SPORE ADVANCES

January – March 2009

Translational Research Program

BRAIN

Duke University

Bigner, Darell, M.D., Ph.D. *(H. Yan ... et al.)*

IDH1 and IDH2 Mutations in Gliomas

The major discovery by the Duke Brain Cancer SPORE, in collaboration with Johns Hopkins, was the discovery of a common mutation of the isocitrate dehydrogenase (IDH1 and IDH2) gene in grade II and III astrocytomas and secondary glioblastomas, and grade II and III oligodendrogliomas and in grade II and III oligoastrocytomas. This common mutation occurs in younger age patients and there is an age independent increase in survival in patients that have the mutation. (NEJM)

http://www.ncbi.nlm.nih.gov/pubmed/19228619?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

University of California, San Francisco

Berger, Mitchel S., M.D. *(R. Ermoian ... et al.)*

Signal Transduction Molecules in Gliomas of all Grades

Expression levels of critical signaling molecules upstream and downstream of mTOR differ between non-tumor brain and gliomas of any grade. mTOR provides a rational therapeutic target in gliomas of all grades, and clinical benefit may emerge as mTOR inhibitors are combined with additional agents. Based on these results we have initiated a Phase II Trial of RAD001 in patients with recurrent low grade glioma. In this study, molecular features, including PTEN status and PKB/Akt phosphorylation will be assessed prospectively in this trial to test the hypothesis that those tumors with PTEN methylation and consequent PKB/Akt phosphorylation will preferentially respond to mTOR inhibition. (J Neurooncol)

http://www.springerlink.com/content/487881603w403178/fulltext.pdf

BREAST

Dana-Farber/ Harvard Cancer Institute

Iglehart, J. Dirk, M.D. *(W. Xian … et al.)*

FGFR1-Transformed Mammary Epithelial Cells are Dependent on RSK Activity for Growth and Survival

These studies provide further support that FGFR1 is involved in lobular carcinoma and identify two potential targets for therapeutic intervention, FGFR1 and its downstream target, Rsk. Small molecule or siRNA inhibition of ribosomal S6 kinase (RSK) activity was found to induce death of the FGFR1-transformed cells in three distinct mouse and human models, without affecting normal breast epithelial cells. (Cancer Res)

http://www.ncbi.nlm.nih.gov/pubmed/19258500

Iglehart, J. Dirk, M.D. *(J. Eeckhoute … et al.)*

Cell-type selective chromatin remodeling defines the active subset of FOXA1-bound enhancers

In previous work supported by the SPORE, we found that the pioneer factor FOXA1 plays a critical role in mediating the action of the estrogen receptor in breast cancer. In this paper, we monitored the chromatin structure at FOXA1 binding sites across the genome and compared breast cancer cells to other cancer types. We find that a significant proportion of the inactive FOXA1-bound regulatory sites in one cell type are actually functional in another cellular context suggesting that mechanisms that restrict the activity of shared FOXA1-bound enhancers likely play a significant role in defining the cell-type-specific functions of FOXA1. (Genome Res)

http://www.ncbi.nlm.nih.gov/pubmed/19129543

Iglehart, J. Dirk, M.D. *(L. Burga … et al.)*

Altered proliferation and differentiation properties of primary mammary epithelial cells from BRCA1 mutation carriers

The data show that primary mammary epithelial cells in BRCA1 mutation carriers have altered proliferation and differentiation properties before they transform into cancer cells. These altered cellular features are associated with heterozygosity for BRCA1, and they do not require loss of heterozygosity. BRCA1 mutant primary mammary epithelial cells show an increase in EGFR pathway activation which could potentially serve as a target for chemoprevention. (Cancer Res)

http://www.ncbi.nlm.nih.gov/pubmed/19190334

Mayo Clinic, Rochester

Ingle, James N., M.D. *(T. Eiseler … et al.)*

Identification of the mechanism by which PKD1 regulates cell migration.

Dr. Storz' group identified the mechanism by which PKD1 inhibits directed cell migration of breast cancer cells. They show that active PKD1 completely blocks the ability of a tumor cell to "remodel" its actin structure, enabling it to migrate and invade. This explains why PKD1 is silenced in some invasive cancers, including breast cancer. (Nat Cell Biol)

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19329994

Ingle, James N., M.D. *(M. Santisteban … et al.)*

Immune-induced epithelial to mesenchymal transition in vivo generates breast cancer stem cells

The breast cancer stem cell (BCSC) hypotheses suggest that breast cancer is derived from a single tumor-initiating cell with stem-like properties, but the source of these cells is unclear. In the present study, they found that epithelial to mesenchymal transition (EMT) of breast cancer epithelial tumor cells could be induced by CD8 T cells which resulted in the generation of BCSCs that had potent tumorigenicity, ability to reestablish an epithelial tumor, and enhanced resistance to drugs and radiation. In contrast to the hierarchal cancer stem cell hypothesis, which suggests that breast cancer arises from the transformation of a resident tissue stem cell, their results show that EMT can produce the BCSC phenotype. (Cancer Res)

http://cancerres.aacrjournals.org/cgi/content/full/69/7/2887

Ingle, James N., M.D. *(S. Amed … et al.)*

Newly discovered breast cancer susceptibility loci on 3p24 and 17q23.2.

Genome-wide association studies (GWAS) have identified a number of breast cancer susceptibility genes. Here, two new loci containing the SLC4A7 and NEK10 genes on chromosome 3p24 and the COX11 gene on chromosome 17q23.2 were identified following replication of findings from a GWAS in a consortium of 37,012 breast cancer cases and 40,069 unaffected controls. These new susceptibility genes may prove useful for improved breast cancer risk assessment. (Nat Genetics)

http://www.nature.com/ng/journal/vaop/ncurrent/abs/ng.354.html

University of North Carolina Chapel Hill

Earp, H. Shelton, III, M.D. *(R. Miliken ... et al.)*

Epidemiology of basal-like breast cancer in African American and white women

Risk factors for the newly identified "intrinsic" breast cancer subtypes (luminal A, luminal B, basal-like and human epidermal growth factor receptor 2-positive/estrogen receptor-negative) were determined in the Carolina Breast Cancer Study, a population-based, case-control study of African-American and white women. Basal-like cases exhibited several associations that differed from those observed for luminal A, including parity, breastfeeding, age at first term full-term pregnancy and body size. The prevalence of basal-like breast cancer was highest among premenopausal African-American women, who may benefit from public health prevention strategies targeted at breast-feeding and body size.. (Epidemiology)

http://www.springerlink.com/content/h749w061034h7655/fulltext.html

University of Texas/MD Anderson Cancer Center

Hortobagyi, Gabriel M., M.D., F.A.C.P *(N. Delk ... et al.)*

The altered subcellular localization of tumor-specific cyclin E isoforms affects Cdk2 complex formation and regulation by the proteasome.

Cyclin E is a cell cycle protein that when deregulated can lead to tumorigenesis. One means of cyclin E deregulation observed in multiple cancer types is the generation of tumorigenic low molecular weight cyclin E isoforms (LMW-E). Delk and colleagues show that the LMW-E proteins have altered localization which consequently alters LMW-E/Cdk2 complex formation and regulation by the E3 ubiquitin ligase, Fbw7. Implications of this work suggest that altered localization may contribute to LMW-E tumorigenic potential by effecting LMW-E associated kinase activity, protein-protein interactions, and regulation by regulatory proteins. (Cancer Res)

http://cancerres.aacrjournals.org/cgi/content/full/69/7/2817

Hortobagyi, Gabriel M., M.D., F.A.C.P *(H. Wingate ... et al.)*

Low-Molecular-Weight cyclin E: Tumor specific in breast cancer and tumorigenic in human mammary epithelial cells.

We showed that the LMW isoforms are tumor specific in normal and tumor tissue from 340 breast cancer patients. Second, we showed that the LMW forms of cyclin E bind to CDK2 more efficiently in a Biocore binding assay using purified proteins. Third, we showed that overexpression of the LMW forms of cyclin E in an otherwise normal cell line resulted in the inability of cells to enter quiescence in response to growth factor deprivation and genomic instability compared to the full-length cyclin E. (Cell Cycle)

http://www.landesbioscience.com/journals/cc/article/8119/

Hortobagyi, Gabriel M., M.D., F.A.C.P *(C. Neal ... et al.)*

14-3-3z Overexpression Defines High Risk for Breast Cancer Recurrence and Promotes Cancer Cell Survival

Here we found that 14-3-3z, a protein which regulates multiple signaling pathways, was overexpressed in 42% of breast cancers and was an independent marker correlated with breast cancer recurrence. Overexpression of 14-3-3z also occurred in other cancer types and was associated with apoptosis resistance in response to low serum conditions and conventional chemotherapy. Thus, 14-3-3z overexpression is a novel molecular marker for disease recurrence in breast cancer patients and may serve as an effective therapeutic target in patients whose tumors overexpress 14-3-3z. (Cancer Res)

http://cancerres.aacrjournals.org/cgi/rapidpdf/0008-5472.CAN-08-2765v1

Vanderbilt University

Arteaga, Carlos, M.D. *(S. Chen ... et al.)*

A novel comprehensive wave-form MS data processing method

Mass spectrometry (MS) can generate high-throughput protein profiles for biomedical research to discover biologically-related protein patterns/biomarkers. The noisy functional MS data collected by current technologies, however, require consistent, sensitive, and robust data-processing techniques for successful biomedical application. We have proposed a new comprehensive MS data preprocessing package (Wave-spec), which includes several novel algorithms and can overcome several conventional difficulties in processing MS data for use in biomedical research. (Bioinformatics)

http://bioinformatics.oxfordjournals.org/cgi/reprint/25/6/808

GASTROINTESTINAL

Johns Hopkins University

Kern, Scott E., M.D. *(JR Brody ... et al.)*

Improving fluorouracil cancer therapy

Fluorouracil remains the anticancer drug most commonly used against gastrointestinal malignancies. By understanding the mechanisms of its action, promising new anticancer drugs are being developed and the patients most likely to benefit are being identified. SPORE

researchers found that some of the older theories were not very good at predicting fluorouracil's effectiveness against different cancers, and they uncovered new evidence for targets of fluorouracil's therapeutic effects that had been generally overlooked previously. (Cancer Res)

http://www.ncbi.nlm.nih.gov/pubmed/19155291

Kern, Scott E., M.D. *(S. Sur ... et al.)*

Predicting which cancer cells respond to new anticancer drugs

Some of the newest and most success designs for anticancer drugs aim to inhibit growth-promoting proteins called kinases. Drugs inhibiting the polo-like kinases were found to be especially toxic against cancers having a particularly common mutation, which affects the p53 gene. This suggests the subset of patients that might respond best to such a therapeutic strategy, and suggests further that their normal cells, which by their natire do not have such cancer mutations, might be spared the undesirable toxicity of this new anticancer approach. (PNAS)

http://www.ncbi.nlm.nih.gov/pubmed/19225112

Kern, Scott E., M.D. *(CA Iacobuzio-Donahue ... et al.)*

DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer.

When patients are diagnosed with pancreatic cancer, aggressive treatment begins and aims to address both the distant spread of the disease and the locally destructive tumor spread, but very little attention had been devoted to the later stage, when the patients actually fail therapy and die. A new and novel study, a "warm autopsy" study, looked carefully for the first time at the actual disease patterns at the time of death; it found two molecularly and clinically distinguishable forms of disease: one with distant metastases, one with locally destructive spread, but minimal overlap between the two groups. New tests performed at the time of diagnosis may be able to divide patients into treatment regimens focused either to local control or, instead, to systemic therapy. (J Clin Oncol)

http://www.ncbi.nlm.nih.gov/pubmed/19273710

Vanderbilt University

Coffey, Robert J., Jr., M.D. *(HC Manning ... et al.)*

Imaging Biomarkers of Response to EGF Receptor Blockade in CRC.

We evaluated three distinct molecular imaging metrics measuring EGF uptake (NIR800-EGF), apoptosis (NIR700-Annexin V), and cellular proliferation (FLT-PET) as potential biomarkers of

response to EGF receptor blockade in preclinical mouse models of CRC. We found that molecular imaging can accurately assess EGF binding, proliferation, and apoptosis in human colorectal cancer xenografts. Each of these imaging approaches appear promising for serial, noninvasive monitoring of the biological effects of EGFR inhibition in preclinical studies and it is anticipated that these assays can be adapted for clinical use. (Clin Cancer Res)

http://clincancerres.aacrjournals.org/cgi/content/full/14/22/7413

Coffey, Robert J., Jr., M.D. *(BJ Xu ... et al.)*

Identification of early intestinal neoplasia protein biomarkers using laser capture microdissection and MALDI MS

Obtaining protein profiles from a homogeneous cell population in tissues can significantly improve our capability in protein biomarker discovery. In this study, unique protein profiles from the top and bottom sections of mouse crypts and ApcMin+/- adenomas were obtained using laser capture microdissection (LCM) combined with matrix-assisted laser desorption/ionization mass spectrometry (MALDI MS). The novel protein biomarkers identified from the top and bottom crypts will increase our knowledge of the specific protein changes taking place during cells migration from the crypt bottom to top and, in addition, the identified cancer protein biomarkers will aid in the exploration of colorectal tumorigenesis mechanisms as well as in the advancement of molecular-based diagnosis of colorectal cancer. (Mol Cell Proteomics)

http://www.mcponline.org/cgi/reprint/M800345-MCP200v1

Coffey, Robert J., Jr., M.D. *(S. Chen ... et al.)*

A novel comprehensive wave-form MS data processing method

Mass spectrometry (MS) can generate high-throughput protein profiles for biomedical research to discover biologically-related protein patterns/biomarkers. The noisy functional MS data collected by current technologies, however, require consistent, sensitive, and robust data-processing techniques for successful biomedical application. We have proposed a new comprehensive MS data preprocessing package (Wave-spec), which includes several novel algorithms and can overcome several conventional difficulties in processing MS data for use in biomedical research. (Bioinformatics)

http://bioinformatics.oxfordjournals.org/cgi/reprint/25/6/808

Coffey, Robert J., Jr., M.D. *(W. Fiske ... et al.)*

ERBBs in the gastrointestinal tract: recent progress and new perspectives.

The gastrointestinal epithelium does much more than provide a physical barrier between the intestinal lumen and our internal milieu and it is actively engaged in absorption and secretion of

salt and water via ion transporters, exchangers and selective ion channels. It is also a continuously self-renewing epithelium that undergoes ordered growth and differentiation along its vertical axis. From this dual perspective, we will consider the actions of the ERBB family of ligands and receptors in the maintenance of gastrointestinal homeostasis and discuss instances when the actions of this family go awry such as in cancer and Ménétrier's disease. (Exp Cell Res)

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WFC-4TW14W4-1&_user=86629&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000006878&_version=1&_urlVersion=0&_userid=86629&md5=8eca825e8bab02b9f6349634d2fab460

Coffey, Robert J., Jr., M.D. *(H. Wu ... et al.)*

Fruit and vegetable intakes are associated with lower risk of colorectal adenomas.

Colorectal cancer is a leading cause of cancer death and most colorectal cancers arise from colorectal adenomas. This study provides additional evidence that high total fruit intake and certain fruit and vegetable intakes such as berries and green leafy vegetables may be associated with a reduced risk of colorectal adenomas. (J Nutr.)

http://jn.nutrition.org/cgi/content/full/139/2/340

Coffey, Robert J., Jr., M.D. *(J. Cates ... et al.)*

Epithelial-mesenchymal transition markers in pancreatic ductal adenocarcinoma.

Expression of transcription factors that mediate epithelial-mesenchymal transition (EMT), such as Twist and Slug, is correlated with poor prognosis in many tumor types. Selected EMT markers were studied in a series of pancreatic ductal adenocarcinomas (PDAs) and benign pancreatic tissues to determine whether expression levels correlated with diagnosis, histologic grade, or patient outcome. Decreased expression of nuclear Twist is observed in malignant pancreatic epithelium; however, use of Twist as a diagnostic marker is precluded because decreased expression is also seen in chronic pancreatitis, but none of the markers studied were predictive of patient outcome. (Pancreas)

http://journals.lww.com/pancreasjournal/Abstract/2009/01000/Epithelial_Mesenchymal_Transition_Markers_in.22.aspx

Coffey, Robert J., Jr., M.D. *(MZ Zhang ... et al.)*

11β Hydroxysteroid Dehydrogenase 2 inhibition suppresses colonic carcinogenesis by selectively blocking the tumor Cyclooxygenase-2 pathway

Studies have shown that COX-2–derived PGE2 promotes CRC progression, and both nonselective COX inhibitors (NSAIDs) and selective COX-2 inhibitors (such as glucocorticoids) reduce the number and size of colonic adenomas. However, increased gastrointestinal side effects of NSAIDs and increased cardiovascular risks of selective COX-2 inhibitors limit their use in

chemoprevention of CRC. We found 11β–hydroxysteroid dehydrogenase type II (11βHSD2) inhibition represents what we believe to be a novel approach for CRC chemoprevention and therapy by increasing tumor glucocorticoid activity, which in turn selectively blocks local COX-2 activity. (JCI)

http://www.jci.org/articles/view/37398

GYNECOLOGY

Johns Hopkins University

Wu, T.C., M.D., Ph.D. *(CW Tseng ... et al.)*

Low-dose radiation enhances therapeutic HPV DNA vaccination in tumor-bearing hosts

We explored the combination of low-dose radiation therapy with DNA vaccination with calreticulin (CRT) linked to the mutated form of HPV-16 E7 antigen (E7(detox)), CRT/E7(detox) in the treatment of E7-expressing TC-1 tumors. We observed that TC-1 tumor-bearing mice treated with radiotherapy combined with CRT/E7(detox) DNA vaccination generated significant therapeutic antitumor effects and the highest frequency of E7-specific CD8(+) T cells in the tumors and spleens of treated mice. Furthermore, treatment with radiotherapy was shown to render the TC-1 tumor cells more susceptible to lysis by E7-specific CTLs. (Cancer Immunol Immunother.)

http://www.springerlink.com/content/5n16x24204032541/

Wu, T.C., M.D., Ph.D. *(KH Noh, TH Kang ... et al.)*

Activation of Akt as a mechanism for tumor immune evasion.

Immune evasion is an important reason why the immune system cannot control tumor growth. To elucidate the mechanism for tumor immune evasion, we generated an immune-resistant human papillomavirus type 16 (HPV-16) E7-expressing tumor cell line by subjecting a susceptible tumor cell line to multiple rounds of in vivo immune selection with an E7-specific vaccine. Our data indicate that the activation of PI3K/Akt pathway represents a new mechanism of immune escape and has important implications for the development of a novel strategy in cancer immunotherapy against immune-resistant tumor cells. (Mol Ther)

http://www.nature.com/mt/journal/v17/n3/abs/mt2008255a.html

Wu, T.C., M.D., Ph.D. *(C. Trimble … et al.)*

A phase I trial of a human papillomavirus DNA vaccine for HPV16+ cervical intraepithelial neoplasia 2/3

This phase I trial aims to evaluate the safety and immunogenicity of a therapeutic human papillomavirus (HPV)16 DNA vaccine administered to women with HPV16+cervical intraepithelial neoplasia (CIN)2/3. This HPV16 DNA vaccine was found to be safe and well tolerated. Whereas it seems possible to elicit HPV-specific T-cell responses in patients with established dysplastic lesions, other factors are likely to play a role in lesion regression. (Clin Cancer Res)

http://clincancerres.aacrjournals.org/cgi/content/full/15/1/361

Wu, T.C., M.D., Ph.D. *(J. Rowley … et al.)*

Expression of IL-15RA or an IL-15/IL-15RA fusion on CD8+ T cells modifies adoptively transferred T-cell function in cis.

In the current study, we explore the functional consequences of IL-15RA, expression on T cells using a novel method to transfect naive CD8(+) T cells. We found that transfection of unstimulated CD8(+) T cells with IL-15RA RNA led to enhanced viability of CD8(+) T cells in response to IL-15, enhanced IL-15-mediated phosphorylation of STAT5 and also promoted IL-15-mediated proliferation in vivo of adoptively transferred naïve CD8(+) T cells. Furthermore, we demonstrated that IL-15RA can present IL-15 via cis-presentation on CD8(+) T cells. (Eur. J. Immunol)

http://www3.interscience.wiley.com/journal/121668163/abstract

Wu, T.C., M.D., Ph.D. *(SW 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 new femtosecond laser technology represents a safe and innovative technology for enhancing DNA gene transfer in vivo. (J Biomed Sci)

http://www.jbiomedsci.com/content/16/1/36

Wu, T.C., M.D., Ph.D. *(B. Karanam ... et al.)*

Vaccination with HPV16 L2E6E7 fusion protein in GPI-0100 adjuvant elicits protective humoral and cell-mediated immunity.

A vaccine comprising human papillomavirus type 16 (HPV16) L2, E6 and E7 in a single tandem fusion protein (termed TA-CIN) has the potential advantages of both broad cross-protection against HPV transmission through induction of L2 antibodies able to cross neutralize different HPV types and of therapy by stimulating T cell responses targeting HPV16 early proteins. However, patients vaccinated with TA-CIN alone develop weak HPV neutralizing antibody and E6/E7-specific T cell responses. Here we test TA-CIN formulated along with the adjuvant GPI-0100, a semi-synthetic quillaja saponin analog that was developed to promote both humoral and cellular immune responses. (Vaccine)

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TD4-4V5DTTX-9&_user=75682&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000006078&_version=1&_urlVersion=0&_userid=75682&md5=dbc56c0af02ae178b2a9fcd69fba729e

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Wu, T.C., M.D., Ph.D. *(Z. Lin ... et al.)*

Expression pattern and subcellular localization of human papillomavirus minor capsid protein L2.

The expression pattern of human papillomavirus (HPV) capsid antigen L2 is poorly described, and the significance of its localization with both promyelocytic leukemia protein (PML) and Daxx in a subnuclear domain, nuclear domain 10 (ND-10), when ectopically expressed in tissue culture cells is controversial. To address whether ND-10 localization of L2 occurs in natural cervical lesions, we used a HPV16 and HPV18 L2-specific monoclonal antibody (RG-1), in addition to rabbit antiserum to HPV6 L2, to localize L2. We have further explored the expression pattern of L2 and its relationship to ND-10 components in human papillomavirus (HPV)-related premalignant or malignant lesions and HPV+ organotypic cultures using RG-1. (Am J Pathol)

http://ajp.amjpathol.org/cgi/content/full/174/1/136

Wu, T.C., M.D., Ph.D. *(Z. Lin ... et al.)*

Combination of proteasome and HDAC inhibitors for uterine cervical cancer treatment.

Here, we examine the hypothesis that inhibition of proteasome function and HDAC activity would synergistically and specifically trigger cervical cancer cell death by the interruption of E6 and E7 signaling. The sensitivity and molecular responses of keratinocytes and HPV-positive and HPV-negative cervical cancer cells and xenografts to combinations of proteasome and HDAC inhibitors were tested and the expression of HDAC1/HDAC2 in situ was examined in cervical cancer, its precursors, and normal epithelium. A combination of proteasome and HDAC inhibitors, including bortezomib and vorinostat, respectively, warrants exploration for the treatment of cervical cancer. (Clin Cancer Res)

http://clincancerres.aacrjournals.org/cgi/content/full/15/2/570

KIDNEY

Dana-Farber/ Harvard Cancer Institute

Atkins, Michael, M.D. *(H. Xie … et al.)*

LDH-A Inhibition represents a potential therapeutic strategy for hereditary leiomyomatosis and renal cell cancer (HLRCC)

HLRCC is a genetic disease caused by a germline inactivating mutation in the gene for the Krebs Cycle enzyme fumarate hydratase (FH), a critical enzyme for oxidative phosphorylation that is necessary to provide energy to the cell. Valera et al showed that FH deficiency leads to upregulation of the activity and expression in HLRCC cells of LDH-A, an enzyme that promotes an alternative energy pathway called fermentative glycolysis. Furthermore, they showed that blocking of LDH-A in FH deficient cells reduces proliferation and induces apoptosis in vitro and tumor growth in a murine xenograft model, both suggesting that small-molecule inhibitors that specifically target LDH-A could be used to treat HLRCC. (Mol Cancer Ther)

http://mct.aacrjournals.org/content/8/3/626.abstract

LUNG

University of Colorado Cancer Center

Bunn, Paul A., Jr., M.D. *(F. Cappuzzo … et al.)*

MYC and EIF3H coamplification significantly improve response and survival of non-small cell lung cancer patients (NSCLC) treated with gefitinib

The identification of a subset of lung cancers that respond to EGFR inhibitors, such as erlotinib or gefitinib, has had a major impact on the treatment and outcome of these individuals. Currently, mutations in the EGFR increased copy number of the receptor identified by FISH identifies patients likely to respond. These results suggest that the responsive subset can be further refined to those tumors that have amplification of MYC and EIF3H. Interesting, similar findings were described in breast cancer treated with Herceptin, which targets the related EGF receptor, Her2 (ErbB2). Biologically, we hypothesize that this constellation of biomarkers corresponds to a subset of cancers that have developed while retaining a more normal epithelial

nature in terms of the growth factor signaling pathways that drive cells to grow and divide. (J Thorac Oncol)

http://www.ncbi.nlm.nih.gov/pubmed/19204574?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Bunn, Paul A., Jr., M.D. *(J. Clarhut … et al.)*

ZEB-1, a repressor of the SEMA3F Semaphorin Tumor Suppressor Gene in Lung Cancer Cells.

This paper describes the discovery that SEMA3F gene expression is regulated, in part, by the transcriptional suppressor, ZEB1. Thus an inducer of the epithelial-mesenchymal transition in lung cancers along with resistance to EGFR inhibitors is also responsible for inhibiting an important tumor suppressor in this disease. The results imply that ZEB1 expression should result in increased tumor-specific neo-angiogenesis by blocking SEMA3F. PMCID: PMC2631140 (Neoplasia)

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

Bunn, Paul A., Jr., M.D. *(L. Marek … et al.)*

Fibroblast Growth Factor (FGF) and FGF Receptor-Mediated Autocrine Signaling in Non-Small Cell Lung Cancer Cells

Fibroblast growth factors (FGFs) and FGF receptors (FGFRs) are co-expressed in a significant number of NSCLC cell lines, especially those that are insensitive to EGFR-specific TKIs such as gefitinib and erlotinib. Growth inhibition of FGF and FGFR expressing NSCLC cell lines by RNAi-mediated FGF2 silencing and by an FGFR-selective TKI demonstrates that the FGFR pathway functions as a dominant autocrine loop driving transformed growth in these lines. Thus, the FGFR pathway is an attractive new target for therapeutic intervention with existing FGFR inhibitors in NSCLC. (Mol Pharmacol)

http://molpharm.aspetjournals.org/cgi/content/full/75/1/196

Bunn, Paul A., Jr., M.D. *(MC Weiser-Evans … et al.)*

Cytosolic phospholipase A2(cPLA2) in macrophages is critical for lung cancer metastasis.

We have developed a novel model to define pathways controlling lung cancer metastasis in which lung cancer cells are directly injected into the lungs of mice, and metastasize to the lymph nodes and distant organs including the liver. Using mice deficient in cPLA2 we have shown that expression of this enzyme in the tumor microenvironment does not affect primary tumor growth but markedly inhibits metastasis; bone marrow transplantation of cPLA2 KO bone marrow into wild type mice was sufficient to inhibit metastasis and promote survival, and this was associated with altered patterns of macrophages surrounding the tumor. These findings demonstrate the importance of macrophages in promoting lung cancer metastasis, and suggest

that targeting the tumor microenvironment will be a valuable strategy in inhibiting lung cancer progression and promoting survival. (Cancer Res)

http://cancerres.aacrjournals.org/cgi/content/full/69/5/1733

Vanderbilt University

Carbone, David P., M.D., Ph.D. *(S. Chen ... et al.)*

A novel comprehensive wave-form MS data processing method

Mass spectrometry (MS) can generate high-throughput protein profiles for biomedical research to discover biologically-related protein patterns/biomarkers. The noisy functional MS data collected by current technologies, however, require consistent, sensitive, and robust data-processing techniques for successful biomedical application. We have proposed a new comprehensive MS data preprocessing package (Wave-spec), which includes several novel algorithms and can overcome several conventional difficulties in processing MS data for use in biomedical research. (Bioinformatics)

http://bioinformatics.oxfordjournals.org/cgi/reprint/25/6/808

LYMPHOMA

University of Iowa/Mayo Clinic

Weiner, George J., M.D. *(W. Chng ... et al.)*

Gene expression profiling of pulmonary mucosa-associated lymphoid tissue lymphoma identifies new biologic insights with potential diagnostic and therapeutic applications.

The study examined the global gene expression profile of MALT lymphoma, the third most common type of lymphoma. A set MALT lymphoma subgroups with distinct pathologic features defined by distinct groups of deregulated genes were identified. The protein products of these genes are potential novel diagnostic and therapeutic targets. (Blood)

http://bloodjournal.hematologylibrary.org/cgi/content/abstract/113/3/635

OVARIAN

University of Washington/Fred Hutchinson Cancer Research Center

Urban, Nicole, Sc.D *(D. Sakar … et al.)*

Quality Assessment and Data Analysis for microRNA Expression Arrays.

MicroRNAs are small (~22 nt) RNAs that regulate gene expression and play important roles in both normal and disease physiology. The use of microarrays for global characterization of microRNA expression is becoming increasingly popular and has the potential to be a widely used and valuable research tool. However, microarray profiling of microRNA expression raises a number of data analytic challenges that must be addressed in order to obtain reliable results. We introduce here a universal reference microRNA reagent set as well as a series of nonhuman spiked-in synthetic microRNA controls, and demonstrate their use for quality control and between-array normalization of microRNA expression data. We also introduce diagnostic plots designed to assess and compare various normalization methods. We anticipate that the reagents and analytic approach presented here will be useful for improving the reliability of microRNA microarray experiments. We demonstrate implementation of our methods using a dataset representing microRNA intensity profiles of two histologic types of ovarian cancer as well as primary cultures of human ovarian surface epithelial cells. (Nucleic Acids Res)

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2632898&blobtype=pdf

PANCREATIC

Mayo Clinic, Rochester

Petersen, Gloria, Ph.D. *(S. Carlson … et al.)*

Molecular imaging of mouse models facilitates evaluation of a potential technology to deliver therapy to pancreatic cancer cells

An engineered measles virus expressing the sodium-iodide symporter gene (MV-NIS) enables noninvasive serial imaging and quantitation. MV-NIS shows oncolytic activity in human pancreatic cancer xenografts. Tumor growth is reduced and survival is increased in mice treated with the virus. (AJR Am J Roentgenol.)

http://www.ajronline.org/cgi/content/full/192/1/279

Petersen, Gloria, Ph.D. *(O. Nolan-Stevaux … et al.)*

Expression of GLI1 is an important requirement for pancreatic cancer cells

Sonic hedgehog protein is absent in the normal pancreas but is highly expressed in pancreatic tumors. Genetic blocking experiments in mouse models to identify important target genes in sonic hedgehog found the expression of GLI1 target genes is maintained. GLI1 expression is required both for survival and for the KRAS-mediated transformed phenotype of cultured pancreatic cancer cells. (Genes & Dev)

http://genesdev.cshlp.org/content/23/1/24.long

Petersen, Gloria, Ph.D. *(M. Truty … et al.)*

KLF14 silences TGFβRII via a novel negative-feedback mechanism.

Transcriptional silencing is a critical mechanism for down-regulating TGFβ receptors at the cell surface. KLF14 represses the TGFβRII, a function that is augmented by TGFβ treatment, and distinct GC-rich sequences used by KLF14 are used to regulate this promoter. This is a novel negative-feedback mechanism in which TGFβRII activation at the cell surface induces the expression of KLF14. This finding expands the network of non-Smad transcription factors that participate in the TGFβ pathway. (J Biol Chem)

http://www.jbc.org/cgi/content/full/284/10/6291

Petersen, Gloria, Ph.D. *(R. Pannala … et al.)*

New onset diabetes is a potentially valuable clue to enable earlier diagnosis of pancreatic cancer

Pancreatic cancer has been shown by Mayo investigators to induce diabetes in the three years prior to the diagnosis of the cancer itself. 80% of pancreatic cancer patients are either hyperglycaemic or diabetic, and older patients with new-onset diabetes have about an eight times higher risk of having pancreatic cancer than the general population. The challenge will be to distinguish pancreatic cancer induced diabetes from type 2 diabetes. (Lancet Oncol)

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6W85-4V7DBRT-T&_user=130561&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000010878&_version=1&_urlVersion=0&_userid=130561&md5=97d912970fba75413036b321eba5483d

PROSTATE

Johns Hopkins University

Nelson, William, M.D., Ph.D. *(K. Sfanos … et al.)*

Characterization of corpora amylacea and calculi in human prostate tissues.

Corpora amylacea and calculi have been known to be commonly present in benign regions of prostate tissues from men with prostate cancer. The study represented the first definitive analysis of the protein composition of these entities, suggesting strongly that acute inflammation played a role in their biogenesis. This intriguing finding is consistent with the hypothesized role for inflammation in prostate carcinogenesis. (PNAS)

http://www.pnas.org/content/106/9/3443.long

Nelson, William, M.D., Ph.D. *(S. Zheng … et al.)*

Genetic variants and family history of prostate cancer useful in screening and early detection of prostate cancer.

In a large cohort study in Sweden, using a cutoff of any 11 risk alleles or family history, the sensitivity and specificity for predicting prostate cancer were 0.25 and 0.86, respectively. The overall predictive performance of prostate cancer using genetic variants, family history, and age, measured by areas under curve was 0.65 (95% confidence interval, 0.63-0.66), similar to that of serum prostate-specific antigen (PSA) testing. Genetic testing may play a role in prostate cancer screening and early detection. (Clin Cancer Res)

http://clincancerres.aacrjournals.org/cgi/content/full/15/3/1105

Nelson, William, M.D., Ph.D. *(R. Hu … et al.)*

New splice variants of the androgen receptor detected in men with androgen-independent disease.

In men with androgen-independent prostate cancer, novel forms of the androgen receptor, generated by abnormal RNA splicing, were detected. The receptors were capable of ligand-independent signaling, providing a new molecular mechanism for androgen-independent prostate cancer progression. (Cancer Res)

http://cancerres.aacrjournals.org/cgi/content/full/69/1/16

Memorial Sloan Kettering Cancer Center

Scardino, Peter T., M.D. *(D. Welsbie ... et al.)*

Histone deacetylases are required for androgen receptor function in hormone-sensitive, castration-resistant prostate cancer

Histone deacetylase (HDAC) inhibitors such as SAHA (vorinostat) and LBH589, which are currently being tested in clinic, could be a therapy for castration-resistant prostate cancer. HDAC inhibitors block the AR-mediated transcriptional activation of many genes, including the TMPRSS2 gene, commonly fused with ETS family members in prostate cancer. HDAC inhibitors retain the ability to block AR activity in models of castration-resistant prostate cancer and merit clinical investigation in this setting. (Cancer Res)

http://cancerres.aacrjournals.org/cgi/content/full/69/3/958

Scardino, Peter T., M.D. *(S. Wenske ... et al.)*

Free PSA and hK2 improve current models for predicting biochemical recurrence

Most pretreatment models to predict biochemical recurrence after radical prostatectomy for prostate cancer rely on total prostate-specific antigen (PSA), clinical stage, and biopsy Gleason grade. Population-based data have shown that levels of PSA and human glandular kallikrein-2 (hK2) are significantly elevated in blood up to 20 years before diagnosis with clinically significant prostate cancer. We found that free PSA hK2 enhanced the predictive accuracy of the standard prediction model. (Int J Cancer)

http://www3.interscience.wiley.com/cgi-bin/fulltext/121402546/HTMLSTART

Scardino, Peter T., M.D. *(P. Helo ... et al.)*

KLK2/3-expressing circulating tumor cells are rare in men with localized prostate cancer but common in men with castration-refractory prostate cancer

We assessed men with localized prostate cancer or castration-refractory prostate cancer (CRPC) and healthy volunteers for circulating tumor cells (CTCs) via real-time reverse transcription polymerase chain reaction assays for kallikrein-related peptidase 2 and 3 (KLK2 and KLK3, ie, prostate-specific antigen) mRNAs. All healthy volunteers were negative for KLK mRNAs. KLK2/3-expressing CTCs are common in men with CRPC and bone metastases but are rare in patients with metastases diagnosed only in soft tissues and patients with localized cancer. (Clin Chem)

http://www.clinchem.org/cgi/content/short/clinchem.2008.117952v1

Scardino, Peter T., M.D. *(M. Leversha … et al.)*

FISH analysis of circulating tumor cells may be a valuable, non-invasive alternative to tumor profiling

This study demonstrated the efficacy of using the fluorescence in situ hybridization (FISH) analyze the androgen receptor (AR) and MYC genomic copy number in circulating tumor cells (CTCs) from patients with progressive castration-resistant metastatic prostate cancer. We analyzed samples from 77 patients with progressive castration-resistant prostate cancer. The CTCs isolated from our patient cohort present a very similar molecular cytogenetic profile to that reported for late-stage tumors. (Clin Cancer Res)

http://clincancerres.aacrjournals.org/cgi/content/full/15/6/2091

Scardino, Peter T., M.D. *(H. Scher … et al.)*

Circulating tumor cell count may predict survival in prostate cancer

We aimed to assess CTC count as a prognostic factor for survival in patients with progressive, metastatic, castration-resistant prostate cancer receiving first-line chemotherapy. We found that CTC number, analyzed as a continuous variable, can be used to monitor disease status and might be useful as an intermediate endpoint of survival in clinical trials. Prospective recording of CTC number as an intermediate endpoint of survival in randomized clinical trials is warranted. (Lancet Oncol)

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6W85-4VKD7Y1-1&_user=281587&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000016018&_version=1&_urlVersion=0&_userid=281587&md5=951b6415d03575fba89baeeeaed11eb4

Scardino, Peter T., M.D. *(A. Gopalan … et al.)*

TMPRSS2-ERG gene fusion is not associated with outcome

A significant number of prostate cancers have been shown to have TMPRSS2-ERG fusion, but the clinical significance of this rearrangement is unclear. We analyzed TMPRSS2-ERG gene rearrangement status by fluorescence in situ hybridization in 521 cases of clinically localized surgically treated prostate cancer and in 40 unmatched metastases. We found that TMPRSS2-ERG fusion was not associated with outcome in patients treated by prostatectomy. (Cancer Res)

http://cancerres.aacrjournals.org/cgi/content/full/69/4/1400

Northwestern University

Lee, Chung, Ph.D. *(W. Xiao … et al.)*

Potential link between U19/Eaf2 and pVHL identified.

Studies have firmly established a key regulatory role for the tumor suppressor pVHL in the regulation of the vascular system and normal spermatogenesis. Here, we report that knockout of the newly identified tumor suppressor U19/Eaf2 also caused vascular system abnormalities and aspermatogenesis, suggesting a potential link between U19/Eaf2 and pVHL. Our observations argue that U19/Eaf2 can modulate HIF1A and angiogenesis, possibly via direct binding and stabilization of pVHL. (Cancer Res)

http://cancerres.aacrjournals.org/cgi/reprint/69/6/2599

Lee, Chung, Ph.D. *(MM Ngyuen … et al.)*

Calreticulin is not required for the cytoplasmic localization of AR

Calreticulin has been implicated as a possible nuclear export factor for AR because the two proteins form a complex. In this study, we assessed whether the cytoplasmic localization of AR requires binding to calreticulin. We found that a mutated calreticulin binding site did not affect the localization of AR, in the absence of androgen AR is localized to the cytoplasm regardless of its ability to interact with calreticulin, and a reduction in the levels or loss of calreticulin did not affect the localization of AR. (Mol Cell Endocrinol)

http://www.ncbi.nlm.nih.gov/pubmed/19150386?log$=activity

University of California, San Francisco

Carroll, Peter, MD, MPH *(L. Fong … et al.)*

Potentiating endogenous antitumor immunity to prostate cancer through combination immunotherapy with CTLA4 blockade and GM-CSF.

Our manuscript describes the clinical and immunologic results of the phase I clinical trial of GM-CSF and CTLA4 blockade in prostate cancer patients. We show that this treatment induces CD8 T cell activation, clinical responses and toxicity in a dose-dependent fashion. Moreover, we demonstrate that this treatment can potentiate endogenous immune responses to known tumor associated antigens including NY-ESO-1. (Cancer Res)

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19147575

Carroll, Peter, MD, MPH *(LS Bouchard … et al.)*

Picomolar sensitivity MRI and photoacoustic imaging of cobalt nanoparticles.

We have developed a nanoparticle that serves a contract reagent for both photoacoustic tomography and Magnetic resonance imaging. This dual-modality PAT/MRI contrast agent demonstrates, so far, the most sensitive detection experiment of magnetic nanoparticles with particle concentrations in the picomolar and tens of picomolars range. The particles may even

be used for stand-alone MRI or PAT. We anticipate that these agents will increase the sensitivity with which early cancer lesions can be detected. (PNAS)

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19251659

Carroll, Peter, MD, MPH *(SL 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