July – October 2008

Translational Research Program

[SPORE ADVANCES]

Brain 5
University of Alabama at Birmingham 5
Gillespie, G. Yancey, Ph.D 5
University of California San Francisco 5
Berger, Mitchel S., M.D. 5
Breast 6
Mayo Clinic, Rochester 6
Ingle, James N., M.D. 6
University of California, San Francisco 8
Gray, Joe W., Ph.D. 8
Baylor College of Medicine 10
Osborne, C. Kent., M.D. 10
Dana-Farber Harvard Cancer Institute 11
Iglehart, J. Dirk, M.D. 11
Cervical and Endometrial 11
Johns Hopkins University, School of Medicine 11
Wu, T.C., M.D., Ph.D. 11
University of Texas MD Anderson Cancer Center 13
Lu, Karen, M.D. 13
Gastrointestinal 15
Johns Hopkins University 15
Kern, Scott E., M.D. 15
University of Arizona 16
Gerner, Eugene W., Ph.D. 16
Vanderbilt University 16
Coffey, Robert J., Jr., M.D. 16
Head and Neck 18
University of Michigan 18
Wolf, Gregory T., M.D. 18
Johns Hopkins University 19

Sidransky, David, M.D. 19
Leukemia 20
University of Texas MD Anderson Cancer Center 20
Issa, Jean-Pierre, M.D. 20
Lung 21
University of Colorado Cancer Center 21
Bunn, Paul 21
Lymphoma 22
University of Iowa- Mayo Clinic 22
Weiner, George J. 22
Johns Hopkins University 22
Ambinder, Richard F., M.D., Ph.D. 22
Ovarian 23
University of Washington, Fred Hutchinson Cancer Research Center 23
Urban, Nicole, Sc.D 23
Pancreatic 24
Mayo Clinic, Rochester 24
Petersen, Gloria M., Ph.D. 24
Prostate 25
University of Washington, Fred Cancer Research Center 25
Nelson, Peter S. 25
University of Michigan 25
Pienta, Kenneth J., M.D. 25
Johns Hopkins University 27
Nelson, William, M.D., Ph.D. 27
Memorial Sloan Kettering Cancer Center 27
Scardino, Peter T., M.D. 27
University of California, Los Angelus 28
Reiter, Robert 28
Melanoma 30
Brigham and Women's Hospital 30

Kupper, Thomas S., M.D. 30
University of Texas MD Anderson Cancer Center 30
Grimm, Elizabeth A., Ph.D 30

Brain

University of Alabama at Birmingham

Gillespie, G. Yancey, Ph.D

CD133 is a marker of bioenergetic stress in human glioma.

Glioma stem cells are believed to be both radiation and chemotherapy resistant and their survival is the cause of tumor recurrence. These data suggest that mitochondrial dysfunction may lead to increased expression of CD133, but more important, further transform the glioma cell to yield greater acquired therapeutic resistance. In other words, normal mitochondrial function is tumor-suppressive.

http://www.ncbi.nlm.nih.gov/pubmed/18985161?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

---

Phase Ib Trial of Mutant Herpes Simplex Virus G207 Inoculated Pre-and Post-tumor Resection for Recurrent GBM.

This trial provided a basis for an ongoing Phase I trial of G207 and irradiation in patients with recurrent GBM. Significant findings are that two injections separated by a 2 to 5 day interval in patients before and after undergoing surgical resection of their recurrent tumor was safe and resulted in a much longer than anticipated overall survival in 2 of 6 patients. Moreover, this trial provided tumor specimens for assessment of viral replication and of patient response to virus injection in the brain.

http://www.ncbi.nlm.nih.gov/pubmed/18957964?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

---

University of California San Francisco

Berger, Mitchel S., M.D.

PI(3) kinase is associated with a mechanism of immunoresistance in breast and prostate cancer.

We have previously shown that PTEN loss correlates with immunoresistance in glioma (Parsa AT et al, Nat Med, 2007), in the present study we show that expression of a pivotal negative regulator of T-cell function, B7-H1, correlates with PI(3) kinase activation in breast and prostate cancer patients (Crane C et. al., Oncogene, 2008). B7-H1-mediated immunoresistance can be attenuated by inhibitors of the PI(3) kinase pathway, and is dependent on S6K1-mediated translational regulation of B7-H1 protein. Activation of the PI(3) kinase pathway is likely a negative predictor of response to cancer vaccines in breast, prostate and brain tumor patients; making our findings of potential interest to SPORE investigators testing cancer vaccines dependent upon T cell mediated lysis of tumor targets.

http://www.ncbi.nlm.nih.gov/pubmed/18850006

Breast

Mayo Clinic, Rochester

Ingle, James N., M.D.

HER receptor signaling confers resistance to the insulin-like growth factor-I receptor inhibitor, BMS-536924.

The insulin-like growth factor receptor (IGF-1R) represents a novel target for anti-cancer therapy in many tumor types including breast cancer and may be a major mechanism of resistance to HER2-targeted therapy. This work demonstrates that crosstalk signaling between the IGF-1R and HER2 occurs bi-directionally, such that co-inhibition of both receptors imparts synergic anti-cancer activity. These data support simultaneous inhibition of IGF-1R and HER2 in HER2+ breast cancer as clinical investigations with IGF-1R inhibitors move forward.

http://mct.aacrjournals.org/cgi/reprint/7/9/2589

Cytochrome P450 2D6 and Homeobox 13/Interleukin-17B receptor: Combining inherited and tumor gene markers for prediction of tamoxifen resistance.

The cytochrome P450 (CYP2D6) enzyme converts tamoxifen to the active metabolite, endoxifen. We hypothesized that CYP2D6 mediated activation would be crucial in tumors with a high HOXB13/IL17BR gene ratio, a marker associated with increased recurrence. We performed a retrospective analysis of tamoxifen- treated, node negative breast cancer patients using both CYP2D6 metabolism information and HOXB13 and IL-17BR RT-PCR profiles. The combined

CYP2D6:HOXB13/IL17BR risk factor was associated with overall survival (p=0.009), with the greatest risk in patients exhibiting both high risk features (decreased CYP2D6 and high HOXB13/IL17BR ratio). In summary, a prospective approach incorporating both host (CYP2D6) and tumor (HOXB13/IL17BR) genetic markers may provide a better indication of tamoxifen resistance than either marker alone.

http://clincancerres.aacrjournals.org/cgi/content/full/14/18/5864

Molecular analysis of metaplastic breast carcinoma: high EGFR copy number via aneusomy.

Metaplastic breast cancer is a rare tumor with an aggressive clinical phenotype and limited treatment options. Gilbert and Goetz et al. confirmed that metaplastic carcinoma exhibits immunohistochemical characteristics consistent with the basal phenotype, and characterized the known molecular markers of response to EGFR and KIT tyrosine kinase inhibitors. Although no activating mutations in EGFR or KIT genes were present, they demonstrated a significant proportion of these tumors had, via aneusomy, high EGFR gene copy number known to be associated with gefitinib response. These findings provide impetus to study EGFR tyrosine kinase inhibitors in the treatment of metaplastic breast cancer.

http://mct.aacrjournals.org/cgi/content/full/7/4/944

An HLA-DR-degenerate epitope pool detects insulin-like growth factor binding protein 2-specific immunity in patients with cancer.

Cancer vaccination in humans has failed due to an inability to generate helper T cell immunity, which is needed for robust and sustained anti-tumor immune responses. In this study, we have identified a pool of four HLA-DR-degenerate human epitopes derived from the insulin-like growth factor binding protein-2 (IGFBP-2). This pool not only detects low level pre-existent immunity but also has the potential to be used in vaccine strategies to generate helper T cell immunity in nearly 80% of patients with IGFBP-2 expressing tumors.

http://cancerres.aacrjournals.org/cgi/content/full/68/12/4893

Functional assays described for classification of BRCA2 variants of uncertain significance.

Individuals found to carry BRCA2 missense mutations cannot currently benefit from improved risk assessment for cancer because the relevance of the many BRCA2 missense mutations to cancer is not known. In this manuscript two functional assays that can be used to assess the functional effects of these mutations are described. Both assays have high sensitivity and specificity for deleterious mutations suggesting that they may be useful for clinical diagnosis.

http://cancerres.aacrjournals.org/cgi/reprint/68/9/3523

Clinically applicable models to characterize BRCA1 and BRC2 variants of uncertain significance.

BRCA1 and BRCA2 breast tumors exhibit specific histological phenotypes. Here histological data from tumors with BRCA1 and BRCA2 missense mutations were combined with genetic data including assessment of how mutations track with cancer in families to establish a model that can be used to predict the cancer relevance of BRCA1 and BRCA2 missense mutations.

http://jco.ascopubs.org/cgi/reprint/JCO.2008.17.8228v1

Prediction and assesment of splicing alterations: Implications for clinical testing.

Many alterations in the non-coding regions of the BRCA1 and BRCA2 genes have been found in individuals with significant family history of breast cancer. These mutations may induce changes in RNA splicing leading to mutant BRCA1 and BRCA2 proteins. Here the process for evaluating mutations for splicing effects is outlined.

http://www3.interscience.wiley.com/cgi-bin/fulltext/121483146/PDFSTART

Assessment of functional effects of unclassified genetic variants.

A number of functional assays that can detect the influence of missense mutations on cancer genes such as the BRCA1 and BRCA2 breast cancer genes, the p16 (CDKN2A) melanoma gene and the MLH1 and MSH2 colon cancer genes have been defined. Here the utility of these assays for clinical diagnostics is evaluated.

http://www3.interscience.wiley.com/cgi-bin/fulltext/121483143/PDFSTART

University of California, San Francisco

Gray, Joe W., Ph.D.

Aging impacts transcriptomes but not genomes of hormone-dependent breast cancers.

A multi-institutional effort involving the UCSF SPORE archive of cryobanked breast cancer samples generated and analyzed DNA and RNA samples from two age-based cohorts of early- vs. late-onset estrogen receptor (ER)-positve ductal breast cancers to evaluate their genetic and epigenetic differences while controlling for breast cancer phenotypic heterogeneity. Findings from the comparative genomic and expression microarray analyses of these two age-based cohorts of ER-positive breast cancer demonstrated that the biology of breast cancer is age-dependent and associated with significantly different transcriptome changes but no significant differences in genomic aberrations. In addition, an age signature consisting of 128 genes differentially epxress between early- and late-onset breast cancers proved to be >80% accurate

at discerning younger ER-positive breast cancers from older ER-positive breast cancers in two other independent data sets. Based on these conclusions, other age cohort studies of this design and type are needed to further generalize about age-related biological differences driving ER-negative breast cancers and different epithelial malignacies. As well, the molecular basis for the epigenetic differences driving age-dependent breast cancer onset need to be further elucidated.

http://breast-cancer-research.com/content/pdf/bcr1765.pdf

Ageing, oxidative stress and cancer: paradigms in parallax.

Age-related diseases like cancer are putatively associated with increased oxidative stress, which might also account for the epigenetic differences identified (above) between early- and late-onset forms of histologically similar ER-positive breast cancers arising in younger vs. older women. An oxidant gene signature was derived using a model ER-positive breast cancer cell line subjected to different forms of oxidant stress in the presence and absence of estrogen responsiveness. This 62 gene endocrine-responsive oxidant stress signature was then used to interrogate a public repository of expression microarray data (including UCSF SPORE data from above) characterizing 394 ER-positive primary breast cancers to demonstrate that, contrary to expectation, those exhibiting greater oxidative stress were more likely to arise earlier in life, demonstrate greater proliferative potential, and be associated with greater metastatic potential and worse disease-free survival. Comparative network analysis indicated that these ER-positive breast tumors arising earlier in life and associated with greater oxidative stress share activated TNF and TGFbeta signaling pathways that converge to stimulate AP-1 and NFkappaB regulated genes, indicating that clinically more aggressive early-onset ER-positive breast cancers may be best treated with AP-1 and NFkappaB inhibitors in addition to standard endocrine agents.

http://www.ncbi.nlm.nih.gov/pubmed/18948997?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

---

Identification of one key mediator of mutant telomerase RNA cytotoxicity in human cancer cells.

While overexpression of mutant telomerase RNA in cancer cells consistently and robustly inhibits the propagation of telomerase-positive cancer cells, the molecular pathways underlying this anticancer effect have not been fully understood. We recently identified the protein kinase ATM as one important mediator of the mutant telomerase RNA anticancer effect. This work improves our understanding of the mechanism by which mutant telomerase RNA blocks cancer cell growth and may ultimately allow us to more effectively target diverse tumor types.

http://www.ncbi.nlm.nih.gov/pubmed/18593932?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

---

Baylor College of Medicine

Osborne, C. Kent., M.D.

Development of resistance to targeted therapies transforms the clinically associated molecular profile subtype of breast tumor xenografts.

The study established and analyzed gene expression profiles of breast cancer tumors from endocrine and anti-HER therapy sensitive and resistant xenograft models in order to elucidate molecular mechanisms of resistance. The results show that in response to various endocrine therapy regimens, these xenograft breast tumors shut down classic estrogen signaling and activate alternative pathways such as HER2 that contribute to treatment resistance. Thus, over time, the molecular phenotype of breast cancer can change, suggesting (1) the need for the integration of, at progression, of a sequential biopsy and biomarker analysis (to improve decision making in the management of advanced breast cancer) and (2) that in some breast cancers a simultaneous blockade of both ER and HER signaling pathways may be required to bypass resistance mechanisms.

http://cancerres.aacrjournals.org/cgi/reprint/68/18/7493

Insulin-like growth factor-I activates gene transcription programs strongly associated with poor breast cancer prognosis.

This is the first study to define IGF gene programs in human cancers and shows that IGF-stimulated gene transcriptional programs are associated with poor prognostic features and outcome in breast cancer. The IGF signature is a strong independent predictor of patient outcome. The signature may identify genes that will serve as biomarkers of IGF responsive tumors and which may respond to anti-IGF-IR therapy.

http://jco.ascopubs.org/cgi/content/full/26/25/4078

Dana-Farber Harvard Cancer Institute

Iglehart, J. Dirk, M.D.

Breast cancer susceptibility loci and mammographic density.

We conducted an analysis in the Nurses' Health Study to assess the relation between 11 well-confirmed breast cancer susceptibility loci (identified by a multistage genome wide association study) and mammographic density. Overall, breast cancer susceptibility loci identified through a genome-wide association study do not appear to be associated with mammographic density.

http://breast-cancer-research.com/content/10/4/R66

Risk prediction models and prediction of estrogen receptor-positive breast cancer.

A number of breast cancer risk prediction models have been developed to provide insight into a woman's individual breast cancer risk. Although circulating levels of estradiol in postmenopausal women predict subsequent breast cancer risk, whether the addition of estradiol levels adds significantly to a model's predictive power has not previously been evaluated. We evaluated this in the Nurses' Health Study and found the age-specific concordance statistic increased significantly from 0.635 +/- 0.007 to 0.645 +/- 0.007 ($P < 0.001$) after the addition of imputed estradiol.

http://breast-cancer-research.com/content/10/4/R55

Cervical and Endometrial

Johns Hopkins University, School of Medicine

Wu, T.C., M.D., Ph.D.

Treatment with proteasome inhibitor bortezomib enhances antigen-specific CD8+ T-cell-mediated antitumor immunity induced by DNA vaccination.

We found that the combination of treatment with the proteoasome inhibitor bortezomib and therapeutic HPV DNA vaccine targeting E7 antigen generated more potent E7-specific CD8+ T cell immune responses and better therapeutic antitumor effects against an E7-expressing tumor, TC-1 in tumor-bearing mice compared to monotherapy. Furthermore, we found that treatment with bortezomib led to increased apoptosis of TC-1 tumor cells and could render the TC-1 tumor cells more susceptible to lysis by E7-specific CD8+ T cells, suggesting that the

combination of bortezomib with therapeutic HPV vaccination may represent a potentially promising approach for the control of cancer.

http://www.springerlink.com/content/aw64635j741t812u/

RNA Interference-Mediated In Vivo Silencing of Fas Ligand as a Strategy for the Enhancement of DNA Vaccine Potency.

We observed that mice vaccinated with E7-expressing DNA co-administered with DNA encoding shRNA targeting FasL generated significantly enhanced E7-specific CD8(+) cytotoxic T cell responses as well as potent therapeutic antitumor effects against E7-expressing tumors. Our data suggest that intradermal administration of DNA encoding shRNA targeting FasL may result in improved survival of CD8+ T cells and may be a potentially useful approach to enhance DNA vaccine potency.

http://www.liebertonline.com/doi/abs/10.1089/hum.2007.059

Cluster intradermal DNA vaccination rapidly induces E7-specific CD8(+) T-cell immune responses leading to therapeutic antitumor effects.

We found that cluster intradermal vaccination with therapeutic HPV DNA vaccines targeting E7 was capable of rapidly generating a significant number of E7-specific CD8+ T cells, resulting in significant therapeutic antitumor effects in vaccinated mice. We also observed that cluster intradermal CRT/E7 DNA vaccination in the presence of tumor generates significantly higher E7-specific CD8+ T-cell immune responses in the systemic circulation as well as in the tumors. Thus, our data indicate that cluster intradermal therapeutic HPV DNA vaccination may be performed before cervical cancer resection in stage IB1 cervical cancer patients without compromising the standard of patient care.

http://www.nature.com/gt/journal/v15/n16/abs/gt200853a.html

Enhancement of CD4(+) T-cell help reverses the doxorubicin-induced suppression of antigen-specific immune responses in vaccinated mice.

We found that treatment with doxorubicin followed by therapeutic HPV DNA vaccination targeting E6 combined with DNA vaccination strategy capable of enhancing CD4+ T help led to enhanced antitumor effects and prolonged survival in TC-1 tumor-bearing mice. Thus, our data suggest that enhancement of CD4(+) T-cell help reverses the doxorubicin-induced suppression of antigen-specific immune responses in vaccinated mice.

http://www.nature.com/gt/journal/v15/n16/abs/gt200879a.html

Combination of treatment with death receptor 5-specific antibody with therapeutic HPV DNA vaccination generates enhanced therapeutic anti-tumor effects.

Our results indicated that mice bearing the E7-expressing tumor, TC-1 treated with MD5-1 monoclonal antibody followed by therapeutic HPV DNA vaccination targeting E7 generated the most potent therapeutic anti-tumor effects as well as highest levels of E7-specific CD8+ T cells among all the groups tested. In addition, treatment with MD5-1 monoclonal antibody was capable of rendering the TC-1 tumor cells more susceptible to lysis by E7-specific cytotoxic T lymphocytes. Thus, our data suggests that the combination of treatment with death receptor 5-specific antibody with therapeutic HPV DNA vaccination generates enhanced therapeutic anti-tumor effects.

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TD4-4SWGB8X-2&_user=5755111&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000000150&_version=1&_urlVersion=0&_userid=5755111&md5=e2935722b22eaff67fe08e0f5b6385d1

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

We observed that TC-1 tumor-bearing mice treated with radiotherapy combined with therapeutic HPV DNA vaccination targeting E7 generated significant therapeutic antitumor effects and the highest frequency of E7-specific CD8(+) T cells in the tumors and spleens of treated mice. Furthermore, radiotherapy treatment rendered TC-1 tumor cells more susceptible to lysis by E7-specific CTLs. Thus, our data indicate that TC-1 tumor-bearing mice treated with the chemotherapy in combination with radiation and therapeutic HPV DNA vaccination generate significantly enhanced therapeutic antitumor effects.

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

University of Texas MD Anderson Cancer Center

Lu, Karen, M.D.

β-catenin mediates glandular formation and dysregulation of beta-β- induced hyperplasia formation in the murine uterus.

We have demonstrated a role for β-catenin in both endometrial function and dysfunction using PRcre/+Ctnnb1f(Ex3)/+ and PRcre/+Ctnnb1f/f mouse models, which exhibit both developmental and fertility defects demonstrating how its regulation is important to adult uterine function, as well as develop endometrial hyperplasia and squamous cell metaplasia, respectively, elucidating a role for β-catenin in endometrial dysfunction. The results of this investigation provide significant insights into our understanding of the importance of β-catenin in female

reproduction and endometrial cancer. By studying the role of the Wnt signaling pathway, further insights into the hormone regulation of the uterus and the ways it is altered in uterine dysfunction can be uncovered.

http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2008363a.html

---

Differential roles of telomere attrition in type I and II endometrial carcinogenesis.

We analyzed the endometria of mice with critical telomere shortening, and found that by 1 year of age, most contained focal, highly atypical preneoplastic lesions that histologically closely resemble EIC, the in situ precursor to serous TII cancers, and it is likely that additional mutations are needed to drive the formation of fully invasive TII cancers in the context of short telomeres, particularly p53, but also perhaps additional oncogenic mutations that promote cell-cycle progression or bypass other cellular senescence checkpoints. Although our findings represent a first step toward the development of mouse models of TII endometrial carcinogenesis, the generation of practicable models will benefit from alternative approaches that do not require serial breeding to generate experimental cohorts. Functional inactivation of components of the Shelterin complex that bind to and protect telomeric DNA offers one promising avenue for such investigations.

http://ajp.amjpathol.org/cgi/content/full/173/2/536

ZEB1 expression in type I vs. type II endometrial cancers: a marker of aggressive disease.

We previously demonstrated that ZEB1 protein is not present in normal endometrial epithelium, and that even in low-grade endometrioid adenocarcinomas it remains confined to the stroma. We now quantitatively demonstrate that ZEB1 is expressed at significantly higher levels in tumor-associated stroma as compared to normal endometrial stroma and also that it is significantly higher in stroma associated with endometrial hyperplasia as compared to normal stroma. ZEB1 may have potential for use as a molecular marker of risk of recurrence of endometrial cancers and may aid in identification of women who would most benefit from surgical staging and adjuvant chemotherapy. Furthermore, if the inappropriate expression of ZEB1 in type II endometrial cancers could be reversed, it might be exploited as a form of differentiation therapy for these highly aggressive forms of endometrial cancer.

http://www.nature.com/modpathol/journal/v21/n7/full/modpathol200882a.html

---

Cost-effectiveness analysis of endometrial cancer prevention strategies for obese women

Oral contraceptives and current screening methods are not cost-effective endometrial cancer prevention strategies for obese women. Risk factors such as morbid obesity and longstanding anovulation may define a subgroup at highest risk of endometrial cancer for whom OCPs may be a cost-effective strategy. Interventions that reduce endometrial cancer risk further or those with additional health benefits are needed in this population.

http://www.greenjournal.org/cgi/content/full/112/1/56

Gastrointestinal

Johns Hopkins University

Kern, Scott E., M.D.

Core signaling pathways in human pancreatic cancers revealed by global genomic analyses.

Of the many differences between normal and cancer cells, it is only the genetic differences that unequivocally distinguish the former from the later.We identified the genetic changes that occur during tumorigenesis of pancreatic cancer, creating the largest study of cancer genetics yet reported. The changes identified could be used for improved predictive, prognostic, and diagnostic mutation-based markers, and some of these mutated genes or intracellular pathways that are enriched in mutations could prove to be attractive for therapeutic targeting.

http://www.ncbi.nlm.nih.gov/pubmed/18772397

Circulating mutant DNA to manage colorectal cancer patients.

We applied a highly sensitive approach to quantify circulating tumor DNA (ctDNA) in plasma samples from subjects undergoing multimodality therapy for colorectal cancer and found that ctDNA measurements could reliably monitor tumor dynamics in subjects with cancer who were undergoing surgery or chemotherapy. We also detected tumor-derived mutant DNA in stool of 92% of similar patients and in plasma in half of the patients.

www.ncbi.nlm.nih.gov/pubmed/18670422: and
http://www.ncbi.nlm.nih.gov/pubmed/18602395

University of Arizona

Gerner, Eugene W., Ph.D.

Genetic Variability as Prognostic or Predictive Factors in Colorectal Intraepithelial Neoplasia.

Acquired or inherited mutations in the adenomatous polyposis coli (APC) tumor suppressor gene are causally linked to colorectal cancer. Given the significance of APC in colorectal cancer, we investigated the association between common single-nucleotide polymorphisms (SNP) in the APC gene and the odds of developing metachronous colorectal adenomas as a surrogate measure of colorectal cancer risk. Our findings support an important role for germ-line allele sequence in the APC gene and individual risk of metachronous adenomatous polyps and thus an overall higher individual risk for the development of colorectal cancer.

http://cancerres.aacrjournals.org/cgi/content/abstract/68/14/6006

Vanderbilt University

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

Use of Fluorescence-activated vesicle sorting for isolation of naked2-associated, basolaterally targeted exocytic vesicles for proteomics analysis.

This is the first large-scale proteomics characterization of a population of basolaterally targeted exocytic vesicles using a new application of flow cytometry that we have developed. These vesicles contain Naked2 a critical negative regulator of Wnt signaling, a pathway that is misregulated in many cancers. We combined biochemical enrichment and Fluorescence-Activated Vesicle Sorting (FAVS) by flow cytometry to purify a discrete pool of myristoylation deficient Naked2-containing exocytic vesicles for large scale LC/LC-MS/MS analysis. Three hundred and eighty-nine proteins were identified in these mutant vesicles and six were confirmed to be present in wild-type Naked2 vesicles

http://www.mcponline.org/cgi/content/full/7/9/1651

Src transformation of colonic epithelial cells: Enhanced anchorage-independent growth in an Apc+/min background.

The potential for biological cooperativity between APC loss-of-function and Src gain-of-function was investigated using mouse colon epithelial cell lines IMCE (APC+/min) and YAMC (APC+/+) expressing oncogenic Src. IMCE-Src cells were found to exhibit increased anchorage-independent proliferation as compared to the YAMC-Src cells, and this property was associated

with elevated beta-catenin transcriptional activity. The selective Src inhibitor, AZD0530, was found to be effective in blocking both cell invasion and anchorage-independent proliferation.

http://www3.interscience.wiley.com/cgi-bin/fulltext/120736190/HTMLSTART

Oncogenic ras and transforming growth factor-β synergistically regulate AU-rich element-containing mRNAs during epithelial to mesenchymal transition.

These studies show that oncogenic Ras and TGF-β synergistically regulate genes containing AREs in cultured rodent intestinal epithelial cells and suggest that posttranscriptional regulation of gene expression is an important mechanism involved in cellular transformation and CRC tumor progression. (Mol Cancer Res 2008;6(7):1124–36)

http://mcr.aacrjournals.org/cgi/content/full/6/7/1124

Global impact of oncogenic Src on a phosphotyrosine proteome.

There is a need to better characterize tumors at the molecular level in order to identify biomarkers of cancer that predict patient responsiveness to specific targeted therapies. Elevated Src activity is associated with progression of many human cancers, and Src has attracted interest as a therapeutic target. This study employed a mass spectrometry-based phosphotyrosine (pTyr) proteomics strategy to reveal a panel of candidate diagnostic biomarkers for elevated Src activity.

http://pubs.acs.org/cgi-bin/article.cgi/jprobs/2008/7/i08/html/pr800187n.html,
http://pubs.acs.org/cgi-bin/sample.cgi/jprobs/2008/7/i08/html/pr8004474.html

---

Molecular imaging of therapeutic response to epidermal growth factor receptor blockade in colorectal cancer.

Non-invasive molecular imaging is capable of visualizing and quantifying cellular and physiological processes in vivo. Manning et al. report concomitant use of three complementary imaging metrics as correlative biomarkers of therapeutic efficacy of cetuximab in human colorectal cancer (CRC) cell line xenografts. The reported imaging approaches, which include metrics of epidermal growth factor (EGF) uptake, apoptosis, and proliferation, were evaluated within the context of cetuximab-sensitive (wild-type KRAS) and cetuximab-resistant (mutant KRAS) models. Imaging data closely agreed with immunohisto-chemical (IHC) analysis of tumor tissues suggesting the suitability of these approaches for serial monitoring of the biological effects of EGF receptor inhibition in vivo.

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

Head and Neck

University of Michigan

Wolf, Gregory T., M.D.

Predictive effects of biomarkers on outcome of individual patients in clinical trials.

In Worden et al., the response to induction chemotherapy and concurrent chemo-radiation for individual patients is shown to be directly related to the presence and copy number of high risk HPV in the patients' oropharyngeal cancers. Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: response and survival positively associated with HPV16 copy number, Worden et al., J Clin Oncol 26:3138-46, 2008

http://jco.ascopubs.org/cgi/content/full/26/19/3138

Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: response and survival positively associated with HPV16 copy number.

In Kumar et al. (JCO) Additional biomarkers (assessed in pretreatment biopsies) and patient factors are used to refine the predicted outcome for each individual patient enrolled in the same trial reported by Worden et al. In this trial Kumar et al. show that together EGFR expression, HPV presence and titer, smoking, and p53 and Bcl-xL as dual markers all predict survival of individual patients. Kumar, et al EGFR, p16, HPV Titer, Bcl-xL and p53, sex, and smoking as indicators of response to therapy and survival in oropharyngeal cancer J Clin Oncol 26:3128-37, 2008

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18474879

EGFR, p16, HPV Titer, Bcl-xL and p53, sex, and smoking as indicators of response to therapy and survival in oropharyngeal cancer.

In Kumar et al., (Arch Otolaryngol Head Neck Surg) the combination of p53 and Bcl-xL in pretreatment biopsies identify three risk groups for larynx preservation in the chemotherapy arm of the VA Larynx Cancer Trial. Those tumors with low p53 and low Bcl-xL all responded to chemotherapy and none of the patients with tumors in this category required laryngectomy. In patients with tumors that express low p53 and High Bcl-xL (previously defined in the laboratory as a cisplatin resistant phenotype) were 16 times more likely to require laryngectomy after induction chemotherapy than those patients with low risk tumors. Patients whose tumors expressed high p53 and either low or high Bcl-xL had intermediate risk of failure to respond to

chemotherapy and had a 4 fold increased risk of laryngectomy after induction chemotherapy.Kumar, et al. Expression of p53 and Bcl-xL as predictive markers for larynx preservation in advanced laryngeal cancer. Arch Otolaryngol Head Neck Surg 134:363-9, 2008

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18474878

Expression of p53 and Bcl-xL as predictive markers for larynx preservation in advanced laryngeal cancer.

These important advances, when further refined, will allow physicians and scientists working together to use the biological marker profile of each patient's oropharynx or larynx cancer together with the patient's behavioral factors to predict response to various therapies and thereby assign each patient to the most effective therapy for their individual tumor and personal characteristics.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18427001

Johns Hopkins University

Sidransky, David, M.D.

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

We observed that TC-1 tumor-bearing mice treated with radiotherapy combined with therapeutic HPV DNA vaccination targeting E7 generated significant therapeutic antitumor effects and the highest frequency of E7-specific CD8(+) T cells in the tumors and spleens of treated mice. Furthermore, radiotherapy treatment rendered TC-1 tumor cells more susceptible to lysis by E7-specific CTLs. Thus, our data indicate that TC-1 tumor-bearing mice treated with the chemotherapy in combination with radiation and therapeutic HPV DNA vaccination generate significantly enhanced therapeutic antitumor effects.

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

Potent inhibition of thyroid cancer cells by the MEK inhibitor PD0325901 and its potentiation by suppression of the PI3K and NF-kappaB pathways.

This study demonstrated that 1) inhibition of thyroid cancer cells by MEK inhibitors is BRAF mutation-dependent 2) Additive or synergistic inhibition could be achieved by simultaneously targeting both the MAP kinase pathway and PI3K/Akt pathway or NFkappa pathway in thyroid cancer cells. The results have strong therapeutic implications for thyroid cancer.

http://www.ncbi.nlm.nih.gov/pubmed/18651802?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

---

BRAF V600E maintains proliferation, transformation, and tumorigenicity of BRAF-mutant papillary thyroid cancer cells.

This study demonstrated that BRAF V600E mutant is required for the maintenance of cell proliferation and tumor growth of thyroid cancers derived from cells harboring this mutation and thus provided important therapeutic implications for targeted therapy of thyroid cancer.

http://www.ncbi.nlm.nih.gov/pubmed/17374713?ordinalpos=7&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

---

Leukemia

University of Texas MD Anderson Cancer Center

Issa, Jean-Pierre, M.D.

Mechanisms of resistance to 5-aza-2'-deoxycytidine in human cancer cell lines.

This study addresses the mechanisms of resistance to the hypomethylating drug decitabine. The main mechanisms of resistance in-vitro relate to pharmacologic parameters, and impact minimally resistance to another hypomethylating drug, azacitidine. The lack of cross resistance between decitabine and azacitidine is of potential clinical relevance.

http://www.ncbi.nlm.nih.gov/pubmed/18931345

An Sp1/Sp3 binding polymorphism confers methylation protection.

This study addresses the mechanisms of DNA hypermethylation in cancer. The main finding is that polymorphisms in the promoter can affect predisposition to methylation by modulating binding of trans-acting protective factors. The data provide a novel mechanism by which genetic polymorphisms can influence an epigenetic state.

http://www.ncbi.nlm.nih.gov/pubmed/18725933

Aberrant CpG island methylation in acute myeloid leukemia is accentuated at relapse.

This study examines epigenetic mechanisms of disease progression in acute myeloid leukemia. The data show marked accentuation of DNA methylation in some patients at relapse post chemotherapy-induced remission. The data suggest that DNA methylation is involved in AML progression and provide a rationale for the use of epigenetic agents in remission maintenance

http://www.ncbi.nlm.nih.gov/pubmed/18523155

Lung

University of Colorado Cancer Center

Bunn, Paul

Increased EGFR gene copy number detected by fluorescent in situ hybridization predicts outcome in non-small-cell lung cancer patients treated with cetuximab and chemotherapy.

EGFR inhibitors have demonstrated significant effect in patients with advanced Non-Small Cell Lung Cancer (NSCLC). It was first demonstrated with the EGFR tyrosine kinase inhibitors (TKIs) in 2nd or 3rd line therapy after failure of conventional chemotherapy. However, most lately the EGFR monoclonal antibody, cetuximab, has been proven effective in patients with advanced NSCLC as 1st line therapy. Although, the agent has been proven effective it is still not known, which patients will have clinical effect of this agent. In this published study from the University of Colorado and the Southwest Oncology Group, we have demonstrated that NSCLC patients, who has a tumor containing increased EGFR gene copy number detected by fluorescence in situ hybridization (FISH) have a significant prolongation of progression free and overall survival after therapy with chemotherapy in combination with cetuximab. The EGFR FISH positive patients (about 50% of the patients) had twice as long progression free survival and overall survival compared to the EGFR FISH negative patients. Thus, the study indicates that EGFR FISH is a strong predictive marker for cetuximab containing therapy in NSCLC. This will now be validated in a large prospective study."

http://jco.ascopubs.org/cgi/content/full/26/20/3351

Lymphoma

University of Iowa- Mayo Clinic

Weiner, George J.

A polymorphism in the complement component C1qA correlates with prolonged response following rituximab therapy of follicular lymphoma.

Despite its certain clinical value, the mechanisms responsible for the efficiency of anti-CD20 therapy of lymphoma remain unclear. We found that a complement polymorphism associates with duration of response to rituximab therapy of follicular lymphoma. In addition to suggesting a potential use for this polymorphism as an outcome predictor of rituximab therapy in patients with follicular lymphoma, the results could have a significant impact on our understanding the role of complement in immunotherapy, and, in turn, make possible the selection of monoclonal antibodies with engineered function and improved clinical response.

http://www.ncbi.nlm.nih.gov/pubmed/18927313

Johns Hopkins University

Ambinder, Richard F., M.D., Ph.D.

Bortezomib-induced enzyme-targeted radiation therapy in herpesvirus-associated tumors.

The study investigates the possibility of using a pharmacologic agent to modulate viral gene expression to target radiotherapy to tumor tissue. In a mouse model, targeting of a therapeutic radiopharmaceutical required activation of viral gene expression by pretreatment with bortezomib to slow or stop tumor growth or to achieve tumor regression. Bortezomib-induced enzyme-targeted radiation therapy illustrates the possibility of pharmacologically modulating tumor gene expression to result in targeted radiotherapy

http://www.nature.com/nm/journal/v14/n10/full/nm.1864.html

Ovarian

University of Washington, Fred Hutchinson Cancer Research Center

Urban, Nicole, Sc.D

Circulating microRNAs as stable blood-based markers for cancer detection.

Improved approaches for the detection of common epithelial malignancies are urgently needed to reduce the worldwide morbidity and mortality caused by cancer. MicroRNAs (miRNAs) are small (≈22 nt) regulatory RNAs that are frequently dysregulated in cancer and have shown promise as tissue-based markers for cancer classification and prognostication, important for Predictive Medicine. We show here that miRNAs are present in human plasma in a remarkably stable form that is protected from endogenous RNase activity. Our results establish the measurement of tumor-derived miRNAs in serum or plasma as an important approach for the blood-based detection of human cancer

http://www.pnas.org/content/105/30/10513

Use of cancer-specific yeast-secreted in vivo biotinylated recombinant antibodies for serum biomarker discovery.

Strategies to discover circulating protein markers of ovarian cancer are urgently needed. We developed a novel technology that permits us to isolate recombinant antibodies directed against the potential serum biomarkers, to facilitate the further development of affinity reagents necessary to construct diagnostic tests. The novel strategy described in this manuscript allows the identification of candidate biomarkers that can be variants of normally expressed proteins or that display cancer-specific post-translational modifications which has important implications for Predictive and Personalized Medicine.

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=18652693

Systematic evaluation of candidate blood markers for detecting ovarian cancer.

We selected 14 candidate blood markers of serous ovarian cancer for which assays were available to measure their levels in serum or plasma, based on our analysis of global gene expression data and on literature searches. We evaluated the performance of these candidate markers individually and in combination by measuring them in overlapping sets of serum (or plasma) samples from women with clinically detectable ovarian cancer and women without ovarian cancer. Based on sensitivity at high specificity, we determined that 4 of the 14 candidate

markers-MUC16, WFDC2, MSLN and MMP7-warrant further evaluation in precious serum specimens collected months to years prior to clinical diagnosis to assess their utility in early detection which has implications for Predictive Medicine.

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=18612378

Combining a symptoms index with CA125 to improve detection of ovarian cancer.

This study pertains to Participatory and Predictive Medicine and sought to examine whether an index based on the specific pattern of symptoms commonly reported by women with ovarian cancer could be used in combination with CA 125 to improve the sensitivity or specificity of experimental methods of screening for ovarian cancer. A prospective case-control study design was used. The addition of a symptom index to CA 125 created a composite index with a greater sensitivity for the detection of ovarian cancer than CA 125 alone and identified >80% of women with early-stage disease.

http://www3.interscience.wiley.com/journal/120195069/abstract?CRETRY=1&SRETRY=0

Pancreatic

Mayo Clinic, Rochester

Petersen, Gloria M., Ph.D

Association with Lymphoblastoid Cell Expression. Cancer Res, 68: 7050-8, 2008

We identified candidate genes including NT5C3, a dephosphorylating enzyme as well as FKBP51, an immunophilin can influence the gemcitabine sensitivity at the cellular level. These proteins are potential biomarkers to determine the response to gemcitabine.

http://cancerres.aacrjournals.org/cgi/content/full/68/17/7050

Mitochondrial Genetic Polymorphisms Do Not Predict Survival in Patients with Pancreatic Cancer. Cancer Epidemiol Biomarkers Prev, 17: 2512-3, 2008

The role of host mitochondrial variation has been hypothesized to influence survival in pancreatic cancer, and a particular polymorphism (16519T) was reported to be associated with worse survival. Our comprehensive analysis of 990 unselected pancreatic adenocarcinoma cases shows that there is no association with survival.

http://cebp.aacrjournals.org/cgi/reprint/17/9/2512

Incidence, Prognosis and Recent Trend Toward Improved Survival.

This is the first comprehensive analysis of SEER data to estimate incidence of PNETs (1.8 in females and 2.6 in males). There has been a trend from 1973 to 2000 of improved survival, not explained by earlier diagnosis or stage migration.

http://annonc.oxfordjournals.org/cgi/content/abstract/19/10/1727

Prostate

University of Washington, Fred Cancer Research Center

Nelson, Peter S.

Association of TMPRSS2-ERG gene fusion with clinical characteristics and outcomes: results from a population-based study of prostate cancer.

Studies have shown that the TMPRSS2-ERG gene fusion is associated with prostate cancer recurrence, progression and disease-specific death. We found no association with prostate cancer-specific death. However, this could be due to the limited number of deaths in the population studied, as there was a suggestion of poor disease-specific survival in patients with multiple copies of the fusion. In addition, we found a significant association between a SNP located in the TMPRSS2 gene and fusion type and number. These findings, if confirmed, may provide insight into the mechanism by which the fusion occurs and have an impact on the method of elucidating indolent from more aggressive prostate cancers.

http://www.biomedcentral.com/1471-2407/8/230

University of Michigan

Pienta, Kenneth J., M.D.

Golgi protein GOLM1 is a tissue and urine biomarker of prostate cancer.

Through meta-analysis of expression array data from multiple prostate cancer studies, we identified GOLM1 (Golgi membrane protein 1, Golm 1) as consistently up-regulated in clinically localized prostate cancer. Prostate epithelial cells were identified as the cellular source of GOLM1 expression using laser capture microdissection. GOLM1 immunoreactivity was detected

in the supernatants of prostate cell lines and in the urine of patients with prostate cancer. transcript levels were measured in urine sediments using quantitative PCR on a cohort of patients presenting for biopsy or radical prostatectomy. We found that urinary GOLM1 mRNA levels were a significant predictor of prostate cancer.

http://www.ncbi.nlm.nih.gov/pubmed/18953438?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

---

A fluorescence in situ hybridization screen for E26 transformation-specific aberrations: identification of DDX5-ETV4 fusion protein in prostate cancer.

Recurrent gene fusions involving E26 transformation-specific (ETS) transcription factors ERG, ETV1, ETV4, or ETV5 have been identified in 40% to 70% of prostate cancers. In this study, we used a comprehensive fluorescence in situ hybridization (FISH) split probe strategy interrogating all 27 ETS family members and their five known 5' fusion partners in a cohort of 110 clinically localized prostate cancer patients.By screening the entire ETS transcription factor family for rearrangements, we found that a large fraction of prostate cancers (44%) cannot be ascribed to an ETS gene fusion, an observation which will stimulate research into identifying recurrent non-ETS aberrations in prostate cancers. Second, we identified SLC45A3 as a novel 5' fusion partner of ERG; previously, TMPRSS2 was the only described 5' partner of ERG. Third, we identified two prostate-specific, androgen-induced genes, FLJ35294 and CANT1, as 5' partners to ETV1 and ETV4. Fourth, we identified a ubiquitously expressed, androgen-insensitive gene, DDX5, fused in frame with ETV4, leading to the expression of a DDX5-ETV4 fusion protein.

http://www.ncbi.nlm.nih.gov/pubmed/18953438?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

---

Chromosome 17q12 variants contribute to risk of early-onset prostate cancer.

Recent studies of sporadic prostate cancer suggest that genetic variation on chromosome 17q is associated with prostate cancer risk. We show that the genetic risk conferred by two of these variants (in the TCF2 gene) is substantially increased, nearly two-fold higher, in men predisposed to develop early-onset prostate cancer. We estimate that men carrying two risk alleles at either of the TCF2 loci are nearly 4 times more likely to develop early onset prostate cancer (<50 years) relative to men with no risk alleles, a finding that hints at the potential for early genetic screening to identify a subset of men who are at greater risk of developing prostate cancer, independent of family history.

http://www.ncbi.nlm.nih.gov/pubmed/18794152?ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

---

Johns Hopkins University

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

Evidence for two independent prostate cancer risk–associated loci in the HNF1B gene at 17q12.

In twin studies, inheritance has been found to contribute more to the development of prostate cancer than any other common human cancer. Genome-wide mapping studies involving prostate cancer kindreds and population cohorts have identified several candidate gene loci altering the risk for prostate cancer. This study, using a Swedish (CAPS with 2,899 prostate cancer cases and 1,722 controls) and an American (JHH with 1,527 prostate cancer cases and 482 controls) cohort, pinpointed several polymorphic variants at HNF1B that increased prostate cancer risk.

http://www.nature.com/ng/journal/v40/n10/abs/ng.214.html

DNA hypomethylation arises later in prostate cancer progression than CpG island hypermethylation and contributes to metastatic tumor heterogeneity.

Over-methylation of CpG dinucleotides, leading to gene silencing, has been found to drive the early pathogenesis of prostate cancer and other common cancers. Under-methylation, which also appears commonly in many cancers, has less well understood role in cancer development. This study found that hypomethylation appeared late during the pathogenesis of prostate cancer (at the time of progression to metastasis), affected repeat sequences prone to recombination (increasing opportunities for genetic instability), and resulted in abnormal expression of normally inactive genes in a heterogeneous fashion.

http://www.ncbi.nlm.nih.gov/pubmed/18974140?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

---

Memorial Sloan Kettering Cancer Center

Scardino, Peter T., M.D.

A panel of kallikrein markers can reduce unnecessary biopsy for prostate cancer: data from the European Randomized Study of Prostate Cancer Screening in Göteborg, Sweden.

Most men with elevated levels of prostate-specific antigen (PSA) do not have prostate cancer, yet many undergo prostate biopsies to determine if they do. The investigators used a panel of four human kallikrein markers (total, free, and intact PSA, as well as human kallikrein 2) to successfully predict the biopsy results of men with elevated levels of PSA. This model could be used to determine which men should be advised to have a biopsy, eliminating the pain, inconvenience, financial costs, and risk of infection for over 750,000 American men who receive unnecessary biopsies each year.

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2474851

University of California, Los Angelus

Reiter, Robert

Pomegranate extract inhibits androgen-independent prostate cancer growth through a nuclear factor-kappaB-dependent mechanism.

In a LAPC4 xenograft model, pomegranate extract (PE) delayed the emergence of LAPC4 androgen-independent xenografts in castrated mice through inhibition of proliferation and induction of apoptosis. Moreover, the observed increase in NF-kappaB activity during the transition from androgen dependence to androgen independence in the LAPC4 xenograft model was abrogated by PE. Our study represents the first description of PE as a promising dietary agent for the prevention of the emergence of androgen independence that is driven in part by heightened NF-kappaB activity.

http://mct.aacrjournals.org/cgi/content/full/7/9/2662

Ellagitannin-rich pomegranate extract inhibits angiogenesis in prostate cancer in vitro and in vivo.

In our study there was a 44% risk of upgrading of Gleason grade when comparing the radical prostatectomy specimen to the prostate biopsy specimen. Cancer found in smaller prostates has an increased risk of upgrading relative to large prostates. This information is important for design of clinical trials and patient counseling. For example, a men with small prostates offered less aggressive prostate cancer therapy may be at a higher risk of recurrence after treatment.

http://www3.interscience.wiley.com/cgi-bin/fulltext/121400357/HTMLSTART

Obesity is a significant risk factor for prostate cancer at the time of biopsy.

In men undergoing prostate biopsy for an abnl DRE or elevated PSA, obesity increases the risk of having prostate cancer. This work is highly relevant to our ongoing studies in obesity and

prostate cancer evaluating if obesity may be a modifiable risk factor and if weight loss has the potential to reduce the risk of prostate cancer.

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6VJW-4T8H36R-5&_user=4423&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_version=1&_urlVersion=0&_userid=4423&md5=79a70196ebba0b6c90682c007d006ab1

Obesity and positive surgical margins by anatomic location after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital database.

Obesity was found to increase the risk of positive surgical margins following radical prostatectomy with the greatest risk being at the prostate apex. Urologists may need to take special efforts to obtain wider surgical margins in obese men.

http://www3.interscience.wiley.com/cgi-bin/fulltext/121372430/HTMLSTART

Impact of nerve sparing on surgical margins and biochemical recurrence: results from the SEARCH database.

We found that unilateral and bilateral nerve sparing in properly selected patients. does not increase the risk of positive surgical margins. These data are important for urologists to consider as we walk the fine line of curing cancer but maintaining quality of life.

http://www.nature.com/pcan/journal/vaop/ncurrent/full/pcan200840a.html

---

Geometric Interpretation of Gene Co-Expression Network Analysis.

The article provides the theoretical backbone for the weighted gene co-expression network analysis software that is used to identify cancer related gene networks. The software implements several options for automatic and manual gene module detection and gene selection ("network screening").

http://www.ploscompbiol.org/article/info:doi/10.1371/journal.pcbi.1000117

Suppression of prostate cancer nodal and systemic metastasis by blockade of the lymphangiogenic axis.

This study evaluated the contribution of blood and lymphatic vascular axis to prostate cancer nodal and systemic metastasis. The findings suggest that blood vasculature plays a dominant role in tumor growth while lymphangiogenesis is more critical for metastasis. This study provides a clearer therapeutic strategy to target these two vascular axes.

http://cancerres.aacrjournals.org/cgi/reprint/68/19/7828

Adenovirus-mediated gene expression imaging to directly detect sentinel lymph node metastasis of prostate cancer.

This study reports a novel technology to directly image and to detect the presence of prostate cancer nodal metastasis. This method exploits the lymphotropic property of adenovirus and the amplified prostate-specific gene expression system incorporated into the viral vector. We showed that specific imaging signal is produced only after the adenoviral vector trafficked to the lymph node and transduce prostate cancer metastasis presented there. The specificity and non-invasive nature of this method constitute an advancement of the current technology.

http://www.nature.com/nm/journal/v14/n8/pdf/nm.1727.pdf

Melanoma

Brigham and Women's Hospital

Kupper, Thomas S., M.D.

Human squamous cell carcinomas evade the immune response by down-regulation of vascular E-selectin and recruitment of regulatory T cells.

Squamous cell carcinomas of the skin can be particularly aggressive and often lethal in immunosuppressed patients, suggested a certain level of immunosurveillance in normal individuals. This study demonstrates that SCC's modify their vasculature so as not express critical leukocyte adhesion molecules, and at the same time recruit and sequester regulatory T cells (Treg), both of which suppress the immune response. the TLR7 agonist imiquimod both enhances E selectin expression on tumor vasculature and facilitates recruitment of effector T cells that kill the tumor, while at the same time paralyzinig the T regulatory cells. This pehnomenon can be generalized to most if not all squamous cell carcinomas of any tissue.

http://jem.rupress.org/cgi/content/full/205/10/2221

University of Texas MD Anderson Cancer Center

Grimm, Elizabeth A., Ph.D

A novel AKT3 mutation in melanoma tumours and cell lines.

We have identified the first melanoma with the mutation of AKT1 that has previously been identified in colon, breast, and lung cancer patients. We have also identified a novel mutation in

AKT3 in melanoma clinical specimens and cell lines, which has never been identified in any other cancer. These findings increase our understanding of the molecular events which may contribute to the pathogenesis of melanoma, and provide new research tools to perform further investigations to identify optimal therapies for patients with these alterations.

http://www.nature.com/bjc/journal/v99/n8/full/6604637a.html

Visualizing fewer than 10 mouse T cells with an enhanced firefly luciferase in immunocompetent mouse models of cancer.

This study describes a new method that, for the first time, allows the sensitive detection of adoptively transferred, melanoma-specific T cells in live animals through whole-body imaging. This technique will directly enhance mechanistic and therapeutic studies of anti-melanoma immunotherapy in animals and holds promise for application in melanoma patients receiving adoptive T cell therapy.

http://www.pnas.org/content/105/38/14342

NF-kappaβ mediates mitogen-activated protein kinase pathway-dependent iNOS expression in human melanoma.

Tumor expression of inducible nitric oxide synthase (iNOS) predicts poor outcomes for melanoma patients. We have reported the regulation of melanoma iNOS by the mitogen-activated protein kinase (MAPK) pathway. In this study, we test the hypothesis that NF-kappaB mediates this regulation.

http://www.nature.com/jid/journal/vaop/ncurrent/abs/jid2008205a.html

---

Microscopic Tumor Burden in Sentinel Lymph Nodes Predicts Synchronous Nonsentinel Lymph Node Involvement in Patients With Melanoma.

JE Gershenwald, RHI Andtbacka, VG Prieto, MM Johnson, A Diwan, JE Lee, PF Mansfield, JN Cormier, CW Schacherer, MI Ross We and others have demonstrated that additional positive lymph nodes (LNs) are identified in only 8% to 33% of patients with melanoma who have positive sentinel LNs (SLNs) and undergo complete therapeutic LN dissection (cTLND). In melanoma patients with positive SLNs, SLN tumor burden, primary tumor thickness, and number of SLNs harvested may be useful in identifying a group at low risk for positive non-SLNs and be spared the potential morbidity of a cTLND.

http://jco.ascopubs.org/cgi/content/full/26/26/4296
