SPORE Scientific Advances

July-December

2010

NCI Translational Research Program

BLADDER

M.D. Anderson Cancer Center

Dinney, Colin, M.D.

(Chen, …et al.)

Genetic variations in the sonic hedgehog pathway affect clinical outcomes in non-muscle-invasive bladder cancer

Non-muscle invasive bladder cancer (NMIBC) accounts for about 80% of all bladder cancer cases and the development of recurrence is the major clinical problem for NMIBC patients. This study identified several novel genetic predictors of recurrence in patients receiving transurethral resection (TUR) only or receiving TUR plus BCG. The identification of clinically applicable biomarkers is critical for personalized management of NMIBC patients. (Cancer Prev Res) - PMCID: PMC2955764

http://www.ncbi.nlm.nih.gov/pubmed/20858759

(Chen, …et al.)

Genetic variations of the PI3K-AKT-mTOR pathway and clinical outcome in muscle invasive and metastatic bladder cancer patients

The phosphoinositide-3 kinase (PI3K)-AKT- mammalian target of rapamycin (mTOR) pathway is an important cellular pathway controlling cell growth, tumorigenesis, cell invasion and drug response. This study systematically evaluated nearly 300 single nucleotide polymorphisms (SNPs) in 20 genes of the PI3K-AKT-mTOR pathway and found 3 SNPs as predictors of overall survival in muscle invasive and metastatic bladder cancer (MIMBC) patients. Three SNPs may provide insight into disease management and development of target therapies. (Carcinogenesis) - PMCID: PMC2915631

http://www.ncbi.nlm.nih.gov/pubmed/20530239

(Su, …et al.)

***TAp63* suppresses metastasis through coordinate regulation of *Dicer* and miRNAs**

We found that the p53 family member, TAp63, suppresses metastasis through regulation of microRNAs. This has implications for using miRNAs as therapy for cancer patients with metastatic disease and alterations in the p53 family. (Nature) - PMCID: PMC3055799

http://www.ncbi.nlm.nih.gov/pubmed/20962848

(Zhang, …et al.)

Autophagy is induced by adenoviral-mediated interferon α treatment in interferon resistant bladder cancer and normal urothelial cells as a cell death protective mechanism but not by the bystander factors produced

We found that Ad-IFNα produces autophagy in both normal human urothelial and cancer cells although it only kills cancer cells. After Ad-IFNαinfection autophagesomes, an early stage of autophagy, were seen in cancer cells whereas autophagolysosomes, a later stage of autophagy, were observed mostly in normal cells by electron microscopy and other studies. These results suggest that the autophagy seen in normal urothelial cells is a protective response and is allowed to be completed, providing a survival mechanism following Ad-IFN treatment, whereas the autophagy produced in interferon resistant cancer cells is not allowed to be completed and is insufficient to significantly suppress Ad-IFNαproduced cytotoxicity. Since intravesical Ad-IFNα treatment is now in clinical trial for the treatment of BCG-resistant non-muscular invasive bladder cancer, in which approximately a 50% complete remission has already been seen without cytotoxicity these results may help explain why the normal urothelium shows no cytotoxic changes while the bladder cancer cells are killed. (Cancer Gene Ther) - PMCID: PMC2906639

http://www.ncbi.nlm.nih.gov/pubmed/20489789

BRAIN

University of California, San Francisco

Berger, Mitchel S., M.D.

(Persson, …et al.)

Non-stem cell origin for oligodendroglioma

Malignant oligodendroglioma tumors, unlike astrocytic tumors, are relatively sensitive to drug therapy and are associated with a relatively good prognosis. This study showed that oligodendroglioma tumors show characteristics of oligodendrocyte progenitor cells rather than of neural stem cells that are believed to be the origin of astrocytic tumors. These results suggest that a progenitor origin rather than a NSC origin underlies improved prognosis in oligodendroglioma patients. (Cancer Cell) - PMCID: PMC3031116

http://www.ncbi.nlm.nih.gov/pubmed/21156288

(Fan, …et al.)

Akt and autophagy cooperate to promote survival of drug-resistant glioma

Autophagy is a pro-survival process activated in glioma cells by inhibition of mTOR signaling. This study showed that inhibitors of PI3K and mTOR signaling, combined with inhibitors of autophagy, cause glioma cells to undergo apoptosis. Moreover, the PI3K-mTOR inhibitor NVP-BEZ235, which is in clinical use, synergized with the inhibitor of autophagy, chloroquine, another agent in clinical use, to induce apoptosis in glioma xenografts in vivo, providing a therapeutic approach potentially translatable to humans. (Sci Signal) - PMCID: PMC3001107

http://www.ncbi.nlm.nih.gov/pubmed/21062993

(Christensen, …et al.)

DNA methylation, isocitrate dehydrogenase mutation, and survival in glioma

Mutations in the isocitrate dehydrogenase (IDH) gene were recently shown to be associated with a specific subset of glioma. This study showed that the tumors from patients with IDH mutations also exhibited a high degree of aberrant DNA methylation, and that the prognosis of these patients was much better than that of patients with non-mutant IDH. IDH mutational status may therefore help stratify patients for clinical trials as well as provide information regarding patient prognosis. (J Natl Cancer Inst) - PMCID: PMC3022619

http://www.ncbi.nlm.nih.gov/pubmed/21163902

(Khayal, …et al.)

Evaluation of diffusion parameters as early biomarkers of disease progression in glioblastoma multiforme

Effective therapy of brain tumors requires effective monitoring drug response. This study showed that changes in brain perfusion measureable by MRI that occur in the period shortly after radiation therapy are greater in patients who progress within 6 months vs those who are progression-free for 6 months after initiation of therapy. The study also showed that the changes in diffusion parameters in this period may be more significant than those that occur early during therapy, suggesting that MRI imaging during therapy may aid in monitoring patient response. (Neuro Oncol) - PMCID: PMC2940691

http://www.ncbi.nlm.nih.gov/pubmed/20501631

Mayo Clinic

O'Neill, Brian, M.D.

(Sarkaria, …et al.)

Combination of temsirolimus (CCI-779) with chemoradiation in newly diagnosed glioblastoma multiforme (GBM) (NCCTG trial N027D) is associated with increased infectious risks

The PI3K/mTOR signaling pathway is hyperactivated in the majority of GBM tumors, and integration of specific inhibitors of this pathway into therapies for GBM is of significant clinical interest.

In this report, we demonstrate a high rate of infectious complications associated with multiple mechanisms of immune suppression following therapy with temsirolimus, radiation and temozolomide in newly diagnosed patients with GBM. These results suggest that specific consideration should be given to potential synergistic mechanisms of immunosuppression when integrating novel PI3K/mTOR inhibitors with temozolomide in GBM. (Clin Cancer Res) - PMCID: PMC2982871

http://www.ncbi.nlm.nih.gov/pubmed/20921209

M.D. Anderson Cancer Center

Yung, Alfred, M.D.

(Bonato, ...et al.)

Bayesian ensemble methods for survival prediction in gene expression data

This study examined gene expression data from TCGA glioblastoma data. It identified a new method of data analysis that provides a new way to analyze survival data. The results directly link to SPORE Project 3 by providing a method to identify biomarkers of outcome in glioblastoma. The study describes an innovative method of data analysis that utilizes a Bayesian approach. This can add to our existing tools by finding novel biomarkers from microarray data. SPORE Project 3 directly interacted with bioinformatics faculty to frame the question and provide guidance as to the clinical relevance of the analysis. (Bioinformatics) - PMCID: PMC3031034
http://www.ncbi.nlm.nih.gov/pubmed/21148161

(Jiang, ...et al.)

RB-E2F1: molecular rheostat for autophagy and apoptosis

Examination of the mechanisms underlying the autophagy induced by Delta-24-RGD led to the finding that the main target of the adenovirus the Rb/E2F1 proteins were involved in the regulation of autophagy. In these studies, transfer of the RB protein resulted in the induction of autophagy by represing E2F1, a factor required for adenovirus replication. Moreover, that transfer of E2F1 to glioma cells resulted in apoptosis. This new information about how the interplay of autophagy and poptosis is regulated may be useful to design more effective theraputic oncolytic viruses. We report for the first time a role for Rb in the regulation of autophagy. Because adenoviruses target this protein for their replication, a mechanistic link between Rb and autophagy is of interest for the development of onoclytic adenoviruses. (Autophagy) - PMID: 20935482
http://www.ncbi.nlm.nih.gov/pubmed/20935482

(Schreck, ...et al.)

The Notch target Hes1 directly modulates Gli1 expression and Hedgehog signaling: a potential mechanism of therapeutic resistance

In this collaborative project, we show that therapeutic targeting of the Notch developmental pathway leads to activation of sonic hedgehog and wingless signaling and a consequent failure in induction of apoptosis in tumor cells. However, targeting both Notch and sonic hedgehog pathways induces apoptosis and abrogates anchorage independent growth. These findings provide some of the earliest evidence that simultaneous targeting of multiple pathways may be more efficacious in eliminating tumor cells and may potentially have greater clinical benefit for patients with brain tumors. The SPORE Career Development Program has provided support for ongoing pre-clinical research in our lab examining the use of gamma secretase inhibitors that target Notch signaling in conjunction with small molecule inhibitors of the developmentally important REST signaling in medulloblastoma. (Clin Cancer Res) - PMID: 21169257
http://www.ncbi.nlm.nih.gov/pubmed/21169257

(Kang, …et al.)

Isolation and perivascular localization of mesenchymal stem cells from mouse brain

Mesenchymal stem cells are of interest because of their potential use in the therapy of a variety of neurological disorders. In this study, we sought to determine the extent to which cells with the features of MSCs exist in normal brain tissue and to determine the location of these cells in the brain. Identifying MSCs in normal brain tissue would provide new insight into the capacity of central nervous system tissues to respond to inflammation and tumor formation. We found that cells similar to bone marrow-derived MSCs in terms of in vitro growth, surface markers, and trilineage mesenchymal differentiation, can be isolated from the brains of normal mice. These brain-derived MSCs are located within the vascular niche and may represent a population of nonneural progenitor/stem cells that act as a source of mesenchymal elements within the brain. They may also participate in the response of the brain to tissue injury and stress, such as stroke, trauma, and tumorigenesis. (Neurosurgery) - PMID: 20651630
http://www.ncbi.nlm.nih.gov/pubmed/20651630

(Tchaicha, …et al.)

A mosaic mouse model of astrocytoma identifies alphavbeta8 integrin as a negative regulator of tumor angiogenesis

Angiogenesis involves a complex set of cell-cell and cell-extracellular matrix (ECM) interactions that coordinately promote and inhibit blood vessel growth and sprouting. This report indicates that tumor cells induce pathological angiogenesis by suppressing expression of the ECM protein receptor alphavbeta8 integrin. Finally, these results show that an adhesion and signaling axis normally involved in developmental brain angiogenesis is pathologically exploited in adult brain tumors, and may be amenable to anti-angiogenenic therapy. This report identifies the novel finding that tumor cells induce pathological angiogenesis by suppressing expression of the ECM protein receptor alphavbeta8 integrin. Diminished integrin expression in astrocytoma cells leads to reduced activation of latent TGFbetas, resulting in impaired TGFbeta receptor signaling in tumor-associated endothelial cells. (Oncogene) - PMCID: PMC3037767
http://www.ncbi.nlm.nih.gov/pubmed/20531304

BREAST

Mayo Clinic

Ingle, James N., M.D.

(Ingle, …et al.)

Genome-wide associations and functional genomic studies of musculoskeletal adverse events in women receiving aromatase inhibitors

Musculoskeletal adverse events (MS-AEs) have become recognized as a major problem for women receiving aromatase inhibitor (AI) adjuvant therapy and were found to be the major reason that women discontinued their AI treatment on NCI clinical trial MA.27. The identification of SNPs and a gene (TCL1A) related to these MS-AEs and to an inflammatory cytokine (IL17) provides a focus for further research to identify women at risk for these side effects and to explore mechanisms for these adverse events. The determination of the mechanism for these MS-AEs would enable a focused approach to amelioration of symptoms thus facilitating compliance and improving the benefits of AIs for women with early breast cancer. (J Clin Oncol) - PMCID: PMC3020700

http://www.ncbi.nlm.nih.gov/pubmed/20876420

(Cichon, …et al.)

Microenvironmental Influences that Drive Progression from Benign Breast Disease to Invasive Breast Cancer

Signals from the tumor microenvironment involved in breast cancer progression represent potential points for therapeutic intervention. This manuscript describes key features of the microenvironment that are involved in progression of benign breast disease to invasive breast cancer; inhibition or modulation of these signals could be a novel strategy for prevention of breast cancer development. (J Mammary Gland Biol Neoplasia) - PMCID: PMC3011086

http://www.ncbi.nlm.nih.gov/pubmed/21161341

University of California, San Francisco

van't Veer, Laura, M.D.

(Stohr, …et al.)

The terminal telomeric DNA sequence determines the mechanism of dysfunctional telomere fusion

This work demonstrated that the terminal telomeric sequence itself determines the mechanism of dysfunctional telomere fusion, with self-complementary terminal sequences in particular engaging an alternative fusion pathway that generates numerous sister chromatid fusions. These results suggest that wild-type telomeric sequence, which lacks significant self-complementarity, may protect genome stability in part through avoidance of this alternative fusion pathway. In addition, these results indicate that mutant telomerase templates that add self-complementary terminal repeats may be optimal for inhibiting proliferation of a wide variety of cancers in a translational setting. (Mol Cell) - PMCID: PMC2920734

http://www.ncbi.nlm.nih.gov/pubmed/20670897

(Lapuk, …et al.)

Exon-level microarray analyses identify alternative splicing programs in breast cancer

Protein isoforms produced by alternative splicing (AS) of many genes have been implicated in several aspects of cancer genesis and progression. These observations motivated a genome-wide assessment of AS in breast cancer. This identified 181 splice events representing 156 genes as candidates for AS about half of which were associated with basal, luminal, or claudin-low breast cancer subtypes. Exons involved in claudin-low subtype-specific AS were significantly associated with the presence of evolutionarily conserved binding motifs for the tissue-specific Fox2 splicing factor. (Mol Cancer Res) - PMCID: PMC2911965

http://www.ncbi.nlm.nih.gov/pubmed/20605923

(Braithwaite, …et al.)

Long-term prognostic role of functional limitations among women with breast cancer

With advances in treatment, more breast cancer survivors are living longer, but it is not known how physical limitations following initial treatment affect morbidity and mortality. In this study of longer-term breast cancer survivors, functional limitations following initial treatment were found to have an adverse effect on overall and competing-cause survival, but not breast cancer–specific survival. Failure to address physical functioning after initial diagnosis and treatment of breast cancer survivors may have adverse effects on their quality of life and longevity. (J Natl Cancer Inst) - PMCID: PMC2950169

http://www.ncbi.nlm.nih.gov/pubmed/20861456

(Swarbrick, …et al.)

miR-380-5p represses p53 to control cellular survival and is associated with poor outcome in MYCN-amplified neuroblastoma

The study describes the discovery of a new oncogenic microRNA that can directly suppress the expression of the tumor suppressor p53. We found that when over-expressed along with activated RAS it could block senescence and transform primary breast epithelial cells in a syngeneic breast cancer transplant model. The miRNA was found to be abundantly expressed in mouse stem cells and primary human neuroblastoma tumors, and was associated with poor outcome in patients when MYCN was over-expressed. Inhibition of this miRNA could up-regulate p53 and resulted in death of human neuroblastoma cells and primary mouse neuroblastoma tumors in vivo. (Nat Med) - PMCID: PMC3019350

http://www.ncbi.nlm.nih.gov/pubmed/20871609

(Yau, …et al.)

A multigene predictor of metastatic outcome in early stage hormone receptor-negative and triple-negative breast cancer

Various multigene predictors of breast cancer clinical outcome have been developed and validated but have proved prognostic only for hormone receptor (HR)-positive subsets. There is a notable absence of and strong clinical need for outcome predictors validated against hormone receptor negative (HRneg) breast cancers, particularly those lacking HER2/ErbB2 overexpression and known as triple-negative (Tneg) cases, which lack targeted therapy options. While these are generally the most aggressive breast cancer subsets, most early stage HRneg and Tneg breast cancer patients are cured

with conservative treatment alone, yet all invariably receive aggressive adjuvant chemotherapy. (Breast Cancer Res) - PMID: 20946665

http://www.ncbi.nlm.nih.gov/pubmed/20946665

University of Chicago

Olopade, Olufunmilayo, M.D.

(Stark, …et al.)

Population differences in the rate of proliferation of international HapMap cell lines

There are many groups (including other Breast SPOREs) utilizing HapMap lymphoblastoid cell lines in pharmacogenomic discovery with the objective to understand genetic variants associated with pharmacologic data. The significance of the work is that we have identified that there is inter-individual and inter-ethnic differences in rate of cellular proliferation for these cell lines. The growth rate differences, to some extent, is due to genetic factors and should be used as a confounder for pharmacogenomic studies that utilize these cell lines. (Am J Hum Genet) - PMCID: PMC2997375

http://www.ncbi.nlm.nih.gov/pubmed/21109222

(Chen, …et al.)

Computerized assessment of breast lesion malignancy using DCE-MRI robustness study on two independent clinical datasets from two manufacturers

We demonstrated the robustness of our computerized classification system in the task of distinguishing between malignant and benign breast lesions on dynamic contrast-enhanced (DCE) MRI images from two manufacturers. Our study showed the feasibility of developing a computerized classification system that is robust across different scanners. (Acad Radiol) - PMCID: PMC2907891

http://www.ncbi.nlm.nih.gov/pubmed/20540907

(Yuan, …et al.)

Multimodality computer-aided breast cancer diagnosis with FFDM and DCE-MRI

A computer-assisted detection-aided scheme that combines features extracted from FFDM and DCE-MRI images may be advantageous to single-modality CAD in the task of differentiating between malignant and benign lesions. (Acad Radiol) - PMID: 20692620

http://www.ncbi.nlm.nih.gov/pubmed/20692620

(Jamieson, …et al.)

Enhancement of breast CADx with unlabeled data

This study is an initial exploration of the potential for leveraging unlabeled data toward enhancing breast computer-assisted detection. (Med Phys) - PMCID: PMC2921421

http://www.ncbi.nlm.nih.gov/pubmed/20879576

(Jansen, …et al.)

Characterizing early contrast uptake of ductal carcinoma in situ with high temporal resolution dynamic contrast-enhanced MRI of the breast: a pilot study

This work demonstrated that high temporal resolution imaging combined with quantitative data analysis improves detection of ductal carcinoma in situ – primarily by improving discrimination between DCIS and normal parenchyma. This has important implications for clinical practice because it suggests ways in which Radiologists can improve sensitivity and specificity for diagnosis of early breast cancer. (Phys Med Biol) - PMID: 20858914

http://www.ncbi.nlm.nih.gov/pubmed/20858914

(Heisen, …et al.)

The use of a reference tissue arterial input function with low-temporal-resolution DCE-MRI data

This work demonstrated a new quantitative approach to analysis of dynamic contrast-enhanced MRI (DCEMRI) data from breast that can improve the diagnostic accuracy. The results show that volume transfer constant, Ktrans, a measure of vascular permeability measurements based on DCEMRI data with modest temporal resolution are significantly improved when a local arterial input function is used as input to the two compartment model. This means that whole breast DCEMRI scans can be analyzed

to produce quantitative parameters that are sensitive to early breast cancers. (Phys Med Biol) - PMID: 20679692

http://www.ncbi.nlm.nih.gov/pubmed/20679692

(Fan, …et al.)

Use of a reference tissue and blood vessel to measure the arterial input function in DCEMRI

Measurement of tumor perfusion with high temporal resolution dynamic contrast-enhanced MRI (DCEMRI) requires quantitative measurement of the contrast media arterial input function (AIF) because variations in local AIF are a major source of variability in contrast media uptake and washout kinetics. We developed a new approach to quantitative measurement of the arterial input function based on use of .signals from a reference tissue (e.g. muscle) and washout-phase signal from an artery. This method can be applied in routine clinical practice to obtain reliable estimates of the AIF – which are then used to increase the accuracy of Ktrans measurements. (Magn Reson Med) - PMCID: PMC2992085

http://www.ncbi.nlm.nih.gov/pubmed/20665893

Dana Farber/Harvard Cancer Center

Winer, Eric, M.D.

(Irie, …et al.)

PTK6 regulates IGF-1-induced anchorage-independent survival

Dr. Irie et al. demonstrate that PTK6 is a regulator of anchorage-independent survival of breast and ovarian tumor cells through modulation of IGF-1 receptor signaling. Effects of PTK6 on anchorage-independence could contribute to the poor outcomes associated with high PTK6 transcript levels found in cohorts of breast cancer patients. This study provides additional support of PTK6 as a potential therapeutic target for breast and ovarian cancer. After further study, inhibition or downregulation of PTK6 may also prove to be an effective strategy in the clinic for enhancing the response of high-grade ER+/Luminal B breast cancers to endocrine therapy or overcoming acquired resistance to these agents. (PLoS One) - PMCID: PMC2909213

http://www.ncbi.nlm.nih.gov/pubmed/20668531

(Domchek, …et al.)

Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality

This study examined the impact risk-reducing mastectomy and salpingo-oophorectomy has on reducing breast and ovarian cancer risk and mortality among women with the BRCA1 and BRCA2 genetic mutations. Women who underwent risk-reducing mastectomy showed a reduced risk of breast cancer. Additionally, researchers observed a significant reduction in all-cause, breast cancer-specific and ovarian cancer-specific mortality in women who underwent risk-reducing salpingo-oophorectomy. This study provides evidence for these surgeries as a preventive intervention option for women with BRCA1 and BRCA2 mutations. The decisions by patients to have risk-reducing surgery can be informed by genetic counseling and evaluation of other factors to determine a more precise estimate of individual risk reduction. (JAMA) - PMCID: PMC2948529

http://www.ncbi.nlm.nih.gov/pubmed/20810374

(Tamimi, …et al.)

Evaluation of a breast cancer risk prediction model expanded to include category of prior benign breast disease lesion

Based on a nested case-control study in the Nurses' Health Study II (a sub-cohort of participants in the Nurses' Health Study), researchers observed that inclusion of a benign breast disease (BBD) category significantly added to a modified Rosner-Colditz breast cancer risk prediction model. The data suggest that including a BBD category may improve breast cancer risk classification but is dependent on consistency of histologic classification of BBD lesions. Researchers note the greatest impact of this risk prediction model will be for women with reported BBD. (Cancer) - PMCID: PMC2962878

http://www.ncbi.nlm.nih.gov/pubmed/20645399

(Aroner, …et al.)

Columnar cell lesions and subsequent breast cancer risk: a nested case-control study

This study provided evidence that the presence of columnar cell lesions (CCL) may be an important marker of breast cancer risk in women with benign breast disease (BBD). The researchers evaluated this association through a nested case-control study of women with BBD within the Nurses' Health Study II (a sub-cohort of participants in the Nurses' Health Study). These data suggest that CCL may be a marker of increased risk among those with non-proliferative disease and suggest it could have

important implications for clinical management of patients with CCL. (Breast Cancer Res) - PMCID: PMC2949654

http://www.ncbi.nlm.nih.gov/pubmed/20691043

(Wu, …et al.)

Gene expression profiling of human breast tissue samples using SAGE-Seq

In this study, researchers show that SAGE-Seq is a powerful and cost-effective method for the gene expression profiling of small numbers of cells isolated from primary human tissue samples. The authors compared traditional SAGE and SAGE-Seq data sets and demonstrate the overwhelming power of SAGE-Seq to detect 20 times more differentially expressed genes with higher statistical confidence. This study provides evidence that this high-throughput sequencing technique will enable researchers to identify genes and pathways abnormally activated in breast cancer that traditional SAGE failed to identify. (Genome Res) - PMCID: PMC2989999

http://www.ncbi.nlm.nih.gov/pubmed/21045080

Vanderbilt University

Arteaga, Carlos, M.D.

(Miller, …et al.)

Hyperactivation of phosphatidylinositol-3 kinase promotes escape from hormone dependence in estrogen receptor–positive human breast cancer

This report included the first association between a PI3K activation signature in primary tumors and a poor response to aromatase inhibitors in ER+ breast cancer. With the availability of PI3K inhibitors in the clinic, this report provides a basis for combinations of currently approved endocrine therapies in breast cancer. We have already initiated a phase Ib/II study of letrozole in combination with the PI3K inhibitors BKM120 and BEZ235 (each, from Novartis) in post-menopausal patients with ER+ metastatic breast cancer that had progressed on primary endocrine therapy. (J Clin Invest) - PMCID: PMC2898598

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2898598/

University of North Carolina, Chapel Hill

Earp, H. Shelton III, M.D.

(O'Brien, …et al.)

Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study

The Carolina Breast Cancer Study (CBCS) is a population-based epidemiologic study of breast cancer in African American and white women. Long-term survival data from the CBCS, showed that basal-like breast cancer (a type of triple-negative breast cancer that expresses basal cytokeratins) carries a poor prognosis in African American as well as white women. Disparities in survival between African American and white women were actually strongest for the luminal A subtype. (Clin Cancer Res) - PMCID: PMC3029098

http://www.ncbi.nlm.nih.gov/pubmed/21169259

Baylor College of Medicine

Osborne, Kent, M.D.

(Rimawi, …et al.)

Reduced Dose and Intermittent Treatment with Lapatinib and Trastuzumab for Potent Blockade of the HER Pathway in HER-2/neu Overexpressing Breast Tumor Xenografts

Resistance to trastuzumab is a recurrent problem in treatment of HER2-positive breast cancers. More potent inhibition of the HER pathways is a promising strategy to overcome this resistance. In this paper, we studied various different combinations against the HER pathways and showed that the combination of lapatinib and trastuzumab is the most effective even with reduced doses or intermittent schedules. These findings warrant testing of reduced dosing and intermittent schedules of lapatinib and trastuzumab in the clinical setting. (Clin Cancer Res) - PMID: 21138857

http://www.ncbi.nlm.nih.gov/pubmed/21138857

(Dave, …et al.)

Loss of phosphatase and tensin homolog or phosphoinositol-3 kinase activation and response to trastuzumab or lapatinib in human epidermal growth factor receptor 2-overexpressing locally advanced breast cancers

There are indications that loss of PTEN or activating mutations of PI3-kinase may be associated with trastuzumab resistance. These studies with HER2-overexpressing cell lines and two neoadjuvant clinical trials with HER2+ breast tumors show that activation of the PI3-kinase pathway is indeed related to trastuzumab resistance, while low PTEN predicts for response to lapatinib. These findings should help predict responses to specific treatments for HER2+ breast cancers, and could suggest a benefit of combining the two agents in a new trial. (J Clin Oncol) - PMID: 21135276

http://www.ncbi.nlm.nih.gov/pubmed/21135276

(Bardhan, …et al.)

Tracking of Multimodal Therapeutic Nanocomplexes Targeting Breast Cancer in Vivo

Nanoparticle-based therapeutics with local delivery and external electromagnetic field modulation hold extraordinary promise for soft-tissue cancers such as breast cancer; however, knowledge of the distribution and fate of nanoparticles in vivo is crucial for clinical translation. Here we demonstrate that multiple diagnostic capabilities can be introduced in photothermal therapeutic nanocomplexes by simultaneously enhancing both near-infrared fluorescence and magnetic resonance imaging (MRI). We track nanocomplexes in vivo, examining the influence of HER2 antibody targeting on nanocomplex distribution over 3 days. (Nano Lett) - PMID: 21090693

http://www.ncbi.nlm.nih.gov/pubmed/21090693

(Suo, …et al.)

Int6 regulates both proteasomal degradation and translation initiation and is critical for proper formation of acini by human mammary epithelium

INT6/EIF3E has been implicated in breast tumorigenesis, but its functional activities remain poorly defined. Here we found that repressing INT6 expression induced transformed properties in normal human mammary epithelium (MCF10A). A reverse-phase protein array screen identified the important coactivator SRC3/AIB1 as one oncoprotein whose level and stability increased when Int6 was silenced in MCF10A cells. The data further suggest that Int6 depletion blocks ubiquitin-dependent proteolysis, leading to accumulation of oncoproteins such as SRC3 that can transform mammary epithelium. Thus, restoration of INT6

expression/activity can lead to a novel therapeutic approach to prevent breast cancer development and/or progression. (Oncogene) - PMCID: PMC3017639

http://www.ncbi.nlm.nih.gov/pubmed/20890303

(Litzenburger, …et al.)

High IGF-IR activity in triple-negative breast cancer cell lines and tumorgrafts correlates with sensitivity to anti-IGF-IR therapy

We previously reported an IGF gene expression signature that is associated with very poor prognosis in breast cancer. We now show that this gene expression signature is reversed by IGF-IR inhibitors in many different cancer models in vitro and in vivo, and that expression of the signature in cell lines and tumors correlates with response to an IGF-IR tyrosine kinase inhibitor (BMS-572840). (Clin Cancer Res) - PMID: 21177763

http://www.ncbi.nlm.nih.gov/pubmed/21177763

(Cheng, …et al.)

Compartmentalized Ras proteins transform NIH3T3 cells with different efficiencies

We are beginning to discover that Ras proteins do different things in different cell compartments. This study shows that an H-Ras mutant restricted to the endomembrane still activates Cdc45 and causes cells to form tumors in nude mice, while an H-Ras mutant confined to the plasma membrane is much weaker in these activities though it is efficient in other Ras activities. However, if constitutively active CDC45 is provided, the transforming ability of plasma membrane H-Ras is restored. This work could suggest new ways of interfering with tumori-genicity, as well as suggesting ways in which Ras may be involved in breast tumor formation even though these tumors rarely show activating mutations in Ras proteins themselves. (Mol Cell Biol) - PMID: 21189290

http://www.ncbi.nlm.nih.gov/pubmed/21189290

(Dong, …et al.)

Genetic manipulation of individual somatic mammary cells in vivo reveals a master role of STAT5a in inducing alveolar fate commitment and lactogenesis even in the absence of ovarian hormones

We found that STAT5 activation can cause alveolar expansion. This impact may occur even in postmenopausal women. Overall, our study suggests that STAT5 may be a key factor in specifying luminal or lobular characteristics in some breast cancers. (Dev Biol) - PMCID: PMC3020144

http://www.ncbi.nlm.nih.gov/pubmed/20691178

University of Alabama at Birmingham

Bland, Kirby, M.D.

(Forero-Torres, …et al.)

Pilot trial of preoperative (neoadjuvant) letrozole in combination with bevacizumab in postmenopausal women with newly diagnosed estrogen receptor- or progesterone receptor-positive breast cancer

The pilot trial suggests that the addition of bevacizumab to letrozole improves efficacy against ER/PR positive breast cancer. The combination of the two medications is safe for the patients. This work led to the development of a randomized trial conducted through the Translational Breast Cancer Research Consortium. (Clin Breast Cancer) - PMID: 20705559

http://www.ncbi.nlm.nih.gov/pubmed/20705559

CERVICAL

Johns Hopkins University, School of Medicine

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

(Kang, …et al.)

Enhancement of protein vaccine potency by in vivo electroporation mediated intramuscular injection

In this paper, we aimed to determine whether intramuscular injection of protein-based vaccines in conjunction with CpG followed by electroporation can lead to increased delivery of the protein-based vaccine into muscle cells, resulting in enhanced vaccine potency. Our study demonstrates that intramuscular administration of protein-based vaccines in conjunction with CpG followed by electroporation can significantly enhance the antigen-specific CD8+ T cell immune responses and antitumor effects in vaccinated mice. Since CpG, protein-based vaccines and electroporation have been employed in clinics, the combination of these technologies may be potentially suitable for future clinical translation. Furthermore, our study is highly innovative since the employment of electroporation to enhance protein-based vaccine potency has not been previously reported. (Vaccine) - PMCID: PMC3026065

http://www.ncbi.nlm.nih.gov/pubmed/21130752

(Zeng, …et al.)

Control of Cervicovaginal HPV-16 E7-Expressing Tumors by the Combination of Therapeutic HPV Vaccination and Vascular Disrupting Agents

Antigen-specific immunotherapy and vascular disrupting agents, such as 5,6-dimethylxanthenone-4-acetic acid (DMXAA), have been used in early phase clinical trials for the treatment of cancers. In the current study, we tested the combination of DMXAA treatment with therapeutic human papillomavirus type 16 (HPV-16) E7 peptide-based vaccination for their ability to generate E7-specific CD8+ T cell immune responses as well as their ability to control E7-expressing tumors in a subcutaneous and a cervicovaginal tumor model. Our data demonstrated that administration of the vascular disrupting agent, DMXAA, enhances therapeutic HPV vaccine-induced CTL responses and antitumor effects against E7-expressing tumors in two different locations. In our study, we have also introduced a novel aggressive tumor model where the HPV-16 E6/E7-expressing TC-1

tumor cells are implanted in the cervicovaginal tract of mice. Our observations serve as an important foundation for further exploration of this combinational therapy for the control of HPV-associated tumors in future clinical trials. (Hum Gene Ther) - PMID: 21128743

http://www.ncbi.nlm.nih.gov/pubmed/21128743

(Peng, …et al.)

Efficient delivery of DNA vaccines using human papillomavirus pseudovirions

In this study, we reported non-replicative human papillomavirus (HPV) pseudovirions as an innovative approach in the delivery of naked DNA vaccines without safety concerns associated with live viral vectors. Our data suggest that DNA vaccines delivered using HPV pseudovirions represent an efficient delivery system that can potentially affect the field of DNA vaccine delivery. Furthermore, DNA vaccines delivered by pseudovirions may represent an opportunity to improve DNA vaccination that may be suitable for clinical translation in different antigenic systems. (Gen Ther) - PMCID: PMC2972366

http://www.ncbi.nlm.nih.gov/pubmed/20668481

(Karanam, …et al.)

Papillomavirus infection requires gamma secretase

The necessary causal association of persistent infection by an "oncogenic" type of human papillomavirus (HPV) with cervical cancer is firmly established. HPV is the most prevalent sexually transmitted infection, and although the majority of patients clear their infection, HPV is directly responsible for 5% of all cancer deaths worldwide. Inhibitor and genetic analyses show that gamma-secretase activity is necessary for papillomavirus infection in vitro and in vivo. (J Virol) - PMCID: PMC2950588

http://www.ncbi.nlm.nih.gov/pubmed/20702627

(Bazzaro, …et al.)

α,β-Unsaturated Carbonyl System of Chalcone-Based Derivatives Is Responsible for Broad Inhibition of Proteasomal Activity and Preferential Killing of Human Papilloma Virus (HPV) Positive Cervical Cancer Cells

Proteasome inhibitors have potential for the treatment of cervical cancer. We describe the synthesis and biological characterization of a new series of 1,3-diphenylpropen-1-one (chalcone) based derivatives lacking the boronic acid moieties of the previously reported chalcone-based proteasome

inhibitor 3,5-bis(4-boronic acid benzylidene)-1-methylpiperidin-4-one and bearing a variety of amino acid substitutions on the amino group of the 4-piperidone. Our lead compound 2 (RA-1) inhibits proteasomal activity and has improved dose-dependent antiproliferative and proapoptotic properties in cervical cancer cells containing human papillomavirus. (J Med Chem) - PMID: 21186794

http://www.ncbi.nlm.nih.gov/pubmed/21186794

ENDOMETRIAL

MD Anderson Cancer Center

Lu, Karen, M.D.

(Nabilsi, …et al.)

Sex hormone regulation of survivin gene expression

We are the first to report that survivin gene expression is changed in response to administration of estrogen and progesterone in the disease-free human endometrium. After a 6-month treatment with estrogen, survivin gene expression was increased and was associated with increased proliferation indices as measured by Ki67 expression. These data suggest that while the IGF1 protein is functionally involved in mediating the proliferative response towards estradiol, the survivin transcript may be more useful than the IGF1 transcript as an indicator of hormone treatment efficacy, specifically as a marker of proliferation in response to estrogen. (J Endocrinol) - PMID: 20798131

http://www.ncbi.nlm.nih.gov/pubmed/20798131

(Lu, …et al.)

Regulation of tumor angiogenesis by EZH2

In this work, we identify Zeste homolog 2 (Ezh2) as a key regulator of tumor angiogenesis. The increase in endothelial Ezh2 is a direct result of VEGF stimulation and indicates the presence of a paracrine circuit that promotes angiogenesis. Ezh2 silencing in the tumor-associated endothelial cells using siRNA, packaged in the chitosan delivery system, resulted in significant growth inhibition, and Ezh2 silencing in tumor endothelial cells resulted in decreased angiogenesis that was mediated by increased levels of the angiogenesis inhibitor, VASH1. (Cancer Cell) - PMCID: PMC2923653

http://www.ncbi.nlm.nih.gov/pubmed/20708159

(Kim, …et al.)

The synergistic effect of Mig-6 and Pten ablation on endometrial cancer development and progression

Our results show the synergistic effect of conditional Pten and Mig-6 loss on endometrial cancer development. This accelerated tumorigenesis is likely due to decreased epithelial apoptosis partly through increased expression of the Birc1 family of apoptotic inhibitors and increased phosphorylation of ERK2. These and future results will contribute to the understanding of the molecular mechanism of tumorigenesis and to the development of therapeutic approaches for endometrial cancer. (Oncogene) - PMID: 20418913

http://www.ncbi.nlm.nih.gov/pubmed/20418913

GI

Johns Hopkins University

Kern, Scott E., M.D.

(Yachida, …et al.)

Distant metastasis occurs late during the genetic evolution of pancreatic cancer

Pancreatic cancer is nearly always lethal, even when found at a small size. It would be valuable to determine how long a period of time, or how big is the "window of opportunity", for clinical detection of these cancers before it is too late, and they have metastasized. Mutations occuring after the neoplasm had initiated, or after the time the cancer had invaded, but before a metastatic cell leaves the primary tumor, could give clues. (Nature) - PMID: 20981102

http://www.ncbi.nlm.nih.gov/pubmed/20981102

(Bozic, …et al.)

Accumulation of driver and passenger mutations during tumor progression

It has been difficult to determine just how quickly human tumors arise and accumulate the causative gene mutations. Tumors are removed at the time of detection, yielding data concerning a given point in time, but not readily uncovering what was the process leading to that point. In order to

understand cancer epidemiology and to make sense of the clinical presentation of tumors, a method to "look back" into the tumor's lifespan was desirable. (Proc Natl Acad Sci USA) - PMCID: PMC2972991

http://www.ncbi.nlm.nih.gov/pubmed/20876136

(Boca, ...et al.)

Patient-oriented gene set analysis for cancer mutation data

Mutations in tumor DNA form "constellations" of mutant cellular systems in each patient's tumor. These relationships are lost when, as is conventionally done, data are grouped for analysis gene-by-gene, ignoring the constellations of each patient. Taking the patient into account was previously done mostly in an anecdotal manner, but not systematically in analyzing large sets of mutational data. (Genome Biol) - PMID: 21092299

http://www.ncbi.nlm.nih.gov/pubmed/21092299

Dana Farber/Harvard Cancer Center

Fuchs, Charles, M.D., M.P.H.

(Corcoran, ...et al.)

BRAF gene amplification can promote acquired resistance to MEK inhibitors in cancer cells harboring the BRAF V600E mutation

Mutations in the BRAF proto-oncogene occur in 10 to 20% of colorectal cancers, and the presence of BRAF mutation predicts for sensitivity to inhibitors of MEK and BRAF in various preclinical models. Nonetheless, clinical trials of single-agent BRAF and MEK inhibitors in advanced colorectal cancer have demonstrated minimal efficacy. In this study, we found that amplification of the BRAF gene conferred acquired resistance to MEK or BRAF inhibition in colorectal cancers; however, combined MEK and BRAF inhibition fully overcame resistance to MEK and BRAF inhibitors alone. (Sci Signal) - PMID: 21098728

http://www.ncbi.nlm.nih.gov/pubmed/21098728

(Chan, ...et al.)

Cathepsin B expression and survival in colon cancer: implications for molecular detection of neoplasia

Although colonoscopy is an excellent screening tool and considered the current gold standard, there is a miss rate for polyps as high as 22%; thus, there is a need to develop novel technologies that would permit the early detection and in situ characterization of early neoplastic colonic lesions with high sensitivity and specificity. We developed a class of "smart" agents that increase their near infrared (NIR) fluorescence after selective interaction with a target protease (cathepsin B) that is overexpressed in colonic adenomas and adenocarcinomas, and, in a mouse model that develops spontaneous focal adenomas and adenocarcinomas (lox APCΔ580 mouse strain, developed by Kucherlapati et al), we demonstrated superior endoscopic detection of preneoplastic lesions when compared to conventional white light examinations (Upadhyay et al. Radiology 2007). To assess the expression of cathepsin B in human colorectal cancer, we assessed tumoral expression in 558 individuals with colorectal cancer and 123 individuals with adenoma, finding expression in the vast majority (>90%) of cancers and adenomas; moreover, in colorectal cancer, increased cathepsin B expression was an independent predictor or patient survival. (Cancer Epidemiol Biomarkers Prev) - PMCID: PMC2976771

http://www.ncbi.nlm.nih.gov/pubmed/20833970

(Ng, …et al.)

Multivitamin use is not associated with cancer recurrence or survival in patients with stage III colon cancer: findings from CALGB 89803

Multivitamin use is widespread in the United States, especially among cancer patients with cancer; however, the influence of multivitamin supplementation on cancer recurrence and death after a curative resection of colon cancer is unknown. We conducted a prospective, observational study of 1,038 patients with stage III colon cancer enrolled in an NCI-sponsored randomized adjuvant chemotherapy trial (CALGB 89803). Fifty percent of patients reported multivitamin use; however, multivitamin use during and after adjuvant chemotherapy was not associated with improved recurrence-free, disease-free, or overall survival. (J Clin Oncol) - PMCID: PMC2954134

http://www.ncbi.nlm.nih.gov/pubmed/20805450

(Baba, …et al.)

Hypomethylation of the IGF2 DMR in colorectal tumors, detected by bisulfite pyrosequencing, is associated with poor prognosis

Constitutive loss of imprinting (LOI) of the insulin-like growth factor 2 (IGF2) gene has been associated with increased risks of colon cancer and adenoma, indicating its role in carcinogenesis. We measured methylation at the IGF2 differentially methylated region (DMR)-0 using a bisulfite-pyrosequencing assay in tumors from 1,178 patients with colorectal cancer and found that

hypomethylation of the IGF2 DMR0 was a significant, independent predictor of inferior overall survival (log-rank P = 0.0006). (Gastroenterology) - PMCID: PMC2995815

http://www.ncbi.nlm.nih.gov/pubmed/20682317

(Verzi, …et al.)

TCF4 and CDX2, major transcription factors for intestinal function, converge on the same cis-regulatory regions

Surprisingly few pathways signal between cells, raising questions about mechanisms for tissue-specific responses. In particular, Wnt ligands signal in many mammalian tissues, including the intestinal epithelium, where constitutive signaling causes colorectal cancer. Genome-wide analysis of DNA cis-regulatory regions bound by the intestine-restricted transcription factor CDX2 in colonic cells uncovered highly significant overrepresentation of sequences that bind TCF4, a transcriptional effector of intestinal Wnt signaling, and chromatin immunoprecipitation confirmed TCF4 occupancy at most such sites and co-occupancy of CDX2 and TCF4 across short distances. A region spanning the single nucleotide polymorphism rs6983267, which lies within a MYC enhancer and confers colorectal cancer risk in humans, represented one of many co-occupied sites and co-occupancy correlated with intestine-specific gene expression and CDX2 loss reduced TCF4 binding. (Proc Natl Acad Sci USA) - PMCID: PMC2930576

http://www.ncbi.nlm.nih.gov/pubmed/20696899

Vanderbilt University

Coffey, Jr., Robert, M.D.

(Thorne, …et al.)

Small-molecule inhibition of Wnt signaling through activation of casein kinase 1α

We have identified CK1alpha as the critical target of a class of small molecules that potently inhibit canonical Wnt signaling. These small molecules, which inhibit Wnt signaling via activation of CK1a, are even effective in cells with mutations in APC or beta-catenin (present in greater than 90% of all sporadic cases of colorectal cancer). These compounds inhibit the growth of colorectal cancer cells to a greater extent (~100-fold) than that of non-transformed cells. (Nat Chem Biol) - PMID: 20890287

http://www.ncbi.nlm.nih.gov/pubmed/20890287

University of Arizona

Gerner, Eugene, Ph. D.

(Thompson, …et al.)

Levels of rectal mucosal polyamines and prostaglandin E2 predict ability of DFMO and sulindac to prevent colorectal adenoma

These data have validated the polyamine pathway as an effective target for preventing the formation of colorectal adenomas, which are risk factors for colorectal cancer. (Gastroenterology) - PMID: 20538001

http://www.ncbi.nlm.nih.gov/pubmed/20538001

(Zell, …et al.)

Ornithine decarboxylase-1 polymorphism, chemoprevention with eflornithine and sulindac, and outcomes among colorectal adenoma patients

These studies have provided evidence for important roles for genetic variability affecting this pathway in colorectal carcinogenesis and helped us appreciate an import role for dietary polyamines as an influencing factor for treatment with DFMO and sulindac in humans. (J Natl Cancer Inst) - PMCID: PMC2950167

http://www.ncbi.nlm.nih.gov/pubmed/20798393

(Goldman, …et al.)

A novel mechanism of acid and bile acid-induced DNA damage involving Na+/H+ exchanger: implication for Barrett's oesophagus

This research revealed a novel mechanism of bile acid induced DNA damage as a consequence of intracellular acidification. Moreover, it showed the endogenous expression of nitric oxide, as a consequence of bile acid exposure, is the culprit behind the increased DNA damage. As a result, the findings elucidate novel targets which could be explored in clinic to prevent DNA damage during gastroesophageal reflux; a major contributor to the development of esopahgeal cancer. (Gut) - PMID: 20876775

http://www.ncbi.nlm.nih.gov/pubmed/20876775

(Goldman, …et al.)

Characterization of squamous esophageal cells resistant to bile acids at acidic pH: implication for Barrett's esophagus pathogenesis

This manuscript provided the first evidence for an in-vitro model of Barrett's esophagus development from squamous-derived esophageal cells. Never before have cells derived from normal epithelium been transformed, in-vitro or in-vivo, to Barrett's esophagus and/or adenocarcinoma. This only remained as speculation or theory. Using a bile acid cocktail and low pH to mimic gastroesophageal reflux, cells developed characteristics of Barrett's esophagus and adenocarcinoma. Clinically, it provides evidence to gastroenterologists that bile acids in refluxate are majorly responsible for the development of esophageal pathology and bile acids, therefore, should be controlled in patients. (Am J Physiol Gastronintest Liver Physiol) - PMCID: PMC3043651

http://www.ncbi.nlm.nih.gov/pubmed/21127259

HEAD & NECK

MD Anderson Cancer Center

Lippman, Scott, M.D.

(Wang, …et al.)

Genetic variations in regulator of G-protein signaling genes as susceptibility loci for second primary tumor/recurrence in head and neck squamous cell carcinoma

The development of second primary tumor (SPT) and recurrence is a major clinical problem for surgically treated patients with early-stage head and neck squamous cell carcinoma (HNSCC). This study identified several novel genetic predictors of SPT/recurrence. The identification of clinically applicable biomarkers will improve the prediction of SPT/recurrence and is important in the achievement of targeted interventions and long-term survival of early-stage HNSCC patients. (Carcinogenesis) - PMCID: PMC2950933

http://www.ncbi.nlm.nih.gov/pubmed/20627871

(Sano, …et al.)

Targeted molecular therapy of head and neck squamous cell carcinoma with the tyrosine kinase inhibitor vandetanib in a mouse model

The in vitro effects of vandetanib (ZACTIMA) were assessed in 2 HNSCC cell lines on cell growth, apoptosis, receptor and downstream signaling molecule expression, and phosphorylation levels. We assessed in vivo effects of vandetanib and/or paclitaxel by measuring tumor cell apoptosis, endothelial cell apoptosis, microvessel density, tumor size, and animal survival. In vitro, vandetanib inhibited the phosphorylation of EGFR and its downstream targets in HNSCC cells and inhibited proliferation and induced apoptosis of HNSCC cells and extended survival and inhibited tumor growth in nude mice orthotopically injected with human HNSCC. (Head Neck) - PMCID: PMC2958241

http://www.ncbi.nlm.nih.gov/pubmed/20629091

Emory University

Shin, Dong Moon, M.D.

(Amin, ...et al.)

Enhanced anti-tumor activity by the combination of the natural compounds (-)-epigallocatechin-3-gallate and luteolin: potential role of p53

Cancer is the second leading cause of death in the United States and worldwide, with a total of 1.47 million new cancer cases and 560,000 deaths projected to occur in the United States in 2010. Chemoprevention is a cost effective alternative to cancer therapy, and natural dietary agents present in fruits, vegetables and spices have drawn a great deal of attention toward cancer prevention because of their wide safety margin. With many currently under clinical investigation, a successful chemopreventive regimen can save millions of lives, however, no promising regimens have been well documented thus far warranting continuing the search for new agents or a combination for chemoprevention. (J Biol Chem) - PMCID: PMC2966071

http://www.ncbi.nlm.nih.gov/pubmed/20826787

(Elrod, ...et al.)

Analysis of death receptor 5 and caspase-8 expression in primary and metastatic head and neck squamous cell carcinoma and their prognostic impact

This study for the first time demonstrated that caspase-8 alone, or together with DR5, has the opposite impact on HNSCC patient survival depending on the presence of metastasis. The findings

suggest the potential roles of caspase-8 and DR5 in regulation of HNSCC metastasis and warrant further investigation on the dual role of caspase-8 including DR5 in cancer development. (PLoS One) - PMCID: PMC2922336

http://www.ncbi.nlm.nih.gov/pubmed/20808443

(Fu, …et al.)

c-Jun NH2-terminal kinase-dependent upregulation of DR5 mediates cooperative induction of apoptosis by perifosine and TRAIL

This study demonstrated that DR5 induction plays a critical role in mediating enhancement of TRAIL-induced apoptosis by perifosine, an alkylphospholipid tested in phase II clinical trials. Perifosine induces DR5 expression through a JNK-dependent mechanism independent of reactive oxygen species. The findings increase our understanding on mechanisms by which perifosine regulates apoptosis, particularly TRAILinduced apoptosis and support the potential application of perifosine and TRAIL combination in treatment of HNSCCs. (Mol Cancer) - PMCID: PMC3018404

http://www.ncbi.nlm.nih.gov/pubmed/21172010

(Thomas, …et al.)

Activation of the p38 pathway by a novel monoketone curcumin analog, EF24, suggests a potential combination strategy

Increasing attention has been given to the anticancer effects of curcumin and the ability of this natural product to inhibit cancer cell proliferation. Inhibition of p38, either by small molecule inhibitors or through an RNAimediated knockdown approach, enhanced the EF24-induced apoptotic death of A549 cells. Inhibition of p38 may boost the EF24 anticancer effect, therefore, EF24 can be developed into for treatment or prevention of carcinogenesis. (Biochem Pharmacol) - PMID: 20615389

http://www.ncbi.nlm.nih.gov/pubmed/20615389

(Huang, …et al.)

A reexamination of active and passive tumor targeting by using rod-shaped gold nanocrystals and covalently conjugated peptide ligands

Using elongated gold nanocrystals investigators showed that targeting ligands only marginally improved total nanoparticle accumulation in xenograft tumor models compared to non-targeted controls, but their use could greatly alter the intra- and extracellular nanoparticle distributions. They

also found that active molecular targeting of the tumor microenvironment does not significantly influence the tumor nanoparticle uptake, suggesting that for photothermal cancer therapy, the preferred route of gold nanorod administration is intratumoral injection instead of intravenous injection. (ACS Nano) - PMCID: PMC2964428

http://www.ncbi.nlm.nih.gov/pubmed/20863096

KIDNEY

Dana-Farber Harvard Cancer Center

Atkins, Michael, M.D.

(Cho, …et al.)

The efficacy of the novel dual PI3-kinase/mTOR inhibitor NVP-BEZ235 compared with rapamycin in renal cell carcinoma

The recent FDA approval of the rapamycin analogues temsirolimus and everolimus for the treatment of patients with advanced renal cancer validated mTOR as an important therapeutic target in this disease. Despite this observed clinical activity, preclinical studies have shown that the effectiveness of mTOR inhibitors as a class in RCC is limited by feedback activation of the PI3 kinase pathway upstream mTOR. Recent work by Cho et al, suggests that drugs that block both mTOR (TORC1 and TORC2) and PI3 kinase can overcome this feedback activation and produce superior antitumor activity in murine human RCC xenograft models relative to rapamycin. (Clin Cancer Res) - PMCID: PMC2905505

http://www.ncbi.nlm.nih.gov/pubmed/20606035

LEUKEMIA

Ohio State University Comprehensive Cancer Center

Byrd, John C., M.D.

(Herman, …et al.)

Phosphatidylinositol 3-kinase-δ inhibitor CAL-101 shows promising preclinical activity in chronic lymphocytic leukemia by antagonizing intrinsic and extrinsic cellular survival signals

Novel kinase inhibitors have significantly revolutionized the therapy of chronic myeloid leukemia. This paper demonstrated significant pre-clinical activity of CAL-101 that targets PI3-kinase delta, an important, constitutively activated kinase in CLL(chronic lymphocytic leukemia). Based upon these data, a phase I study in CLL and related disorders was initiated that has demonstrated dramatic activity, minimal toxicity, and prolonged sustained remissions. (Blood) - PMCID: PMC2951855

http://www.ncbi.nlm.nih.gov/pubmed/20522708

(Hertlein, …et al.)

17-DMAG targets the nuclear factor-kappaB family of proteins to induce apoptosis in chronic lymphocytic leukemia: clinical implications of HSP90 inhibition

To date, therapeutic agents targeting IKK-α and IKK-β have not been available. Herein we demonstrate 17-DMAG to dually target these two proteins through an HSP90 dependent mechanism with down-stream evidence of NF-KB inhibition. These findings have translated to a phase I study of 17-DMAG in previously treated CLL(chronic lymphocytic leukemia) sponsored trough CTEP(Cancer Therapy Evaluation Program). (Blood) - PMCID: PMC2904580 [Available on 2011/7/8]

http://www.ncbi.nlm.nih.gov/pubmed/20351313

(Hertlein, …et al.)

Milatuzumab immunoliposomes induce cell death in CLL by promoting accumulation of CD74 on the surface of B cells

CD74 is an antigen expressed on B-cells that is targeted by the antibody milatuzumab. This paper demonstrates the pre-clinical activity of milatuzumab with cross-linking antibody and establishes the potential of a novel immune liposome to deliver a death signal under more physiologic conditions. This has prompted further in vivo studies in xenograft models to determine if this enhances activity over the free antibody to justify further development in collaboration with Immunomedics. (Blood) - PMCID: PMC2953888 [Available on 2011/10/7]

http://www.ncbi.nlm.nih.gov/pubmed/20574049

(Blum, …et al.)

Dose escalation of lenalidomide in relapsed or refractory acute leukemias

Adult AML(acute myeloid leukemia) has a poor outcome with currently available therapies making identification of new treatments a high priority. This study identified the single agent activity of lenalidomide in previously treated AML and also suggested its potential to augment control of relapsed disease after allogeneic transplant through a potential graft versus leukemia mechanism. Based upon this work, several clinical trials have been undertaken at the Ohio State University (OSU) and in the Cancer and Leukemia Group B (CALGB) to study lenalidomide in AML therapy. (J Clin Oncol) - PMID: 20956622

http://www.ncbi.nlm.nih.gov/pubmed/20956622

(Schwind, …et al.)

Prognostic significance of expression of a single microRNA, miR-181a, in cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study

Patients with AML(acute myeloid leukemia) and normal karyotype have varied clinical outcome. This work identifies miR-181a silencing as a significant adverse prognostic factor in AML. This will be used to both risk stratify patients and also potentially to derive new therapies targeting this molecular defect that are under study currently. (J Clin Oncol) - PMCID: PMC3018359 [Available on 2011/12/20]

http://www.ncbi.nlm.nih.gov/pubmed/21079133

MD Anderson Cancer Center

Issa, Jean-Pierre, M.D.

(Si, …et al.)

Chromatin remodeling is required for gene reactivation after decitabine-mediated DNA hypomethylation

The DNA hypomethylating drug decitabine (DAC) reactivates silenced gene expression in cancer and is approved for the treatment of the myelodysplastic syndrome. Gene reactivation after DAC is variable and incompletely understood. Here, we established a cell line system (YB5) derived from the SW48 colon cancer cell line to study DAC-induced reactivation. By comparing DAC-treated sorted GFP(green fluorescent protein)-positive and GFP-negative cells, we found that their methylation levels were similarly decreased but that histone modifications and histone H3 densities were remarkably different. Despite a similar degree of (incomplete) DNA hypomethylation, GFP-positive cells reverted to an active chromatin structure marked by higher H3K9 acetylation, lower H3K27 trimethylation, and lower promoter nucleosome density. GFP-negative cells had histone modifications and promoter nucleosome density, similar to parental cells. On DAC withdrawal, gradual resilencing and remethylation occurred in both GFP-positive and GFP-negative cells, and the resilencing correlated with a gradual increase in nucleosome occupancy in GFP-positive cells. The data suggests mechanisms by which hypomethylation therapy in the clinic might fail (inadequate chromatin resetting), which leads to strategies for identification of better epigenetic therapies. (Cancer Res) - PMCID: PMC2932851

http://www.ncbi.nlm.nih.gov/pubmed/20713525

(Liu, …et al.)

Homologous recombination as a resistance mechanism to replication-induced double-strand breaks caused by the antileukemia agent CNDAC

The nucleoside analog 2'-C-cyano-2'-deoxy-1-β-D-arabino-pentofuranosyl-cytosine (CNDAC), currently in clinical trials for hematologic malignancies, has a novel action mechanism of causing a single-strand break after its incorporation into DNA. Double-strand breaks (DSBs) are generated thereafter in vivo and, if not repaired, pose lethal impact on cell survival. This study sought to define the mechanisms by which CNDAC-induced DSBs are formed and repaired. We demonstrated that single-strand breaks induced by CNDAC incorporation into DNA were converted to DSBs when cells progressed into the subsequent S-phase. CNDAC-induced DSBs were products of replication, rather than a consequence of apoptosis. ATM, the activator of homologous recombination (HR), was essential for cell survival after CNDAC treatment in cell lines and in primary acute myeloid leukemia samples, as were the HR components, Rad51, Xrcc3, and Brca2. Furthermore, formation of sister chromatid exchanges, a hallmark of HR, increased significantly after CNDAC-treated cells had progressed into a second replication cycle. In contrast, neither the replication stress sensor ATR nor DNA-PK, the initiator of

nonhomologous end-joining of DSB, was involved in repair of CNDAC-induced damage. (Blood) - PMCID: PMC2947394

http://www.ncbi.nlm.nih.gov/pubmed/20479284

(Ma, …et al.)

Adoptive transfer of PR1 cytotoxic T lymphocytes associated with reduced leukemia burden in a mouse acute myeloid leukemia xenograft model

Peroxisome proliferator-activated receptor-gamma (PPARgamma) is a member of the nuclear receptor (NR) family of transcription factors with important regulatory roles in cellular growth, differentiation, and apoptosis. Using proteomic analysis, we showed expression of PPARgamma protein in a series of 260 newly diagnosed primary acute myelogenous leukemia (AML) samples. Forced expression of PPARgamma enhanced the sensitivity of myeloid leukemic cells to apoptosis induced by PPARgamma agonists 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) and 15-deoxy-(12,14)-15DPGJ(2), through preferential cleavage of caspase-8. No effects on cell cycle distribution or differentiation were noted, despite prominent induction of p21 in PPARgamma-transfected cells. In turn, antagonizing PPARgamma function by small interfering RNA or pharmacologic PPARgamma inhibitor significantly diminished apoptosis induction by CDDO. Overexpression of coactivator protein DRIP205 resulted in enhanced differentiation induction by CDDO in AML cells through PPARgamma activation. (Cytotherapy) - PMID: 20735170

http://www.ncbi.nlm.nih.gov/pubmed/20735170

(Estecio, …et al.)

Genome architecture marked by retrotransposons modulates predisposition to DNA methylation in cancer

Epigenetic silencing plays an important role in cancer development. An attractive hypothesis is that local DNA features may participate in differential predisposition to gene hypermethylation. We found that, compared with methylation-resistant genes, methylation-prone genes have a lower frequency of SINE and LINE retrotransposons near their transcription start site. In several large testing sets, this distribution was highly predictive of promoter methylation. The data may help select methylation-based tumor markers, and identify factors associated with clinical failure of hypomethylation therapy. (Genome Res) - PMCID: PMC2945186

http://www.ncbi.nlm.nih.gov/pubmed/20716667

(Kanodia, …et al.)

PR1-specific T cells are associated with unmaintained cytogenetic remission of chronic myelogenous leukemia after interferon withdrawal

Interferon-alpha (IFN) induces complete cytogenetic remission (CCR) in 20-25% CML patients and in a small minority of patients; CCR persists after IFN is stopped. IFN induces CCR in part by increasing cytotoxic T lymphocytes (CTL) specific for PR1, the HLA-A2-restricted 9-mer peptide from proteinase 3 and neutrophil elastase, but it is unknown how CCR persists after IFN is stopped. We reasoned that PR1-CTL persist and mediate CML-specific immunity in patients that maintain CCR after IFN withdrawal. We found that PR1-CTL were increased in peripheral blood of 7/7 HLA-A2+ patients during unmaintained CCR from 3 to 88 months after IFN withdrawal, as compared to no detectable PR1-CTL in 2/2 IFN-treated CML patients not in CCR. Unprimed PR1-CTL secreted IFNgamma and were predominantly CD45RA+/-CD28+CCR7+CD57-, consistent with functional naïve and central memory (CM) T cells. Similarly, following stimulation, proliferation occurred predominantly in CM PR1-CTL, consistent with long-term immunity sustained by self-renewing CM T cells. PR1-CTL were functionally anergic in one patient 6 months prior to cytogenetic relapse at 26 months after IFN withdrawal, and in three relapsed patients PR1-CTL were undetectable but re-emerged 3-6 months after starting imatinib. (PLoS One) - PMCID: PMC2909896

http://www.ncbi.nlm.nih.gov/pubmed/20668669

LUNG

University of Pittsburgh

Siegfried, Jill M., Ph.D.

(Stabile, …et al.)

Combined Analysis of Estrogen Receptor b-1 and Progesterone Receptor Expression Identifies Lung Cancer Patients with Poor Outcome

A better understanding of the role and interaction of hormone and growth factor pathways in the lung is necessary to elucidate novel effective preventative and treatment strategies for lung cancer. This work examined the combined effect of expression of estrogen receptor b-1 and progesterone receptor in tissues from lung cancer patients and the influence of expression of other markers including the epidermal growth factor receptor and aromatase on patient survival. The correlations between expression of these markers and their combined influence on patient survival suggest that phenotyping these interacting markers together in lung cancer patients may better predict survival and suggest which patients could be candidates for hormonal therapy for lung cancer treatment. (Clin Cancer Res) - PMID: 21062926

http://www.ncbi.nlm.nih.gov/pubmed/21062926

University of Colorado Cancer Center

Bunn, Paul, M.D.

(Ware, …et al.)

Rapidly acquired resistance to EGFR tyrosine kinase inhibitors in NSCLC cell lines through de-repression of FGFR2 and FGFR3 expression

Despite good initial response of lung tumors bearing activating mutations in EGFR to tyrosine kinase inhibitors, the majority will develop resistance. This study demonstrates that fibroblast growth factor receptor (FGFR) 2 and 3 are transcriptionally induced following treatment of EGFR dominant lung cancer cell lines with EGFR-specific TKIs. Moreover, addition of exogenous FGF2 or FGF7 significantly limits the efficacy of EGFR-specific TKIs due to the induced FGFRs. The results reveal induced FGFR2 and FGFR3 following TKI treatment as a potentially novel resistance mechanism and highlights the potential utility of treatment of EGFR driven lung cancers with combinations of EGFR and FGFR-specific TKIs. (PLoS One) - PMCID: PMC2994708

http://www.ncbi.nlm.nih.gov/pubmed/21152424

(Camidge, …et al.)

Optimizing the detection of lung cancer patients harboring anaplastic lymphoma kinase (ALK) gene rearrangements potentially suitable for ALK inhibitor treatment

Rearrangements of the anaplastic lymphoma kinase (ALK) gene were described in a subset of non-small cell lung cancers in 2007. With the availability of specific targeted anti-ALK therapy (PF-02341066, crizotinib) within clinical trials, accurate screening techniques for identifying these patients have become increasingly important. In this study we demonstrate how utilizing specific clinical and molecular pathological factors (adenocarcinoma, less than or equal to 10 pack year smoking history, EGFR and KRAS wildtype) can significantly enrich for ALK positive patients detected using FISH break-apart probe. In addition, we show that the proposed cutpoint of >15% positive cells accurately distinguishes true signal from noise and establish >60 tumor nuclei to be counted in order to ensure 100% sensitivity and specificity. (Clin Cancer Res) - PMID: 21062932

http://www.ncbi.nlm.nih.gov/pubmed/21062932

(Kwak, …et al.)

Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer

PF-02341066 (crizotinib) is a small molecule inhibitor of ALK and MET. In this phase I study, ALK positive NSCLC patients, detected with the FISH break-apart probe were treated at the recommended phase II dose of crizotinib within a molecularly defined expanded cohort. The drug was well tolerated at 250mg BID. (N Engl J Med) - PMCID: PMC3014291

http://www.ncbi.nlm.nih.gov/pubmed/20979469

(Ostroff, …et al.)

Unlocking biomarker discovery: large scale application of aptamer proteomic technology for early detection of lung cancer

Currently, no clinically useful blood test for lung cancer exists. This study reports the use of a highly multiplexed aptamer based assay to develop a blood test based on a 12 protein panel giving sensitivity/specificity of 91%/84% on a training set and 89%/84% on a validation set. The potential clinical impacts of such a test would include both informing clinical decision making in regard to CT detected lung nodules and general population screening. (PLoS One) - PMCID: PMC2999620

http://www.ncbi.nlm.nih.gov/pubmed/21170350

(Karoor, …et al.)

Vascular endothelial growth factor receptor 2-targeted chemoprevention of murine lung tumors

Angiogenesis is necessary for tumor growth, yet targeted antiangiogenic agents have not been assessed in preclinical models. This study demonstrated that vandetanib is a highly effective chemopreventive agent in two chemical carcinogenesis models. This could potentially be translated to chemoprevention of second primary lung cancers in surgically treated patients. (Cancer Prev Res) - PMCID: PMC2933287

http://www.ncbi.nlm.nih.gov/pubmed/20647338

Vanderbilt University

Carbone, David P., M.D., Ph.D.

(Su, …et al.)

A platform for rapid detection of multiple oncogenic mutations with relevance to targeted therapy in non-small-cell lung cancer

The identification of somatically acquired tumor mutations is increasingly important in the clinical management of cancer because the sensitivity of targeted drugs is related to the genetic makeup of individual tumors. Thus, mutational profiles of tumors can help prioritize anticancer therapy. We report herein the development and validation of two multiplexed assays designed to detect in DNA from FFPE tissue more than 40 recurrent mutations in nine genes relevant to existing and emerging targeted therapies in lung cancer. These robust, reliable, and relatively inexpensive assays should help accelerate adoption of a genotype-driven approach in the treatment of lung cancer. (J Mol Diagn) - PMID: 21227397

http://www.ncbi.nlm.nih.gov/pubmed/21227397

(Sun, …et al.)

Lung adenocarcinoma from East Asian never-smokers is a disease largely defined by targetable oncogenic mutant kinases

In this surgical series, 52 resected lung adenocarcinomas from never-smokers (100 cigarettes in a lifetime) at a single institution (Fudan University, Shanghai, China) were analyzed concurrently for mutations in EGFR, KRAS, NRAS, HRAS, HER2, BRAF, ALK, PIK3CA, TP53 and LKB1. 90% (47 of 52; 95% CI, 0.7896 to 0.9625) of lung adenocarcinomas from never-smokers were found to harbor well-known oncogenic mutations in just four genes: EGFR, KRAS, ALK, HER2. (J Clin Oncol) - PMCID: PMC2974342

http://www.ncbi.nlm.nih.gov/pubmed/20855837

Johns Hopkins University

Baylin, Stephen B., M.D.

(Solis, …et al.)

Nrf2 and Keap1 abnormalities in non-small cell lung carcinoma and association with clinicopathologic features

This is the first comprehensive retrospective study which investigated the expression of these two proteins (Nrf2 and KEAP1) in a large series of NSCLC tissue specimens with annotated clinicopathologic characteristics, including outcome, and evaluated the relationship between nuclear Nrf2 expression and outcome in patients treated with platinum-based adjuvant chemotherapy. The study revealed that Nrf2 expression may play a role in response to adjuvant platinum-based chemotherapy in patients with squamous cell carcinoma. Thus, Identifying patients with abnormal Nrf2 expression may be important for selection for chemotherapy in NSCLC. (Clin Cancer Res) - PMCID: PMC2920733

http://www.ncbi.nlm.nih.gov/pubmed/20534738

(Malhotra, …et al.)

Global mapping of binding sites for Nrf2 identifies novel targets in cell survival response through ChIP-Seq profiling and network analysis

The identification of a well-defined Nrf2 regulatory program is a critical step in advancing translational research. Nrf2 plays an important role in promoting growth of tumor cells as well as protects normal cells against a variety of environmental stressors and carcinogens. The integrated analysis of the experimental data highlights the broad influence of Nrf2, providing a blueprint for the regulation of cytoprotective genes and genes involved in critical homeostatic function such as cell proliferation. (Nucleic Acids Res) - PMCID: PMC2943601

http://www.ncbi.nlm.nih.gov/pubmed/20460467

H. Lee Moffitt Cancer Center

Haura, Eric, M.D.

(Sosa-Garcia, …et al.)

A role for the retinoblastoma protein as a regulator of mouse osteoblast cell adhesion: implications for osteogenesis and osteosarcoma formation

The RB1 tumor suppressor gene is clearly one of the most important in human cancer, particularly small-cell lung cancer. In this work we demonstrate that RB1 regulates a vast number of genes involved in cell adhesion. We propose that the ability of RB1 to influence cell adhesion, in addition to its well know ability to regulate cell cycle, may explain its unusual potency as a tumor suppressor. (PLoS One) - PMCID: PMC2978706

http://www.ncbi.nlm.nih.gov/pubmed/21085651

(Brazelle, …et al.)

Histone deacetylase inhibitors downregulate checkpoint kinase 1 expression to induce cell death in non-small cell lung cancer cells

Histone deacetylase inhibitors have potential as chemotherapeutic agents, however their mechanism of action are not completely understood. In this work we demonstrate that histone deacetylase inhibitors lead to downregulation of the CHK1 kinase. These results define a pathway through which Chk1 inhibition can mediate HDACi-induced mitotic entry and cell death and suggest that Chk1 could be an early pharmacodynamic marker to assess HDACi efficacy in clinical samples (PLoS One) - PMCID: PMC3001870

http://www.ncbi.nlm.nih.gov/pubmed/21179472

Dana-Farber Harvard Cancer Center

Johnson, Bruce, M.D.

(Sequist, …et al.)

Genotypic and Histological Evolution of Lung Cancers Acquiring Resistance to EGFR Inhibitors.

To understand the exact mechanism of the drug resistance acquisition in NSCLC patients treated with EGFR inhibitors, the investigators analyzed tumor biopsies from patients at the time they acquired resistance. The disease underwent various courses: in some patients the resistance gateway mutation T790 appeared, in others amplification of the MET tyrosine kinase receptor occurred; another group of patients developed new patterns of resistance with the amplification of the EGFR gene and mutations of PIK3CA gene. In a few patients, lung cancers transitioned from epithelial to mesenchymal (more aggressive) morphology or they converted from the non-small cell lung cancer phenotype to small cell lung cancer. The genetic and histological analysis provides new insights into drug resistance evolution in lung cancers and suggests that serial biopsies may be essential in the quest to reverse or even prevent the development of drug resistance. (Sci Transl Med) - PMID: 21430269

http://www.ncbi.nlm.nih.gov/pubmed/21430269

LYMPHOMA

Baylor College of Medicine

Heslop, Helen, M.D.

(Cruz, …et al.)

Adverse events following infusion of T cells for adoptive immunotherapy: a 10-year experience

In view of recent reports of catastrophic reactions to 'first-in-man' biologic agents we reviewed our experience with infusions of 381 T cell products to 180 recipients, enrolled on 18 studies, receiving T cells targeting malignancies or post-transplant viral infections. There were no grade 3-4 infusion reactions during initial monitoring or 24-h follow-up. Twenty-four mild (grade 1-2) AE occurred in 21 infusions either during or immediately following infusion (up to 6 h), most commonly nausea and vomiting (10/24, 41.6%), probably because of the dimethyl sulfoxide cryoprotectant, and hypotension (20.8%), attributable to diphenhydramine pre-medication. (Cytotherapy) - PMCID: PMC2914831

http://www.ncbi.nlm.nih.gov/pubmed/20429793

(Turnis, …et al.)

IRAK-M removal counteracts dendritic cell vaccine deficits in migration and longevity

In this manuscript the authors show that viability, function and migration of dendritic cells can be enhanced by removal of the IL-1R-associated kinase M (IRAK-M). Absence of IRAK-M leads to increased activation of the p38-MAPK and NF-κB pathways, which, in turn, improves DC migration to lymph nodes, increases their longevity, and augments their secretion of Th1-skewing cytokines and chemokines. IRAK-M(-/-) DCs also increase the proliferation and activation of antigen-specific T cells. These findings have implications for the design of vaccines for lymphoma. (J Immunol) - PMID: 20817880

http://www.ncbi.nlm.nih.gov/pubmed/20817880

(Lukov, …et al.)

LYL1 degradation by the proteasome is directed by a N-terminal PEST rich site in a phosphorylation-independent manner

The lymphoblastic leukemia 1 (LYL1) gene is a proto-oncogenic transcription factor found upregulated in patients with T-cell acute lymphoblastic leukemia and lymphoma and understanding LYL1 degradation could suggest post-translational mechanisms for upregulation of LYL1 that may contribute to its oncogenic role. In this report the investigators identify a PEST sequence motif located in the N-terminus of LYL1, which determines the efficiency of LYL1 degradation by the proteasome. The absence of the PEST degradation site leads to accumulation or upregulation of LYL1. (PLoS One) - PMCID: PMC2937031

http://www.ncbi.nlm.nih.gov/pubmed/20844761

(Melenhorst, …et al.)

Allogeneic virus-specific T cells with HLA alloreactivity do not produce GVHD in human subjects

In a recent report the majority of virus-specific cytotoxic T-lymphocyte (CTL) lines showed in vitro cross-reactivity against allo-human leukocyte antigen (HLA) molecules as measured by interferon-γ secretion raising concerns that allogeneic lines may cause GVHD. We therefore reviewed our clinical experience with adoptive transfer of allogeneic hematopoietic stem cell transplantation donor-derived virus-specific CTLs in 153 recipients, including 73 instances where there was an HLA mismatch. There was no de novo acute graft-versus-host disease after infusion, and incidence of graft-versus-host disease reactivation was low and not significantly different in recipients of matched or mismatched CTL. These data indicate that the adoptive transfer of partially HLA-mismatched virus-specific CTL is safe despite in vitro recognition of recipient HLA molecules. (Blood) - PMCID: PMC2996125

http://www.ncbi.nlm.nih.gov/pubmed/20709906

(Sirin, …et al.)

The orphan nuclear receptor Nurr1 restricts the proliferation of haematopoietic stem cells

In this manuscript the authors show that demonstrate that Nurr1, a nuclear receptor transcription factor, has a regulatory role in maintaining hemopoietic stem cells in a quiescent state. Overexpression of Nurr1 drives early haematopoietic progenitors into quiescence but loss of only one allele of Nurr1 is sufficient to induce HSCs to enter the cell cycle and proliferate. These finding have significance for lymphomagenesis and tumor stem cell biology (Nat Cell Biol) - PMID: 21076412

http://www.ncbi.nlm.nih.gov/pubmed/21076412

University of Iowa

Weiner, George, M.D.

(Shanafelt, …et al.)

Vitamin D insufficiency and prognosis in chronic lymphocytic leukemia (CLL)

Serum samples from patients with new, untreated CLL were assayed for vitamin D levels. Approximately 30% of patients had low levels and these patients had a statistically significant longer time to requiring treatment and an inferior survival than those with normal vitamin D levels. Whether replacement of vitamin D would prolong the time to treatment and increase the survival of these patients requires further study. (Blood) - PMID: 21048153

http://www.ncbi.nlm.nih.gov/pubmed/21048153

(Drake, …et al.)

Vitamin D insufficiency and prognosis in non-Hodgkin's lymphoma

Low levels of vitamin D are very common in the United States, and recent data suggest that vitamin D insufficiency is related to inferior prognosis in several cancers. In a large prospective cohort of nearly 1000 newly diagnosed patients with non-Hodgkin lymphoma (NHL) from the Molecular Epidemiology Resource of the University of Iowa/Mayo Clinic Lymphoma SPORE, we found that 44% of patients had insufficient 25(OH)D levels (<25 ng/mL) at diagnosis. Patients with diffuse large B-cell lymphoma and T-cell lymphoma who had insufficient levels of 25(OH)D had inferior event-free and overall survival after accounting for clinical variables. Whether normalizing vitamin D levels in these patients improves outcomes will require testing in future trials. (J Clin Oncol) - PMCID: PMC2953973

http://www.ncbi.nlm.nih.gov/pubmed/20713849

(Takizawa, …et al.)

Genetic reporter system for oncogenic Igh-Myc translocations in mice

Reciprocal chromosomal translocations that illegitimately recombine cellular oncogenes with immunoglobulin genes have long been recognized as hallmarks of both B-cell and plasma-cell neoplasms in humans. The t(8;14)(q24;q32) translocation, most commonly observed in the post-germinal center B-cell tumor, Burkitt lymphoma, is of special interest because it results in the deregulated expression of a gene that is among the most important cancer genes—MYC; it is the first cancer-associated translocation to have been characterized at the molecular level—balanced (reciprocal) genetic exchange of MYC with the Ig heavy-chain locus, IGH; it is widely believed to be a very early, if not initiating, transforming event in neoplastic B-cell development; and, unlike the great majority of oncogene-activating translocations found in human lymphoma and leukemia, it has a direct counterpart in mice—T(12;15)(Igh–Myc)— that is itself the hallmark of peritoneal BALB/c plasmacytoma. This paper reports an advance in fundamental research on lymphoma w/o immediate clinical impact, but with exciting implications for the design and development of innovative future approaches to lymphoma therapy and prevention. (Oncogene) - PMID: 20453890

http://www.ncbi.nlm.nih.gov/pubmed/20453890

(Jevremovic, …et al.)

CD5+ B-cell lymphoproliferative disorders: Beyond chronic lymphocytic leukemia and mantle cell lymphoma

In this study we reviewed the tissue pathology of CD5+ B-cell lymphoproliferative disorders (LPD) that did not fulfill diagnostic criteria for chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL) on flow cytometric studies of peripheral blood or bone marrow. Although CD5 positivity was most commonly associated with CLL and MCL, a significant minority of cases did not fall into these two categories and instead were most commonly diagnosed as phenotypically unusual CLL, marginal zone lymphoma and lymphoplasmacytic lymphoma. Applying strict flow cytometry criteria, using genetic studies, and deferring to a lymph node/tissue diagnosis in non-classical cases are critical for accurate diagnosis and classification of CD5+ B-cell LPD. (Leuk Res) - PMID: 20362334

http://www.ncbi.nlm.nih.gov/pubmed/20362334

MYELOMA

Dana-Farber Harvard Cancer Institute

Anderson, Kenneth, M.D.

(Görgün, …et al.)

Immunomodulatory effects of lenalidomide and pomalidomide on interaction of tumor and bone marrow accessory cells in multiple myeloma

The paper examined the in vitro effects of immunomodulatory agents (IMiDs) on cytokine signaling triggered by interaction of effector cells with multiple myeloma and bone marrow stroma cells. IMiDs diminished interleukin-2, interferon gamma, and IL-6 regulator suppressor of cytokine signaling (SOCS) 1 expression in immune cells from both bone marrow and peripheral blood of myeloma patients. IMiDs also induced more potent cytotoxic T cell responses against SOCS1 re-expressing-myeloma cells than unmodified myeloma cells. These data therefore demonstrate that modulation of SOCS1 may enhance immune response and efficacy of IMiDs in multiple myeloma. (Blood) - PMCID: PMC2995353

http://www.ncbi.nlm.nih.gov/pubmed/20651070

OVARY

Fred Hutchinson Cancer Research Center

Urban Nicole, Sc. D.

(Ramirez, …et al.)

Use of a single-chain antibody library for ovarian cancer biomarker discovery

The discovery of novel early detection biomarkers of disease could offer one of the best approaches to decrease the morbidity and mortality of ovarian and other cancers. We report on the use of a single-chain variable fragment antibody library for screening ovarian serum to find novel biomarkers for the detection of cancer. We created a sublibrary of antibodies that bind proteins differentially expressed in cancer and printed it on antibody microarrays. Our use of recombinant antibody

microarrays for unbiased discovery found targets for ovarian cancer detection in multiple sample sets, supporting their further study for disease diagnosis. (Mol Cell Proteomics) - PMCID: PMC2938096

http://www.ncbi.nlm.nih.gov/pubmed/20467042

(Wurz, …et al.)

MiR-221 and MiR-222 alterations in sporadic ovarian carcinoma: Relationship to CDKN1B, CDKNIC and overall survival

MicroRNAs are often aberrantly expressed in human neoplasms and are postulated to play a role in neoplastic initiation and progression. We characterized miR-221 and miR-222 expression in 49 sporadic high grade ovarian carcinomas and correlated these findings with protein expression of CDKN1B and CDKN1C as assessed by immunohistochemistry. Expression of miR-221 and miR-222 were closely correlated with each other (p=0.0001). Interestingly, a lower ratio of miR-221 to miR-222 expression was significantly correlated with worse overall survival (p=0.01) and remained a significant predictor of overall survival in multivariate analysis (p=0.03). Higher miR-222 and miR-221 expression were significantly associated with decreased p57 expression (p=0.009 and 0.01). (Genes Chromosomes Cancer) - PMCID: PMC2869465

http://www.ncbi.nlm.nih.gov/pubmed/20461750

(Ventura, …et al.)

Activation of the MEK-S6 pathway in high-grade ovarian cancers

The primary objective of this study was to show the activation and analyze the regulation of the MEK- S6 kinase pathway in high-grade ovarian cancer. Our data suggest that MEK is a potential drug target in high-grade ovarian cancer, however, cancer cells with hyperactive AKT and cancer cells in ascites may be less responsive to MEK inhibition. The phosphorylation of S6 as a specific biomarker for either MEK or PI3-kinase pathway activation but it should be used with caution to determine which of these two pathways is active. (Appl Immunohistochem Mol Morphol) - PMCID: PMC2989426

http://www.ncbi.nlm.nih.gov/pubmed/20661131

Fred Hutchinson Cancer Research Center

Cramer, Daniel, M.D.

(Cramer, …et al.)

Correlates of the preoperative level of CA125 at presentation of ovarian cancer

This study identifies several epidemiologic factors that elevate levels of CA125 including parity, prior breast cancer, and family history of breast or ovarian cancer as well as factors that lower CA125 including greater BMI, colitis and appendectomy. These are factors that may need to be considered in the clinical interpretation of CA125 for monitoring disease or future use in screening. (Gynecol Oncol) - PMCID: PMC2980911

http://www.ncbi.nlm.nih.gov/pubmed/20850174

(Cramer, …et al.)

CA125 immune complexes in ovarian cancer patients with low CA125 concentrations

This paper describes an assay to detect CA125 bound in an immune complex (with anti-CA-125 antibodies) that may be "hiding" CA125 in ovarian cancer patients with low CA125. This could become a test complementary to CA125 for clinical monitoring of patients or use in early detection. (Clin Chem) - PMID: 20943848

http://www.ncbi.nlm.nih.gov/pubmed/20943848

(Konstantinopoulos, …et al.)

Gene Expression Profile of BRCAness That Correlates With Responsiveness to Chemotherapy and With Outcome in Patients With Epithelial Ovarian Cancer

In addition to patients with germline BRCA1/2 mutations, PARP inhibition might be a useful therapy for patients with sporadic cancers that have a BRCAness phenotype, characterized by defective homologous recombination. However, it is not always possible to identify such patients on the basis of molecular- or protein-based biomarkers. We have developed a gene expression profile of BRCAness that appears to correlate with responsiveness to platinum and PARP inhibitors and may identify a subset of sporadic patients with improved clinical outcome after platinum-based therapy. (J Clin Oncol) - PMCID: PMC2917311

http://www.ncbi.nlm.nih.gov/pubmed/20547991

(Levanon, …et al.)

Primary ex vivo cultures of human fallopian tube epithelium as a model for serous ovarian carcinogenesis

This paper describes an ex-vivo model system that recapitulates changes that may occur in-vivo in the pathway from normal tubal epithelium to serous ovarian cancer. These changes include secretion of markers associated with ovarian cancer, accumulation of DNA damage, and morphologic changes. (Oncogene) - PMCID: PMC2829112

http://www.ncbi.nlm.nih.gov/pubmed/19935705

MD Anderson Cancer Center

Bast, Robert, M.D.

(Wong, …et al.)

BRAF mutation is rare in advanced-stage low-grade ovarian serous carcinomas

The low frequency of BRAF mutations in advanced-stage, low-grade serous carcinomas, which contrasts with previous findings, suggests that aggressive, low-grade serous carcinomas are more likely derived from serous borderline tumors without BRAF mutation. In addition, advanced-stage, low-grade carcinoma patients with BRAF or KRAS mutation have a better apparent clinical outcome. (Am J Pathol) - PMCID: PMC2947258

http://www.ncbi.nlm.nih.gov/pubmed/20802181

(Lu, …et al.)

Regulation of tumor angiogenesis by EZH2

In this work, we identify EZH2 as a key regulator of tumor angiogenesis. The increase in endothelial EZH2 is a direct result of VEGF stimulation and indicates the presence of a paracrine circuit that promotes angiogenesis. Ezh2 silencing in the tumor associated endothelial cells using siRNA, packaged in the chitosan delivery system, resulted in significant growth inhibition in an orthotopic ovarian cancer model. Ezh2 silencing in tumor endothelial cells resulted in decreased angiogenesis that was mediated by increased levels of the angiogenesis inhibitor, VASH1. Combined, these data provide a significant conceptual advance in our understanding of the regulation of angiogenesis in ovarian carcinoma and support the potential for targeting ezh2 as a therapeutic approach. (Cancer Cell) - PMCID: PMC2923653

http://www.ncbi.nlm.nih.gov/pubmed/20708159

(An, …et al.)

Messenger RNA expression and methylation of candidate tumor-suppressor genes and risk of ovarian cancer-a case-control analysis

To investigate the association of expression and promoter methylation of tumor-suppressor genes with risk of ovarian cancer, we conducted a case-control study of 102 patients with serous epithelial ovarian cancer and 100 patients without ovarian cancers. We measured mRNA expression levels) and methylation status five candidate genes (BRCA1, BRCA2, hMLH1, MGMT, and DNMT3B) in tumors from the cases and normal ovaries from the controls. We found that mRNA expression levels of the five genes were decreased in tumors than in normal ovaries. (Int J Mol Epidemiol Genet) - PMCID: PMC2916180

http://www.ncbi.nlm.nih.gov/pubmed/20689651

(Bast, …et al.)

Personalizing therapy for ovarian cancer: BRCAness and beyond

This is a review article. Striking responses to poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors in patients with inactivating germline mutations of BRCA1 or BRCA2 have provided one of the best examples to date of personalized therapy for ovarian cancer. The challenge remains to develop a convenient and accurate method to identify ovarian cancers with BRCAness and, in particular, to identify patients likely to benefit from PARP inhibitor therapy. Personalizing therapy will require the study of large numbers of patients who are willing to undergo biopsies, have their cancers analyzed by contemporary techniques, and participate in clinical trials of targeted therapy with translational correlates based on the genotype and phenotype of their tumors. Studies of PARP inhibitors for patients with ovarian cancers that exhibit BRCA dysfunction provide a logical first step. (J Clin Oncol) - PMID: 20547987

http://www.ncbi.nlm.nih.gov/pubmed/20547987

(Schlumbrecht, …et al.)

Molecular clustering based on ERα and EIG121 predicts survival in high-grade serous carcinoma of the ovary/peritoneum

We hypothesized that analysis of a panel of estrogen-induced genes can predict the outcome in ovarian carcinoma and potentially differentiate between tumors of varying hormonal responsiveness.The expression of ERa and six genes known to be induced by estrogen in the female reproductive tract (namely EIG121, sFRP1, sFRP4, RALDH2, PR, and IGF-1) was measured using quantitative RT-PCR.In contrast to other hormonally driven cancers, high expression of ERa and the estrogen-induced gene EIG121 predicts shorter OS in patients with high-grade serous ovarian carcinoma. Such a biomarker panel may potentially be used to guide management with estrogen antagonists in this patient population. (Mod Pathol) - PMID: 21102415

http://www.ncbi.nlm.nih.gov/pubmed/21102415

PANCREAS

Mayo Clinic

Petersen, Gloria, M.D.

(Rowley, …et al.)

Inactivation of Brca2 promotes Trp53-associated but inhibits KrasG12D-dependent pancreatic cancer development in mice

The study is significant because it establishes BRCA2 as a pancreatic cancer predisposition gene that can be targeted for genetic testing, suggests that PARP inhibitors may be an effective therapy for pancreatic cancers arising in BRCA2 mutation carriers, and identifies Kras inhibition as a possible therapeutic strategy for these patients. (Gastroenterology) - PMID: 21199651

http://www.ncbi.nlm.nih.gov/pubmed/21199651

(McWilliams, …et al.)

Prevalence of CDKN2A mutations in pancreatic cancer patients: implications for genetic counseling

This is the largest study to date of assessing p16/CDKN2A germline mutations in unselected pancreatic cancer patients. This study established the prevalence of these mutations in this population, and provided pancreatic cancer and melanoma risk estimates for persons carriers of mutations. It also explored gene-environment influences on lifetime risk. (Eur J Hum Genet) - PMID: 21150883

http://www.ncbi.nlm.nih.gov/pubmed/21150883

(McWilliams, …et al.)

Obesity adversely affects survival in pancreatic cancer patients

This is the definitive study firmly establishing increasing body-mass index as an adverse survival factor in all stages of pancreatic cancer. This will influence clinical trial design along with providing potential targets for therapeutic studies, such as the insulin pathway. (Cancer) - PMCID: PMC2963722

http://www.ncbi.nlm.nih.gov/pubmed/20665496

(Singh, …et al.)

Sequential activation of NFAT and c-Myc transcription factors mediates the TGF-beta switch from a suppressor to a promoter of cancer cell proliferation

This works demonstrate that NFAT transcription factors are mediators of this TGF-β proliferative response in pancreatic cancer cells. TGF-β mediated signaling has a significant role in the regulation of pancreatic carcinogenesis, initially as a tumor suppressor and then as a positive mediator of tumor progression. (J Biol Chem) - PMCID: PMC2930723

http://www.ncbi.nlm.nih.gov/pubmed/20516082

PROSTATE

Johns Hopkins University

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

(Aloia, …et al.)

XMRV: a new virus in prostate cancer?

Several poorly-controlled published studies hinted at a role for XMRV, a xenotropic murine leukemia virus-related virus, in the pathogenesis of human prostate cancer. In the largest (n = 800), and most carefully conducted analysis yet undertaken, no evidence of a causal role for XMRV was evident. (Cancer Res) - PMCID: PMC3005136

http://www.ncbi.nlm.nih.gov/pubmed/20966126

University of Michigan

Pienta, Kenneth J., M.D.

(Palanisamy, …et al.)

Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma

Although recurrent gene fusions involving erythroblastosis virus E26 transformation-specific (ETS) family transcription factors are common in prostate cancer, their products are considered 'undruggable' by conventional approaches. Recently, rare targetable gene fusions involving the anaplastic lymphoma receptor tyrosine kinase (ALK) gene, have been identified in 1-5% of lung cancers, suggesting that similar rare gene fusions may occur in other common epithelial cancers, including prostate cancer. (Nat Med) - PMCID: PMC2903732

http://www.ncbi.nlm.nih.gov/pubmed/20526349

(Qin, …et al.)

HPeak: an HMM-based algorithm for defining read-enriched regions in ChIP-Seq data

Protein-DNA interaction constitutes a basic mechanism for the genetic regulation of target gene expression but is difficult to characterize protein-bound DNA on a large scale. Coupling chromatin immunoprecipitation (ChIP) with next-generation sequencing, (ChIP-Seq provides a direct survey of the cistrom of transcription factors and other chromatin-associated proteins. (BMC Bioinformatics) - PMCID: PMC2912305

http://www.ncbi.nlm.nih.gov/pubmed/20598134

(Yu, …et al.)

The neuronal repellent SLIT2 is a target for repression by EZH2 in prostate cancer

Through genome-wide location analysis we identified SLIT2 as a target of polycomb group (PcG) protein EZH2. The EZH2-containing polycomb repressive complexes bound to the SLIT2 promoter inhibiting its expression. SLIT2 was downregulated in a majority of metastatic prostate tumors, showing a negative correlation with EZH2. (Oncogene) - PMCID: PMC2948081

http://www.ncbi.nlm.nih.gov/pubmed/20622896

MD Anderson Cancer Center

Logothetis, Christopher, M.D.

(Luo, …et al.)

Metabolic regulator betaKlotho interacts with fibroblast growth factor receptor 4 (FGFR4) to induce apoptosis and inhibit tumor cell proliferation

FGF signaling normally drives cell growth in development, response to injury and can drive tumors. By a receptor complex interactive membrane protein called klotho, the same signaling system can be turned to endocrine control of metabolism in liver, adipose tissue and kidney. The co-factor coverts pro-growth signaling into pro-apoptotic cell death signaling system that is tumor suppressive providing an avenue to convert the tumor promotion signaling into tumor suppression. (J Biol Chem) - PMCID: PMC2943257

http://www.ncbi.nlm.nih.gov/pubmed/20657013

University of California, Los Angeles

Reiter, Robert, M.D.

(Wang, …et al.)

Prognostic value and function of KLF4 in prostate cancer: RNAa and vector-mediated overexpression identify KLF4 as an inhibitor of tumor cell growth and migration

We found that KLF4, a transcription factor, is significantly downregulated in prostate cancer cell lines compared with non-tumorigenic prostate cells. Tissue microarray analysis of tumors and patient-matched controls indicated downregulation of KLF4 in tumors that metastasized and In vitro analysis indicated that overexpression of KLF4 inhibited prostate cancer cell proliferation and survival and altered the expression of several downstream cell-cycle–related genes. Therefore, KLF4 functions as an inhibitor of tumor cell growth and migration in prostate cancer and decreased expression has prognostic value for predicting prostate cancer metastasis. (Cancer Res) - PMID: 21159640

http://www.ncbi.nlm.nih.gov/pubmed/21159640

(Tanaka, …et al.)

Monoclonal antibody targeting of N-cadherin inhibits prostate cancer growth, metastasis and castration resistance

N-Cadherin is upregulated in castration-resistant prostate cancer which may promote castration resistance and metastasis. Monoclonal antibodies against the ectodomain of N-cadherin reduced proliferation, invasion and metastasis and delay the time to emergence of castration resistance. It also affects tumor histology and angiogenesis, and reduces both AKT serine-threonine kinase activity and serum interleukin-8 (IL-8) secretion. (Nat Med) - PMID: 21057494

http://www.ncbi.nlm.nih.gov/pubmed/21057494

(Goldstein, …et al.)

Identification of a cell of origin for human prostate cancer

Luminal cells are believed to be the cells of origin for human prostate cancer, because the disease is characterized by luminal cell expansion and the absence of basal cells, yet functional studies addressing the origin of human prostate cancer have not previously been reported because of a lack of

relevant in vivo human models. We show that basal cells from primary benign human prostate tissue can initiate prostate cancer in immunodeficient mice. The cooperative effects of AKT, ERG, and androgen receptor in basal cells recapitulated the histological and molecular features of human prostate cancer, with loss of basal cells and expansion of luminal cells expressing prostate-specific antigen and alpha-methylacyl-CoA racemase. (Science) - PMCID: PMC2917982

http://www.ncbi.nlm.nih.gov/pubmed/20671189

(Sun, …et al.)

Intracellular fates of cell-penetrating block copolypeptide vesicles

Overall, our studies demonstrated that our novel polypeptide vesicles are able to enter cells intact with their cargos, and although some manage to escape from early endosomes, most are trapped within these intracellular compartments. On the basis of these findings, we can conclude that a mechanism for endosomal disruption should be incorporated into block copolypeptide vesicles to enhance their release into the cytoplasm. The development of vesicles with pH switchable endosomal and vesicle disruptive capability is currently underway to improve their ability to delivery drugs to prostate cancer cells. (Biomacromolecules) - PMID: 21128599

http://www.ncbi.nlm.nih.gov/pubmed/21128599

Dana Farber/Harvard Cancer Center

Kantoff, Philip, M.D.

(Penney, …et al.)

Genome-wide association study of prostate cancer mortality

While many risk loci have been discovered for prostate cancer pathogenesis, no genome wide scans have focused on lethal prostate cancer. We did not find any variants that achieved genome wide significance. Common genetic determinants of lethal prostate cancer are likely to have odds ratios of less than 2. (Cancer Epidemiol Biomarkers Prev) - PMID: 20978177

http://www.ncbi.nlm.nih.gov/pubmed/20978177

(Pomerantz, …et al.)

Analysis of the 10q11 cancer risk locus implicates MSMB and NCOA4 in human prostate tumorigenesis

Beginning in 2006, researchers have identified several genetic variants that are associated with prostate cancer risk, however the majority of prostate cancer risk variants do not reside in genes and determining the genes involved in the development of disease has proved challenging. We interrogated a known prostate cancer risk polymorphism on chromosome 10 and implicated two genes- MSMB and NCOA4- in the risk of developing prostate cancer. (PLoS Genet) - PMCID: PMC2978684

http://www.ncbi.nlm.nih.gov/pubmed/21085629

University of Washington/Fred Hutchinson Cancer Research Center

Nelson, Peter, M.D.

(Morrissey, ...et al.)

Inhibition of angiopoietin-2 in LuCaP 23.1 prostate cancer tumors decreases tumor growth and viability

Angiopoietin-2 is a protein that is involved in angiogenesis (new blood vessel formation) which is required for the growth and survival of solid tumors. Our results demonstrate that inhibiting angiopoietin-2 activity impedes angiogenesis and growth of LuCaP 23.1 prostate cancer xenografts. Based on these data, we hypothesize that angiopoietin-2 inhibition in combination with other therapies may represent a potential therapy for patients with metastatic disease. (Prostate) - PMID: 20583134

http://www.ncbi.nlm.nih.gov/pubmed/20583134

(Sun, ...et al.)

Castration resistance in human prostate cancer is conferred by a frequently occurring androgen receptor splice variant

This paper describes a new splice variant of the androgen receptor that occurs after castration and makes the tumor resistant to castration. Importantly, although a previous splice variant has been described, this is the first to be described in lethal human metastases. The clinical significance is that it may be a biomarker as to when the tumor will be resistant to standard castration. (J Clin Invest) - PMCID: PMC2912187

http://www.ncbi.nlm.nih.gov/sites/ppmc/articles/PMC2912187/

Northwestern University

Lee, Chung, Ph.D.

(Yu, …et al.)

The neuronal repellent SLIT2 is a target for repression by EZH2 in prostate cancer

This is the first study to demonstrate that the neuronal repellent SLIT2 is down-regulated in prostate cancer. SLIT2 down-regulation in prostate cancer is mediated by polycomb group protein EZH2 as well as SLIT2 promoter hypermethylation. The reduced SLIT2 expression in prostate cancer predicts poor clinical outcome. (Oncogene) - PMCID: PMC2948081

http://www.ncbi.nlm.nih.gov/pubmed/20622896

(Lakshman, …et al.)

Endoglin suppresses human prostate cancer metastasis

This study demonstrates that loss of endoglin expression can increase the ability of human prostate cancer cells to metastasize. During progression of prostate cancer disease, endoglin expression is lost. This study suggests that people whose cancer has lost expression of endoglin, or signaling proteins in the endoglin signaling pathway, are at higher risk of prostate cancer metastasis and should be monitored more closely, and treated more aggressively. (Clin Exp Metastasis) - PMCID: PMC3046557

http://www.ncbi.nlm.nih.gov/pubmed/20981476

(Gudmundsson, …et al.)

Genetic correction of PSA values using sequence variants associated with PSA levels

We detected a genome-wide significant association between PSA levels and single-nucleotide polymorphisms (SNPs) at six loci: 5p15.33 (rs 2736098), 10q11 (rs10993994), 10q26 (rs10788160), 12q24 (rs11067228), 17q12 (rs4430796), and 19q13.33 [rs17632542 (KLK3: I179T)], each with P(combined) <3 × 10(-10). Among 3834 men who underwent a biopsy of the prostate, the 10q26, 12q24, and 19q13.33 alleles that associate with high PSA levels are associated with higher probability of a negative biopsy (odds ratio between 1.15 and 1.27). Assessment of association between the six loci and prostate cancer risk in 5325 cases and 41,417 controls from Iceland, the Netherlands, Spain, Romania, and the United States showed that the SNPs at 10q26 and 12q24 were exclusively associated with PSA

levels, whereas the other four loci also were associated with prostate cancer risk. (Sci Transl Med) - PMID: 21160077

http://www.ncbi.nlm.nih.gov/pubmed/21160077

(Helfand, ...et al.)

Genetic prostate cancer risk assessment: common variants in 9 genomic regions are associated with cumulative risk

A cumulative model including the 9 single nucleotide polymorphisms provided greater prostate cancer risk stratification than a model restricted to the original 5 single nucleotide polymorphisms described. (J Urol) - PMID: 20620408

http://www.ncbi.nlm.nih.gov/pubmed/20620408

Lee, Chung, Ph.D.

(Yu, ...et al.)

Overexpression of transforming growth factor β1 in malignant prostate cells is partly caused by a runaway of TGF-β1 auto-induction mediated through a defective recruitment of protein phosphatase 2A by TGF-β type I receptor

These results suggest that TGF-b1 overexpression in malignant cells is caused, at least in part, by TGF-b1 auto-induction through ERK activation due to defective recruitment of PP2A-Ba by TbRI which inhibits ERK activation in benign cells. (Urology) - PMCID: PMC2997920

http://www.ncbi.nlm.nih.gov/pubmed/21030067

Memorial Sloan-Kettering Cancer Center

Scher, Howard I., M.D.

(Taylor, ...et al.)

Integrative genomic profiling of human prostate cancer

Annotation of prostate cancer genomes provides a foundation for discoveries that can have an impact on disease understanding and treatment. Our analysis showing the high impact of CNA data on risk of relapse relative to transcriptome profiling demonstrate the broad utility of this integrated prostate oncogenome data set. The high prevalence of this important disease and the relative paucity of large comprehensive genomic data sets in prostate cancer make this a unique public resource for the cancer research community. (Cancer Cell) - PMID: 20579941

http://www.ncbi.nlm.nih.gov/pubmed/20579941

(Benchikh, ...et al.)

A panel of kallikrein markers can predict outcome of prostate biopsy following clinical work-up: an independent validation study from the European Randomized Study of Prostate Cancer screening, France

This study applied a previously published predictive model based on the kallikrein panel to 262 men undergoing prostate biopsy following an elevated prostate-specific antigen (PSA) (≥ 3 ng/ml) and further clinical work-up during the European Randomized Study of Prostate Cancer screening, France. The predictive accuracy of the model was compared to a "base" model of PSA, age and digital rectal exam (DRE). We found that our model of kallikrein markers (total PSA, free PSA, intact PSA and human kallikrein-related peptidase 2) had significantly higher accuracy than the base model in predicting cancer. (BMC Cancer) - PMCID: PMC2996396

http://www.ncbi.nlm.nih.gov/pubmed/21092177

(Gupta, ...et al.)

A four-kallikrein panel for the prediction of repeat prostate biopsy: data from the European Randomized Study of Prostate Cancer screening in Rotterdam, Netherlands

In a study cohort of 925 men with a previous negative prostate biopsy and elevated prostate-specific antigen (PSA), the full kallikrein panel had higher discriminative accuracy than PSA and digital rectal examination (DRE) alone. The four-kallikrein panel predicts the result of repeat prostate biopsy in men with elevated PSA while dramatically decreasing unnecessary biopsies. Use of the model to determine repeat biopsy in men with elevated PSA would dramatically reduce rebiopsy rates, while delaying the diagnosis of only a small number of cancers, almost all of which are low grade. (Br J Cancer) - PMCID: PMC2938258

http://www.ncbi.nlm.nih.gov/pubmed/20664589

(Vickers, …et al.)

A panel of kallikrein marker predicts prostate cancer in a large, population-based cohort followed for 15 years without screening

As many as 750,000 men undergo prostate biopsy unnecessarily because of prostate-specific antigen (PSA) elevations, which can be caused by benign disease. The PSA test has only modest diagnostic specificity at commonly used cut-points and is therefore an imperfect test for prostate cancer. This study shows that a prespecified statistical model, based on a panel of four kallikrein markers (total, free, and intact PSA and hK2), is a highly accurate predictor that a man with elevated PSA would be clinically diagnosed with an advanced cancer in the absence of screening. (Cancer Epidemiol Biomarkers Prev) - PMCID: PMC3035761

http://www.ncbi.nlm.nih.gov/pubmed/21148123

SKIN/MELANOMA

University of Pittsburgh

Kirkwood, John, M.D.

(Gogas, …et al.)

Evaluation of six CTLA-4 polymorphisms in high-risk melanoma patients receiving adjuvant interferon therapy in the He13A/98 multicenter trial

Polymorphisms of CTLA4 have been suggested to be important predictors benefit from immunotherapy. This study of six candidate polymorphisms has shown no demonstrable role as predicting the benefit of IFNα, the only adjuvant therapy approved by regulatory authorities worldwide, for melanoma. (J Transl Med) - PMCID: PMC2988721

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2988721

(Gogas, …et al.)

Correlation of molecular human leukocyte antigen typing and outcome in high-risk melanoma patients receiving adjuvant interferon

Adjuvant immunotherapy of melanoma is presently decided on the basis of relapse risk and general population benefits and toxicities of IFNα. Biomarkers that permit selection of patients with increased likelihood of benefit from adjuvant IFNα immunotherapy would improve the risk/benefit ratio. Human leukocyte antigens (HLA) of the class I and II major histocompatibility complexes (MHC) have been suggested to predict therapeutic response and/or overall survival of melanoma. No significant differences between the distribution of HLA genotypes in the melanoma and healthy controls were found. The HLA-Cw*06 allele was found to correlate with improved relapse-free and overall survival of melanoma treated with IFNα. The median relapse-free survival for Cw*06-positive patients was 100 months vs. 37 months for Cw*06-negative patients (P <.013). Median overall survival for Cw*06-positive patients has not yet been reached, where it is 79 months in Cw*06-negative patients (P <.025). Only HLA-Cw*06, an allele previously correlated with susceptibility to psoriasis, was found to correlate with relapse-free and overall survival with IFNα. (Cancer) - PMCID: PMC2970916

http://www.ncbi.nlm.nih.gov/pubmed/20549830

(Vujanovic, …et al.)

Virally infected and matured human dendritic cells activate natural killer cells via cooperative activity of plasma membrane-bound TNF and IL-15

Recombinant adenovirus-engineered dendritic cells (Ad.DC) are potent immunologic anti-cancer vaccines. The effectiveness of Ad.DC-based vaccines was shown to depend in part on the ability of Ad.DC to crosstalk with natural killer (NK) cells in a murine model, in vivo. Our findings in the human setting demonstrate that Ad.DC can efficiently promote innate immune function by activation of NK cells through the cooperative activities of trans-membrane TNF and trans-presented-IL-15 via cell-to-cell contact. (Blood) - PMID: 20430958

http://www.ncbi.nlm.nih.gov/pubmed/20430958

(Muthuswamy, …et al.)

PGE(2) transiently enhances DC expression of CCR7 but inhibits the ability of DCs to produce CCL19 and attract naive T cells

The papers reports on the regulation of CCR7/CCL19 system involved in the homing of DCs, T cells, and melanoma cells, to central lymphoid organs. We show that prostaglandin E(2), an inflammatory mediator often used to increase CCR7 expression in the dendritic cells (DCs) used as melanoma vaccines suppresses the production of the endogenous CCR7 ligand, CCL19, in DCs. In contrast to the PGE(2)-matured DCs, DCs matured in the presence of toll-like receptor (TLR) ligands and interferons produce high levels of both CCL19 and CCR7 mRNA/protein, but show selectively reduced expression of surface CCR7, which is compensated after DC removal from the CCL19-rich maturation

environment. The differences in CCL19-producing ability imprinted during DC maturation result in their different abilities to attract CCR7(+) naive T cells. These data help to explain the impact of PGE(2) on CCR7 expression in maturing DCs and demonstrate a novel mechanism of regulatory activity of PGE(2), mediated by the inhibition of DCs ability to attract naive T cells. (Blood) - PMCID: PMC2938836

http://www.ncbi.nlm.nih.gov/pubmed/20498301

(Zhao, …et al.)

Intratumoral IL-12 Gene Therapy Results in the Crosspriming of Tc1 Cells Reactive Against Tumor-associated Stromal Antigens

Paper reports that while melanoma antigens presented by different types of mature dendritic cells (DCs) are similarly effective in inducing CD8+ T cell expansion, the acquisition of CTL function and peripheral-type chemokine receptors, CCR5 and CXCR3, requires Ag presentation by a select type of DCs. Both "standard" DCs (matured in the presence of PGE2) and type 1-polarized DCs (DC1s) (matured in the presence of IFNs and TLR ligands, which prevent DCs "exhaustion") are similarly effective in inducing CD8+ T cell expansion and acquisition of CD45RO+IL-7R+IL-15R+ phenotype. However, granzyme B expression, acquisition of CTL activity, and peripheral tissue-type chemokine responsiveness are features exclusively exhibited by CD8+ T cells activated by DC1s. This advantage of DC1s was observed in polyclonally activated naive and memory CD8(+) T cells and in blood-isolated melanoma-specific CTL precursors. Our data help to explain the dissociation between the ability of cancer vaccines to induce high numbers of tumor-specific CD8+ T cells in the blood of cancer patients and their ability to promote clinical responses, providing for new strategies of cancer immunotherapy. (Mol Ther) - PMID: 21189473

http://www.ncbi.nlm.nih.gov/pubmed21189473

(Bose, …et al.)

Sunitinib facilitates the activation and recruitment of therapeutic anti-tumor immunity in concert with specific vaccination

Paper reports that the TKI sunitinib potentiates the anti-melanoma efficacy of peptide-based vaccines by i.) acutely reducing local mmune-suppression in the tumor microenvironment via antagonism of MDSC and Treg cells, ii.) facilitating the activation and expansion of anti-tumor CD8+ T cells in lymph nodes and spleen, and iii.) activating the tumor vasculature (VCAM-1 and CXCR3 ligands) to recruit vaccine-induced, Type-1 effector T cells. These data support the development/performance of phase I/II clinical trials implementing melanoma vaccines combined with sunitinib administration. (Int J Cancer) - PMID: 21170961

http://www.ncbi.nlm.nih.gov/pubmed/21170961

Brigham and Women's Hospital

Kupper, Thomas, M.D.

(Panka, …et al.)

An inexpensive, specific and highly sensitive protocol to detect the BrafV600E mutation in melanoma tumor biopsies and blood

This paper describes a novel PCR-based technique that can be used to detect melanoma cells harboring the BRAFV600E mutation in circumstances in which the tumor cells constitute only a minor fraction of the cells in the specimen to be tested. The technique is particularly applicable to the analysis of blood for circulating tumor cells. (Melanoma Res) - PMCID: PMC2936688

http://www.ncbi.nlm.nih.gov/pubmed/20679909