in tamoxifen-resistant tumors. Our data suggest a role for AR overexpression as a novel mechanism

of hormone resistance, so that AR may offer a new clinical therapeutic target in human breast cancers. (Breast Cancer Res Treat)

http://www.springerlink.com/content/ek7xw23584216544/fulltext.pdf

Cervical

Johns Hopkins University
Wu, T.C., M.D., Ph.D.

(***Best**... et al*)

Administration of HPV DNA vaccine via electroporation elicits the strongest CD8+ T cell immune responses compared to intramuscular injection and intradermal gene gun delivery

Electroporation and gene gun-mediated particle delivery are leading methods of DNA vaccine delivery that can generate protective and therapeutic levels of immune responses in experimental models. In this study, we perform a head-to-head comparison of three methods of vaccination - conventional intramuscular injection, electroporation-mediated intramuscular delivery, and epidermal gene gun-mediated particle delivery - in the ability to generate antigen-specific cytotoxic CD8+ T cell responses as well as anti-tumor immune responses against an HPV-16 E7 expressing tumor cell line using the pNGVL4a-CRT/E7(detox) DNA vaccine. We conclude that electroporation is a promising method for delivery of HPV DNA vaccines and should be considered for DNA vaccine delivery in human clinical trials. (Vaccine)

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TD4-4WT3XNW-3&_user=75682&_rdoc=1&_fmt=&_orig=search&_sort=d&_docanchor=&view=c&_acct=C000006078&_version=1&_urlVersion=0&_userid=75682&md5=bbbad39049ddad07debf9a25d68b1ff7

(***Chuang**... et al*)

Combination of viral oncolysis and tumor-specific immunity to control established tumors

Chuang CM, Monie A, Wu A, Pai SI, Hung CF. Clin Cancer Res. 2009 Jul 15;15(14):4581-8. Epub 2009 Jul 7. The application of oncolytic viruses is a potential strategy for controlling advanced-stage cancer because intratumoral (i.t.) injection of an oncolytic virus, such as vaccinia virus, results in tumor cell lysis and subsequent release of tumor antigens into the microenvironment. In the current study, we observed that in tumor-bearing mice primed with DNA encoding an immunogenic foreign antigen, ovalbumin (OVA) followed by a boost with i.t. administration of vaccinia virus encoding the same foreign antigen, OVA, can generate enhanced antitumor effects through the combination of viral oncolysis and tumor-specific immunity. Thus, the current study may provide a novel therapeutic strategy for the control of advanced-stage cancers. (Clin Cancer Res)

http://clincancerres.aacrjournals.org/cgi/content/full/15/14/4581

(***Chuang**... et al*)

Combination of apigenin treatment with therapeutic HPV DNA vaccination generates enhanced therapeutic antitumor effects

Antigen-specific immunotherapy has emerged as a novel alternate therapy for advanced stage cancers, which may be employed in conjunction with conventional therapies. In the current study, we found that treatment with the chemotherapeutic agent, apigenin in combination with DNA vaccines encoding the HPV-16 E7 antigen linked to heat shock protein 70 (HSP70) led to the control of the E7-expressing tumors, TC-1. Thus, apigenin represents a promising chemotherapeutic agent, which may be used in combination with immunotherapy for the treatment of advanced stage cancers. (J Biomed Sci)

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=19473507

(***Jagu**... et al*)

Concatenated multitype L2 fusion proteins as candidate prophylactic pan-human papillomavirus vaccines

In the current study, we hypothesized that vaccination with concatenated multitype L2 fusion proteins derived from known cross-protective epitopes of several divergent human papillomavirus (HPV) types might enhance immunity across clinically relevant HPV genotypes. We found that the HPV-16 L2 polypeptides generated robust HPV-16-neutralizing antibody responses, albeit lower than those to HPV-16 L1 VLPs, and lower responses against other HPVs. In contrast, vaccination with the multitype L2 fusion proteins 11-200 x 3 and 11-88 x 5 induced high serum neutralizing antibody titers against all heterologous HPVs tested. 11-200 x 3 formulated in GPI-0100 adjuvant or alum with 1018 ISS protected mice against HPV-16 challenge (reduction in HPV-16 infection vs phosphate-buffered saline control, $P < .001$) 4 months after vaccination as well as HPV-16 L1 VLPs, but 11-200 x 3 alone or formulated with either alum or 1018 ISS was less effective (reduction in HPV-16 infection, $P < .001$).Thus, concatenated multitype L2 proteins in adjuvant have potential as pan-oncogenic HPV vaccines. (J Natl Cancer Inst)

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=19470949

(***Lu**... et al*)

Treatment with demethylating agent, 5-aza-2'-deoxycytidine enhances therapeutic HPV DNA vaccine potency

DNA methylation has been shown to lead to silencing of the genes that would affect the expression of the encoded antigen of the DNA vaccines. In the current study, we found that CRT/E7 DNA vaccination combined with demethylating agent, 5-aza-2'-deoxycytidine (DAC) led to upregulation of CRT/E7 expression, resulting in improved DNA vaccine potency. Thus, our data suggest that combination of CRT/E7 DNA vaccination with DAC treatment may represent a potentially promising approach to control HPV-associated malignancies. (Vaccine)

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TD4-4VP66BN-7&_user=75682&_rdoc=1&_fmt=&_orig=search&_sort=d&_docanchor=&view=c&_acct=C000006078&_version=1&_urlVersion=0&_userid=75682&md5=da19306cf935a11e2b8c109a28978e5e

(***Tsen**... et al*)

Femtosecond laser treatment enhances DNA transfection efficiency in vivo

In this report, we employed a very low power, near-infrared femtosecond laser technique to enhance the transfection efficiency of intradermally and intratumorally administered DNA plasmid. We found that femtosecond laser treatment can significantly enhance the delivery of DNA into the skin and into established tumors in mice. This femtosecond new laser technology represents a safe and innovative technology for enhancing DNA gene transfer in vivo. (J Biomed Sci)

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=19338665

GI

Vanderbilt University
Coffey, Robert J., Jr., M.D.

(***McConnell**... et al*)

The enterocyte microvillus is a vesicle-generating organelle

We demonstrated the release of vesicles enriched in active brush boarder enzymes by brush boarder enterocytes into the intestinal lumen and knockout mice devoid of myosin-1a display significantly altered vesicle production. It is likely that these vesicles play an important role in maintaining homeostasis of the normal intestinal flora and perturbations of appropriate vesicle release could have significant implications for malabsorption disease, inflammatory bowel disease and gastrointestinal cancer. (J. Cell Biol)

http://jcb.rupress.org/cgi/content/full/jcb.200902147/DC1

Johns Hopkins University
Kern, Scott E., M.D.

(***Blackford**... et al*)

SMAD4 mutations are associated with poor prognosis in pancreatic carcinoma

A comprehensive search for mutations among all genes of 24 pancreatic cancers was recently completed, finding 39 genes that were mutated in two or more tumors Among these 39 genes, when studied in a larger panel of 114 patients, only SMAD4 mutations were associated with worse prognosis (HR = 1.92), indicating a special property not identified in any other gene of the genome. Mutations in SMAD4 may provide improved predictive, prognostic, and diagnostic mutation-based

markers, and could aid statistical stratification to improve the power of clinical trials in pancreatic cancer. (Clin Cancer Res)

http://www.ncbi.nlm.nih.gov/pubmed/19584151

(***Blackford***... *et al*)

Genetic mutations associated with cigarette smoking in pancreatic cancer

Cigarette smoking causes many cancers, including pancreatic, but it was unknown which, if any, global genetic changes in tumors could be attributed to smoking-induced mutations. We comprehensively searched for mutations among all genes of 24 pancreatic cancers and among the most commonly mutated genes in another 90 patients, finding that cancers in patients that had previously smoked had nearly a third more mutant genes than those of patients that had never smoked. A missing link in the smoking-to-cancer causal relationship is now available with our measurement of increased gene mutations in the tumors of smokers, and clues as to the types of cigarette-induced mutations are now more comprehensively determined. (Cancer Res)

http://www.ncbi.nlm.nih.gov/pubmed/19351817

(***Jones***... *et al*)

PALB2 mutations cause inherited pancreatic cancers

Inherited risk for pancreatic cancer runs in hundreds of families in the USA alone, but less than 20% of the families were explainable by known inherited mutations. Comprehensive sequencing of all exons of the genomes of 24 pancreatic cancers identified a germline mutation in PALB2, and followup studied identified similar inherited mutations among a panel of families at high risk for pancreatic cancer but not in control persons.It has often been suggested that whole-genome sequencing might identify new causes of disease, and indeed the first example of success using this approach was provided by this current work, enabling identification of individuals that need to be clinically treated differently both prior to and after developing a cancer. (Science)

http://www.ncbi.nlm.nih.gov/pubmed/19264984

Gyn

University of Texas MD Anderson Cancer Center

Lu, Karen, M.D.

(***Coffey***... *et al*)

EphA2 overexpression is associated with lack of hormone receptor expression and poor outcome in endometrial cancer

EphA2 is a tyrosine kinase receptor in the ephrin family that is implicated in oncogenesis and angiogenesis.

We found that EphA2 overexpression was associated with aggressive phenotypic features in endometrioid endometrial carcinoma and was associated inversely with estrogen receptor and progesterone receptor expression. Thus, EphA2 may be an important therapeutic target, especially in patients with hormone receptor-negative endometrial carcinoma. (Cancer)

http://www3.interscience.wiley.com/journal/122358753/abstract?CRETRY=1&SRETRY=0

(***Jeong***... *et al*)

Mig-6 modulates uterine steroid hormone responsiveness and exhibits altered expression in endometrial disease

An imbalance caused by increased estrogen (E2) action and/or decreased progesterone (P4) action can result in abnormal endometrial proliferation/endometrial adenocarcinoma, and we demonstrate here that absence of Mig-6 in mice results in the inability of P4 to inhibit E2-induced uterine weight gain and E2-responsive target genes expression. The observation that endometrial carcinomas in women have a significant reduction in Mig-6 expression provides compelling support for an important growth regulatory role for Mig-6 in the uterus of both humans and mice. We demonstrate that Mig-6 is a critical regulator of the response of the endometrium to E2 in regulating tissue homeostasis, and identify a PR/SRC-1/Mig-6 regulatory pathway that is critical in the suppression of endometrial cancer. (Proc Natl Acad Sci U S A)

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=19439667

(***Nabils***... *et al*)

DNA methylation inhibits p53-mediated survivin repression

The molecular progression of endometrial cancer is poorly understood, and both genetic and epigenetic factors play a role. Our data indicates that demethylation of the survivin promoter by decitabine results in p53-dependent survivin repression and that p53 binding can be inhibited by DNA methylation. Demethylation induced by decitabine is traditionally thought to be active in tumors by allowing the re-expression of tumor suppressor genes, however our results indicate that an additional important mechanism is to decrease the expression of oncogenes. (Oncogene)

http://www.nature.com/onc/journal/v28/n19/abs/onc200962a.html

Head and Neck

University of Texas MD Anderson Cancer Center
Lippman, Scott, M.D.

(***Chakravarty***... *et al*)

Phosphorylated insulin like growth factor-I receptor expression and its clinico-pathological significance in histologic subtypes of human thyroid cancer

The analysis in this paper indicates that pIGF-IR is upregulated in a majority of follicular thyroid carcinomas, suggesting it may be a potential target for therapy for patients with this disease. In addition, since low pIGF-IR expression was found to correlate with aggressive human thyroid carcinoma, the data also suggest that IGF-IR may not be needed for progression of anaplastic thyroid carcinoma, possibly because other cell signaling pathways are activated and obviate the need for IGF-IR signaling. (Exp Biol Med)

http://www.ebmonline.org/cgi/content/full/234/4/372

(***Sano**... et al*)

The effect of combination anti-endothelial growth factor receptor and anti-vascular endothelial growth factor receptor 2 targeted therapy on lymph node metastasis: a study in an orthotopic nude mouse model of squamous cell carcinoma of the oral tongue

Therapy targeting the EGFR and VEGFR signaling pathways with combined monoclonal antibodies showed significant antitumor activity against an orthotopic mouse model of squamous cell carcinoma of the oral tongue (SCCOT) and also inhibited the incidence of cervical lymph node metastases in vivo. This treatment blocked the phosphorylation of these receptors, inducing both endothelial apoptosis and tumor apoptosis, and decreasing tumor MVD and proliferation. These results suggest that this combination treatment may be an effective strategy against metastatic SCCOT and warrants further preclinical trials. (Arch Otolaryngol Head Neck Surg)

http://archotol.ama-assn.org/cgi/content/full/135/4/411

(***Holsinger**... et al*)

Durable long-term remission with chemotherapy alone for stage II to IV laryngeal cancer

Thirty-one previously untreated patients with resectable laryngeal cancer (T2-4, No-1, Mo) were enrolled in study of induction chemotherapy with or without conservation laryngeal surgery (CLS). Chemotherapy alone in selected patients with T2-4, No-1 laryngeal cancer was shown to provide durable disease remission at 5 years and, for patients with partial responses, CLS provided a high rate of laryngeal preservation. This prospective study suggests that chemotherapy alone may cure selected patients with laryngeal cancer, warranting further prospective investigation. (J Clin Oncol)

http://jco.ascopubs.org/cgi/content/full/27/12/1976

(***Pu**... et al*)

Cyclooxygenase-2 gene polymorphisms reduce the risk of oral premalignant lesions

The authors conducted a case-control study to evaluate the effects of 3 potentially functional COX-2 polymorphisms on the risk of oral premalignant lesions (OPL). They found the exon 10 +837T-->C variant and a common halotype that contained the variant allele of this SNP were associated with reduced risks of OPL and that interaction effects were observed between specific COX-2 variants and tobacco smoking in the modulation of OPL risk. This study provides the first epidemiologic

evidence indicating that potentially functional polymorphisms of the COX-2 gene may have an impact on individual susceptibility to OPLs. (Cancer)

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19197984

(***Roblyer**... et al*)

Objective detection and delineation of oral neoplasia using autofluorescence imaging

Autofluorescence images (AI) were obtained from patients with suspicious lesions and normal volunteers, resulting in 284 regions of interest (ROI). A classification algorithm, developed using a training set of ROI from the first cohort of subjects and then validated in ROIs from the second cohort, was found to discriminate between neoplastic and non-neoplastic tissue with high sensitivity (94%) and specificity (87%) rates and, when applied to images of the entire oral cavity, created visual "disease-probability maps." As low-cost digital cameras with acceptable resolution to record tissue autofluorescence are readily available, use of quantitative AI may provide a simple and objective method to improve community-based screening of oral cancers and premalignancies. (Cancer Prev Res)

http://cancerpreventionresearch.aacrjournals.org/cgi/content/full/2/5/423?view=long&pmid=19401530

Johns Hopkins University
Sidransky, David, M.D.

(***Best**... et al*)

Electroporation mediated administration of a DNA vaccine elicits the strongest anti- tumor responses in vivo

We have determined that administration of a therapeutic HPV DNA vaccine via electroporation elicits the strongest anti- tumor immune responses in vivo as compared to gene gun or intramascular injection. Based on this finding, we plan to administer our HPV DNA vaccine via electroporation in our phase I HPV vaccine clinical trial. (Vaccine)

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TD4-4WT3XNW-3&_user=10843&_rdoc=1&_fmt=&_orig=search&_sort=d&_docanchor=&view=c&_acct=C000000150&_version=1&_urlVersion=0&_userid=10843&md5=476c0682ced634490d647c8c06787bbd

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University of Texas MD Anderson Cancer Center

Issa, Jean-Pierre, M.D.

(***Kantarjian***... *et al*)

Targeting DNA methylation

This article reviews advances in the exiciting area of epigenetic therapy. (Clin Cancer Res)

http://clincancerres.aacrjournals.org/cgi/content/full/15/12/3938

(***Chen***... *et al*)

Mechanism of action of SNS-032

Inhibitors of cyclin-dependent kinases (Cdks) have been reported to have activities in chronic lymphocytic leukemia cells by inhibiting Cdk7 and Cdk9, which control transcription. Here we studied the novel Cdk inhibitor SNS-032, which exhibits potent and selective inhibitory activity against Cdk2, Cdk7, and Cdk9. These data support the clinical development of SNS-032 in diseases that require short-lived oncoproteins for survival. (Blood)

http://bloodjournal.hematologylibrary.org/cgi/content/full/113/19/4637

(***Zeng***... *et al*)

Targeting the leukemia microenvironment

SDF-1alpha/CXCR4 signaling plays a key role in leukemia/bone marrow microenvironment interactions. We previously reported that bone marrow-derived stromal cells inhibit chemotherapy-induced apoptosis in acute myeloid leukemia (AML). Here we demonstrate that the CXCR4 inhibitor AMD3465 antagonized stromal-derived factor 1alpha (SDF-1alpha)-induced and stroma-induced chemotaxis and inhibited SDF-1alpha-induced activation of prosurvival signaling pathways in leukemic cells. (Blood)

http://bloodjournal.hematologylibrary.org/cgi/content/full/113/24/6215

(***Chakraborty***... *et al*)

Jak2 inhibition deactivates Lyn kinase through the SET-PP2A-SHP1 pathway

Chronic myelogenous leukemia (CML) patients treated with imatinib mesylate (IM) become drug resistant by mutations within the kinase domain of Bcr-Abl, and by other changes that cause progression to advanced stage (blast crisis) and increased expression of the Lyn tyrosine kinase, the regulation of which is not understood yet. In Bcr-Abl+ cells inhibition of Jak2, a downstream target of Bcr-Abl, by either Jak2 inhibitors or Jak2-specific short interfering RNA (siRNA) reduced the level

of the SET protein, and increased PP2A Ser/Thr phosphatase and Shp1 tyrosine phosphatase activities, which led to decreased levels of activated Lyn. Activation of PP2A combined with Jak2 inhibition enhanced the reduction of activated Lyn kinase compared with Jak2 inhibition alone. In contrast, inhibition of either PP2A or Shp1 combined with Jak2 inhibition interfered with the loss of Lyn kinase activation more so than Jak2 inhibition alone, indicating the involvement of PP2A and Shp1 in the inactivation of the Lyn kinase caused by Jak2 inhibition. These results indicate that Lyn is downstream of Jak2, and Jak2 maintains activated Lyn kinase in CML through the SET-PP2A-Shp1 pathway. (Oncogene)

http://www.nature.com/onc/journal/v28/n14/abs/onc20097a.html

Lung

University of Colorado Cancer Center

Bunn, Paul, M.D.

(***Clarhaut**... et al*)

ZEB-1, A repressor of the semaphoring 3F tumor suppressor gene in lung cancer cells

We have shown that ZEB1, an inducer of the epithelial-mesenchymal transition in lung cancers and a mediator of E-cadherin loss, also represses SEMA3F, an important tumor suppressor in lung cancers. This finding links the loss of tumor suppressor function of SEMA3F with the invasive and metastatic properties induced by ZEB activation. Moreover, ZEB1-induced angiogenic responses in an in vitro assay were inhibited by SEMA3F. Thus ZEB-induced SEMA3F loss contributes to pro-tumorigenic phenotypes stimulated by ZEB. (Neoplasia)

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=19177200

(***Kelly**... et al*)

A randomized phase II chemoprevention trial evaluating the effects of 13-cis-retinoic acid with or without alpha tocopherol or observation on bronchial epithelium in subjects at high risk for lung cancer

We conducted a phase II trial of the effects of 13 cis retinoic acid on endobronchial dysplasia. No effect on either endobronchial dysplasia or proliferation was found. This is in accordance with phase III trials and suggests that prior to moving to phase III trials, potential chemopreventive agents should significantly exceed the effects seen for 13 cis retinoic acid. In addition, these results provide important information to inform power analyses of future phase II trials. A randomized phase II chemoprevention trial evaluating the effects of 13-cis-retinoic acid with or without alpha tocopherol or observation on bronchial epithelium in subjects at high risk for lung cancer. (Cancer Prev Res)

http://cancerpreventionresearch.aacrjournals.org/cgi/content/full/2/5/440?view=long&pmid=19401528

(***Kono**... et al*)

The fibroblast growth factor receptor signaling pathway as a mediator of intrinsic resistance to EGFR-specific tyrosine kinase inhibitors in non-small cell lung cancer

Our recent studies highlight the fibroblast growth factor receptor (FGFR) pathway as an alternative growth factor signaling system that promotes oncogenic growth of non-small cell lung cancer cells, especially in cell lines that fail to respond to EGFR inhibitors. Importantly, small molecule inhibitors have been developed that exhibit excellent inhibitory activity towards FGFRs. Thus, FGFR inhibitors could be rapidly extended into pre-clinical and clinical studies for assessment of activity against non-small cell lung cancer. (Drug Resist Updat)

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WDK-4WFGRWM-1&_user=418620&_rdoc=1&_fmt=&_orig=search&_sort=d&_docanchor=&view=c&_acct=C000019840&_version=1&_urlVersion=0&_userid=418620&md5=d207d57cec4f122b461ce008f2119c97

(***Witta**... et al*)

ErbB-3 expression is associated with E-cadherin and their coexpression restores response to gefitinib in non-small cell lung cancer (NSCLC)

We have previously shown that E-cadherin expression associates with gefitinib activity.In the current study we demonstrated that E-cadherin is significantly co-expressed with ErbB-3, and for tumors with low E-cad/ErbB-3 expression (resistant to gefitinib) a combination of gefitinib and a HDAC inhibitor can restore the activity of gefitinib and the co-expression of E-cadherin/ErbB-3. (Ann Oncol)

http://annonc.oxfordjournals.org/cgi/content/full/20/4/689

University of Pittsburgh
Siegfried, Jill M., Ph.D.

(***Traynor**... et al*)

Pilot study of gefitinib and fulvestrant in the treatment of post-menopausal women with advanced non-small cell lung cancer

This advance is significant because it is the first report of safety and feasibility of utilizing an anti-estrogenic drug along with an anti-EGFR agent in women with advanced lung cancer. The combination showed activity with 41% overall survival at 1 year. Women whose tumors had high levels of nuclear Estrogen Receptor beta showed the best response to this combination, supporting a role for ER beta in lung cancer. (Lung Cancer)

http://www.ncbi.nlm.nih.gov/sites/entrez

University of Rochester

Fisher, Richard, M.D.

(***Dasmahapatra**... et al*)

Bcl-2 antagonists interact synergistically with bortezomib in DLBCL cells in association with JNK activation and induction of ER stress

These studies demonstrated that small molecule inhibitors of Bcl-2 family proteins interacted synergistically with the proteasome inhibitor bortezomib in DLBCL non-Hodgkin lymphoma cells in association with activation of the stress-related JNK kinase. Notably, this strategy was effective in both GC-DLBCL as well as in ABC-DLBCL cells. The implications of these findings are that regimens combining clinically relevant Bcl-2 antagonists with proteasome inhibitors such as bortezomib may be active in patients with DLBCL, including those with the more aggressive ABC-DLBCL subtype. (Cancer Biol Ther)

http://www.landesbioscience.com/journals/cbt/article/10-DasmahapatraCBT8-9.pdf

University of Iowa

Weiner, George J., M.D.

(***Norian**... et al*)

Synergistic induction of apoptosis in primary B-CLL cells after treatment with recombinant tumor necrosis factor-related apoptosis-inducing ligand and histone deacetylase inhibitors

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is currently being investigated as a therapeutic agent for a variety of malignancies, as it triggers apoptosis specifically in transformed cells. Here, we investigated the extent to which pretreatment of TRAIL-resistant primary B-cell chronic lymphocytic leukemia (B-CLL) cells with histone deacetylase inhibitors (HDACis) could render them susceptible to killing by TRAIL. We found that HDAC inhibition in B-CLL cells led to increased TRAIL receptor expression, increased caspase activation, decreased expression of antiapoptotic regulators such as Bcl-2, and ultimately, enhanced TRAIL-induced apoptosis; however, untransformed peripheral blood mononuclear cells remained largely resistant to TRAIL, even in the presence of HDACis. (J Oncol)

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=19547714

(***Yang**... et al*)

Malignant B cells skew the balance between regulatory T cells and TH17 cells in B-cell non-Hodgkin's lymphoma

We observed a significantly low frequency of TH17 cells, including several samples with no detectable amount of interleukin (IL)-17-producing cells present in the tumor microenvironment of B-cell lymphoma We found that, in the absence of lymphoma B cells, treatment with IL-1beta/IL-6 or lipopolysaccharide (LPS) enhanced IL-17 expression in CD4+ T cells and this enhancement was attenuated when CD4+ T cells were cocultured with lymphoma B cells. We also found that the reversal of lymphoma-associated Treg cell activity by LPS or CpG-A resulted in an enhancement of IL-17-producing cells. Taken together, our study indicated that lymphoma B cells play an important role in skewing the balance between Treg and TH17 cells resulting in the establishment of a profoundly inhibitory tumor microenvironment. (Cancer Res)

http://www.ncbi.nlm.nih.gov/pubmed/19509224?ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Ovarian

Fred Hutchinson Cancer Research Center

Urban, Nicole, Sc.D

(***Barua**... et al*)

Histopathology of ovarian tumors in laying hens: a preclinical model of human ovarian cancer

The high mortality rate due to ovarian cancer (OVCA) is attributed to the lack of an effective early detection method. Animal models are used to elucidate disease etiologies and pathogenesis that are difficult to study in humans. Laying hen is the only available animal that develops OVCA spontaneously; however, detailed information on ovarian tumor histology is not available. The goal of this study was to determine the histological features of malignant ovarian tumors in laying hens. A total of 155 young and old (1-5 years of age) laying hens (Gallus domesticus) were selected randomly and evaluated grossly and microscopically for the presence of ovarian tumors. The tumors found were similar in histology classification and stage to those found in humans, demonstrating the feasibility of the hen model for additional delineation of the mechanism underlying ovarian carcinogenesis, as well as preclinical testing of new agents for the prevention and therapy of this disease. (Int J Gynecol Cancer)

http://www.ncbi.nlm.nih.gov/pubmed/19509547

(***Lowe**... et al*)

The temporal stability of the Symptom Index among women at high-risk for ovarian cancer

We conducted a longitudinal analysis of symptom reporting from 123 women at increased risk for ovarian cancer based on a family history of cancer or a BRCA I/II mutation to evaluate the temporal stability of self-reported symptoms known to be associated with ovarian cancer. Data on symptoms were collected at two time points using a Symptoms Index that included abdominal pain, pelvic pain, feeling full quickly, inability to eat normally, abdominal bloating, and increased abdominal size. There were no statistically significant patterns of change for symptom reporting between time points, suggesting that reports of symptoms by women participating in screening are likely to be stable over time. (Gynecol Oncol)

http://www.ncbi.nlm.nih.gov/pubmed/19427026

(***Strauss**... et al*)

Epithelial Phenotype Confers Resistance of Ovarian Cancer Cells to Oncololytic Adenoviruses

We studied the susceptibility of primary ovarian cancer cells to oncolytic adenoviruses. Using gene expression profiling of cancer cells either resistant or susceptible to viral oncolysis, we discovered that the epithelial phenotype of ovarian cancer represents a barrier to infection by commonly used oncolytic adenoviruses targeted to coxsackie-adenovirus receptor or CD46. Specifically, we found that these adenovirus receptors were trapped in tight junctions and not accessible for virus binding. Our study provides a venue for improved virotherapy of cancer. (Cancer Res)

http://cancerres.aacrjournals.org/cgi/content/full/69/12/5115

(***Tuve**... et al*)

In situ adenovirus vaccination engages T effector cells against cancer

The efficacy of cancer immunotherapy is limited because of central and peripheral immune tolerance towards tumor-antigens. We propose a novel approach based on the fact that the immune system has not evolved tolerance towards adenoviruses (Ads) and that Ads have not evolved efficient mechanisms for immune-escape. Intratumoral injection with replication-deficient, transgene-devoid Ad induced immune responses at two different anatomical sites in mice: the tumor-draining lymph nodes and the tumor microenvironment.

Importantly, Ad-specific T cells were anti-tumor-reactive despite the presence of active regulatory T cell-mediated immune tolerance inside MMC tumors and anti-tumor efficacy of Ad was increased by pre-immunization against Ad despite the production of Ad-neutralizing antibodies. (Vaccine)

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TD4-4W324HS-5&_user=10843&_rdoc=1&_fmt=&_orig=search&_sort=d&_docanchor=&view=c&_acct=C000000150&_version=1&_urlVersion=0&_userid=10843&md5=7dd1072cb27d5f41efeecdbed2e5f358

(***Wyman**... et al*)

Repertoire of microRNAs in epithelial ovarian cancer as determined by next generation sequencing of small RNA cDNA libraries

MicroRNAs (miRNAs) are small regulatory RNAs that are implicated in cancer pathogenesis and have recently shown promise as blood-based biomarkers for cancer detection. Epithelial ovarian cancer is a deadly disease for which improved outcomes could be achieved by successful early detection and enhanced understanding of molecular pathogenesis that leads to improved therapies. A critical step toward these goals is to establish a comprehensive view of miRNAs expressed in epithelial ovarian cancer tissues as well as in normal ovarian surface epithelial cells. This report expands the body of miRNAs known to be expressed in epithelial ovarian cancer and provides a useful resource for future studies of the role of miRNAs in the pathogenesis and early detection of ovarian cancer. (PLoS)

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=19390579

Pancreatic

Mayo Clinic, Rochester
Petersen, Gloria M., Ph.D.

(***McWilliams**... et al*)

A novel DNA repair gene variant increases risk for pancreatic cancer

Variants of 26 genes in the nucleotide excision repair pathway were examined in a case-control study of 1,143 pancreatic adenocarcinoma patients and 1,097 healthy controls. An MMS19L variant (chromosome 10q24.1) was associated with increased risk (P = 0.023), and haplotype analysis of this gene also showed a significant association (P = 0.0132). (Cancer Epidemiol Biomarkers Prev)

http://cebp.aacrjournals.org/cgi/reprint/18/4/1295

(***Pannala**... et al*)

Progressively increasing blood sugar levels precede the diagnosis of pancreatic cancer by up to two years

To more carefully understand the relationship between new onset diabetes and pancreatic cancer, changes in the time preceding diagnosis of cancer of fasting blood glucose (FBG) and body mass index (BMI) before pancreatic cancer diagnosis were examined. Data on 736 pancreatic cancer patients and 1875 controls from 1981 to 2004 were collected. FBG between cases and controls did not differ from five years to two years prior to pancreatic cancer diagnosis, but significantly increased from then on. BMI was similar, but decreased in the cases one year prior to diagnosis. (Am J Gastroenterol)

http://www.nature.com/ajg/journal/vaop/ncurrent/abs/ajg2009253a.html

(***Wu**... et al*)

A gene involved in microcephaly plays a role in regulating BRCA2 in DNA repair

Microcephalin (MCPH1) is a protein that is involved in the cellular response to DNA damage. MCPH1 is recruited to sites of DNA double-strand breaks, and the mechanism is shown to be through binding BRCA2 at the NH2 terminus and determining the localization of BRCA2 and Rad51 to DNA damage sites. (Cancer Res)

http://cancerres.aacrjournals.org/cgi/reprint/69/13/5531

Prostate

University of California, San Francisco
Carroll, Peter, M.D., MPH

(***Carver**... et al*)

Risk assessment for prostate cancer metastasis and mortality at the time of diagnosis

To assess the accuracy of the Cancer of the Prostate Risk Assessment (CAPRA) score, validated previously to predict pathological and biochemical outcomes after radical prostatectomy, in predicting metastases, prostate cancer-specific mortality, and all cause mortality, we studied 10,627 men with clinically localized prostate cancer from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry who underwent radical prostatectomy, radiation therapy (external beam or interstitial), androgen deprivation monotherapy, or watchful waiting / active surveillance and had at least six months of follow-up post-treatment.

The CAPRA score predicted prostate cancer endpoints with good accuracy, specifically for predicting metastases (c-index = 0.78); prostate cancer-specific mortality (c-index = 0.80); and all-cause mortality (c-index = 0.71). It is the first risk instrument able to predict distal endpoints across multiple different primary treatments. (J Natl Cancer Inst)

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19509351

(***Conti**... et al*)

Pathological outcomes of candidates for active surveillance of prostate cancer

To ensure that active surveillance is a viable treatment option with the best outcomes for men with prostate cancer, one must better define the criteria that identify appropriate candidates for such a therapeutic approach. Our report correlates the pathologic findings of prostatectomy specimens to the preoperative clinical parameters of men that met various enrollment criteria for current active surveillance protocols, so that in the future, men can be counseled better as to their risks of adverse outcomes and chances of success with active surveillance as their primary treatment choice. As at least 20% of men diagnosed with prostate cancer meet these criteria currently, these results could be applied to over 40,000 men diagnosed with prostate cancer annually. (J Urol)

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19233388

(***Cooperberg**... et al*)

Adequacy of lymphadenectomy among men undergoing robot-assisted laparoscopic radical prostatectomy

To compare rates of lymph node dissection (LND) and nodal yields between patients treated with open radical retropubic prostatectomy (ORRP) and robot-assisted RRP (RARP) in a contemporary single-institution series, data from 1278 consecutive patients (716 ORRP and 562 RARP) from one institution were accrued prospectively in an institutional database and were assessed using the Cancer of the Prostate Risk Assessment (CAPRA) score and the likelihood of LND, nodal yield, and likelihood of node positivity were compared between ORRP and RARP. Men undergoing LND had a higher disease risk than those not undergoing LND, and among men undergoing LND, 5.8% of ORRP and 4.1% of RARP patients had positive nodes ($P < 0.01$). While the indications for LND and template dissection should be the same regardless of surgical approach, the nodal yield was adequate using both approaches; the yield was higher among ORRP than RARP patients, but the difference was not large, and is less remarkable than the wide variation in yield within each approach. (BJU Int)

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19549119

(***Eisenberg**... et al*)

Prognostic Implications of an Undetectable Ultrasensitive Prostate-Specific Antigen Level after Radical Prostatectomy

To determine whether an undetectable ultrasensitive prostate-specific antigen undetectable (USPSA) level obtained after surgery is a predictor of biochemical recurrence (BCR)-free survival. Of the 525 men from the Urologic Oncology Database at the University of California San Francisco who were study eligible, we found that 456 patients (87%) had undetectable USPSA and 69 patients (13%) had detectable USPSA immediately post-prostatectomy. Our data suggests that an undetectable USPSA after radical prostatectomy is a prognostic indicator of BCR-free survival at 5 yr and may aid in predicting outcome in higher risk patients. (Eur Urol)

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19375843

(***Conrad**... et al*)

Human antibodies targeting cell surface antigens overexpressed by the hormone refractory metastatic prostate cancer cells: ICAM-1 is a tumor antigen that mediates prostate cancer cell invasion

To identify cell surface antigens that accompany prostate cancer transition from hormone-sensitive to hormone-refractory metastatic tumor types, we selected a naïve phage antibody display library to identify human single chain antibodies that bind specifically to hormone-refractory C4-2B but not its hormone-sensitive parent line LNCaP. We identified a panel of human single chain antibodies with this targeting specificity, and further identified one of the antibody-targeted antigens as the ICAM-1/CD54/human rhinovirus receptor that mediates C4-2B cell invasion through extracellular matrix in vitro. ICAM-1 is thus differentially expressed during the transition of the hormone-sensitive prostate cancer cell line LNCaP to its hormone-refractory derivative C4-2B, plays an important role in imparting the C4-2B line with the ability to invade, and may therefore be a target for therapeutic intervention. (J Mol Med)

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19219419

Dana-Farber Harvard Cancer Institute Cancer Institute

Kantoff, Philip, M.D.

(***Cai**... et al*)

Androgen receptor expression in prostate cancer cells is suppressed by activation of epidermal growth factor receptor and ErbB2

Prostate cancers (PCa) that relapse after androgen deprivation therapies (castration-resistant PCa, CRPC) express high levels of androgen receptor (AR) and androgen-regulated genes, and evidence from several groups indicates that ErbB family receptor tyrosine kinases (EGFR and ErbB2) may contribute to enhancing this AR activity. We found that activation of these kinases decreased

expression of endogenous AR in PCa cell lines, with one mechanism being an increase in AR mRNA degradation., although AR protein levels did not decline in CRPC cells due to increased AR protein stability. These findings show that EGFR and ErbB2 can negatively regulate AR mRNA and may provide an approach to suppress AR expression in CRPC. (Cancer Res)

http://cancerres.aacrjournals.org/cgi/content/full/69/12/5202

(***Chen**... et al*)

Androgen receptor phosphorylation and activity are regulated by an association with protein phosphatase 1

Androgen receptor (AR) is phosphorylated at multiple sites in response to ligand binding, but the functional consequences and mechanisms regulating AR phosphorylation remain to be established. This study reveals a critical role of PP1 in regulating AR protein stability and nuclear localization through dephosphorylation of S650. Moreover, AR may function as a PP1 regulatory subunit and mediate PP1 recruitment to chromatin, where it can modulate transcription and splicing. (J Biol Chem)

http://www.jbc.org/content/284/38/25576.long#ack-1

(***Mucci**... et al*)

Polymorphism in endostatin, an angiogenesis inhibitor, and prostate cancer risk and survival: A prospective study

Endostatin inhibits endothelial cell proliferation and migration, prerequisites of angiogenesis. A functional missense mutation (D104N) in endostatin was associated with an increased prostate cancer risk in a small study. We undertook a larger, prospective study within the Physicians' Health Study to examine D104N and prostate cancer risk and progression among 544 incident prostate cancer cases (1982-1995) and 678 matched controls. (Int J Cancer)

http://www3.interscience.wiley.com/cgi-bin/fulltext/122253776/HTMLSTART

(***Pomerantz**... et al*)

The 8q24 cancer risk variant rs6983267 shows long-range interaction with MYC in colorectal cancer

A gene desert on chromosome 8q24 is a hotspot for risk variants contributing to multiple epithelial cancers, including prostate, colon, breast, and bladder cancers. These publications outline a systematic approach for understanding the functional consequences of inherited variants located outside of known protein-coding regions. The manuscripts demonstrate that MYC is the likely gene driving colorectal cancer (and presumably the other cancers as well). (Note: Additional title: Evaluation of the 8q24 prostate cancer risk locus and MYC expression located at http://cancerres.aacrjournals.org/cgi/content/full/69/13/5568) (Nat Genet)

http://www.nature.com/ng/journal/v41/n8/full/ng.403.html

(***Stark**... et al*)

Gleason score and lethal prostate cancer: does 3 + 4 = 4 + 3?

We compared the discrimination of standardized and original grading with C-statistics from models of 10-year survival. Results For prostatectomy specimens, 4 + 3 cancers were associated with a three-fold increase in lethal PCa compared with 3 + 4 cancers (95% CI, 1.1 to 8.6). The discrimination of models of standardized scores from prostatectomy (C-statistic, 0.86) and biopsy (C-statistic, 0.85) were improved compared to models of original scores (prostatectomy C-statistic, 0.82; biopsy C-statistic, 0.72). CONCLUSION: Ignoring the predominance of Gleason pattern 4 in GS 7 cancers may conceal important prognostic information. A standardized review of GS can improve prediction of PCa survival. (J Clin Oncol)

http://jco.ascopubs.org/cgi/content/full/27/21/3459

Northwestern University

Lee, Chung, Ph.D.

(***Zhang**... et al*)

Nuclear Factor-kB-Mediated Transforming Growth Factor-β-Induced Expression of Vimentin Is an Independent Predictor of Biochemical Recurrence after Radical Prostatectomy

Prostate cancer obtained at the time of radical prostatectomy contains molecular signatures that can predict disease outcome. TGF-beta mediated epithelial-to-mesenchymal transition in prostatectomy specimens can be used to identify high risk cases for disease recurrence. Identification of these high risk patients following radical prostatectomy can alert the patient and the doctor to implement aggressive treatment strategy prior to disease recurrence. (Clin Cancer Res)

http://clincancerres.aacrjournals.org/cgi/content/full/15/10/3557

Johns Hopkins University

Nelson, William, M.D., Ph.D.

(***Liu**... et al*)

Copy number analysis indicate clonal origin of lethal prostate cancer

Using high-resolution genome analysis to study metastatic deposits recovered at autopsies of men dying of prostate cancer, most of the many somatic genome aberrations detected were shared across each metastatic lesion, indicating that a single cancer clone was responsible for lethal prostate cancer progression. (Nat Med)

http://www.ncbi.nlm.nih.gov/pubmed/19363497?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

(***Wada**... et al*)

Cyclophosphamide augments antitumor immunity in an autochthonous prostate cancer model

Various immunotherapy approaches have exhibited little clinical utility thus far for prostate cancer, or for other "non-immunogenic" solid organ cancers. This study showed that cyclophosphamide treatment, by transiently depleting "regulatory" T-cells, improved anti-tumor immune responses directed against prostate cancer in a mouse model. The finding paves the way for refined clinical trials of prostate cancer vaccine therapy given along with cyclophosphamide to improve anti-cancer efficacy. (Cancer Res)

http://www.ncbi.nlm.nih.gov/pubmed/19435909?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Memorial Sloan-Kettering Cancer Center

Scardino, Peter T., M.D.

(***Li**... et al*)

Prognostic value of Akt-1 in human prostate cancer: a computerized quantitative assessment with quantum dot technology

In this study Ayala and colleagues use image deconvolution, nanotechnology and image deconvolution to quantitate Akt-1 expression in human prostate cancer. On multivariate analysis Akt-1 was independently predictive of biochemical recurrence and Akt-1 levels were also predictive of prostate cancer specific death. Thus objective analysis of Akt-1 expression by image analysis can be used a predictive marker of progression and death from prostate cancer and can therefore be useful in identification of patients needing adjuvant therapy following radical prostatectomy. (Clin Cancer Res)

http://clincancerres.aacrjournals.org/cgi/content/abstract/15/10/3568

(***Carver**... et al*)

Aberrant ERG expression signals cancer progression in the prostate

Aberrant expression of ERG is a progression event in prostate tumorigenesis. Prostate cancer specimens containing the TMPRSS2-ERG rearrangement are significantly enriched for loss of the tumor suppressor PTEN. ERG has a distinct role in prostate cancer progression and cooperates with PTEN haploinsufficiency to promote progression of high-grade prostatic intraepithelial neoplasia to invasive adenocarcinoma. (Nat Genet)

http://www.nature.com/ng/journal/v41/n5/abs/ng.370.html

(***O'Brien**... et al*)

PSA velocity and doubling time do not improve predictions of prostate cancer outcome over pretreatment PSA alone

PSA velocity and doubling time predict metastases and biochemical recurrence in men undergoing radical prostatectomy for prostate cancer. However, in an analysis of 2,938 patients with two or more PSA values before radical prostatectomy, these measures of PSA dynamics did not enhance the predictive accuracy of pretreatment PSA alone. (J Clin Oncol)

http://jco.ascopubs.org/cgi/content/full/27/22/3591

Skin

Dana-Farber Harvard Cancer Institute

Anderson, Kenneth, M.D.

(***Fulciniti**... et al*)

DKKAnti-DKK1 mAb (BHQ880) targets bone as a potential therapeutic agent for multiple myeloma

Decreased activity of osteoblasts (OBs) contributes to osteolytic lesions in multiple myeloma (MM). The production of the soluble Wnt inhibitor Dickkopf-1 (DKK1) by MM cells inhibits OB activity, and its serum level correlates with focal bone lesions in MM. We here demonstrate both anabolic bone effects and significant inhibition of MM cell growth in the presence of bone marrow stromal cells (BMSCs) both in vitro and in vivo using DKK1 neutralizing antibody (BHQ880). These results confirm DKK1 as an important therapeutic target in MM and provide the rationale for the first clinical trial of BHQ880 to improve bone disease and to inhibit MM growth. (Blood)

http://bloodjournal.hematologylibrary.org/cgi/content/full/114/2/371?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=BHQ880&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT

(***Hideshima**... et al*)

Bortezomib induces canonical nuclear factor-kappaB activation in multiple myeloma cell

Bortezomib is a proteasome inhibitor with remarkable preclinical and clinical antitumor activity in multiple myeloma (MM). The initial rationale for its use in MM was inhibition of nuclear factor (NF)-kappaB activity by blocking proteasomal degradation of inhibitor of kappaBalpha (IkappaBalpha). This study suggests that bortezomib may under certain circumstances activating NF-kB and that its cytotoxicity cannot be fully attributed to inhibition of canonical NF-kappaB activity in MM cells. (Blood)

http://bloodjournal.hematologylibrary.org/cgi/content/full/114/5/1046

(***Greene**... et al*)

Frequencies of NRAS and BRAF Mutations Increase from the Radial to the Vertical Growth Phase in Cutaneous Melanoma

A lack of consensus exists with regards to the relative rates of NRAS and BRAF mutations in the radial (RGP) and vertical (VGP) growth phases of individual melanoma tumors. This study was conducted to test the hypothesis that mutations are acquired with progression from RGP to VGP. Using laser capture microdissection, pure tumor DNA was obtained from 15 in situ melanomas, and from the RGP and VGP of 29 invasive tumors. NRAS exon 2 and BRAF exon 15 DNA were amplified by PCR and sequenced. Mutations were present in 6 of 15 in situ melanomas (40%). Of 29 invasive tumors, 16 exhibited RGP mutations (55.2%); 22 showed VGP mutations (75.9%). Paired RGP/VGP mutation analysis revealed a trend toward discordance in the distribution of mutations, favoring VGP localization (P ¼0.07). Of 15 samples, 12 with mutations in both phases had an increased proportion of mutated DNA in the VGP, measured on DNA chromatograms (P ¼0.08). Limitations of this study include a relatively small sample cohort selected for technical reasons from a larger population, presenting the risk of selection bias. These concerns notwithstanding our findings support the hypothesis that NRAS and BRAF mutations increase with tumor progression from superficial to invasive disease. (J Invest Dermatol)

http://www.nature.com/jid/journal/v129/n6/full/jid2008374a.html