

GW Cancer Center Participates in the American Association for Cancer Research Annual Meeting 2018

Researchers from the George Washington University (GW) Cancer Center will be participating at the American Association for Cancer Research Annual Meeting held April 14-18, 2018 in Chicago. At the meeting, Eduardo Sotomayor, MD, director of the GW Cancer Center, will speak at the AACR-MICR Distinguished Lectureship on "Finding a niche to develop a Translational Program: Mantle cell lymphoma as a model for translational science." Post-meeting, he will also begin his role as a new member of the AACR Science Policy and Government Affairs Committee.

GW Cancer Center researchers Cath Bollard, MD, and Kieron Dunleavy, MD, will also be presenting. Bollard will chair Session ED45, "[New insights into the biology and treatment of virus-associated malignancies](#)" and present, "[Virus directed T cell therapies for virus-associated cancers](#)." Dunleavy will also present during Session ED45, on "[Recent advances in the biology and management of EBV-associated lymphomas](#)." Jie Chen, PhD from Sotomayor's laboratory will be presenting in Session 4967, on "[HDAC11 function as a transcriptional regulator in immature myeloid cells to myeloid-derived suppressor cells transition](#)."

GW Cancer Center researchers are presenting the following posters:

498/28 - Dual functions of miR-200b in triple-negative breast cancer metastasis and chemoimmuno-resistance

X. Tan, S. Ren, W. Lee, X. Wu, K. Rezaei, Y-g. Man, P. Latham, R. S. Siegel, R. F. Brem, Z. Li, X. Chang, S. W. Fu

Poster Session: PO.MCB10.01 - MicroRNA Regulation in Cancer Biology

April 15, 1:00 PM - 5:00 PM

Triple-negative breast cancer (TNBC) is a subtype of breast cancer that is negative for estrogen and progesterone receptors (ER/PR) and human epidermal growth factor receptor 2 (HER2). It is typically associated with high rate of metastasis and limited targeted treatment options. Chemotherapy is the standard treatment for metastatic TNBC. However, the development of chemoresistance limits its clinical application. Elevated expression of immune-related genes in TNBC suggests that immunotherapy strategies may provide new therapeutic options for TNBC. ([Read more](#))

506/6 - miR-203a-3p may play a tumor suppressor role in esophageal cancer by targeting GATA Binding Protein 6

C. Yin, X. Tan, Q. Tan, J. Wang, J. Zhang, X. Wu, T. Chen, H. Jiao, S. W. Fu

Poster Session: PO.MCB10.02 - Noncoding RNAs as Oncogenes and Tumor Suppressors
April 15, 1:00 PM - 5:00 PM

Esophageal cancer (EC) is the eighth most common cancer and the sixth most common cause of cancer death worldwide. MicroRNAs (miRNAs) are small 19-22nt non-coding single-strand RNAs that regulate diverse cellular processes and are dysregulated in a variety of cancers including EC. Using bioinformatics analysis, we identified a list of dysregulated miRNAs from most recent studies on miRNA expression profiling in EC, including miR-203a-3p, which was reported as a tumor suppressor miRNA and dysregulated in many malignancies. GATA Binding Protein 6 (GATA6) is a member of zinc finger transcription factors that is amplified or overexpressed in many tumors, such as breast cancer, pancreatic cancer, esophageal cancer, etc. Our bioinformatics analysis showed that GATA6 is a potential target of miR-203a-3p. Therefore, we hypothesize that miR-203a-3p functions as a tumor suppressor miRNA in esophageal cancer by targeting GATA6. ([Read more](#))

5126/7 - Modulation of lactate in the tumor microenvironment with lactate transporter inhibitor in a melanoma syngeneic mouse model

S. R. Noonpalle, J. Kim, M. Hadley, E. Palmer, D. Banik, T. Knox, S. Ephrame, P. Vembu, S. Rudish, S. Moufarrij, J. Escobedo, V. Sandanayaka, A. Villagra

Poster Session: PO.TB06.06 - Metabolism and the Microbiome: Defining the Greater Microenvironment
April 18, 8:00 AM - 12:00 PM

Solid tumors often have altered metabolism that depend on aerobic glycolysis for energy and macromolecules for cell survival thereby generating lactate as a metabolic byproduct. Lactate is transported across the cell membrane into tumor microenvironment (TME) using monocarboxylate transporters, MCT1 and MCT4. MCTs facilitate proton linked transport of monocarboxylate molecules such as lactate, pyruvate, and ketone bodies across the plasma membrane. Lactate released by glycolytic cells into the TME results in a metabolic symbiosis when other tumor cells utilize lactate as an energy source that undergo oxidative metabolism which is referred to as "lactate shuttle". Moreover, lactate induces inhibitory pathways on immune cells, especially on cytotoxic CD8+ T-cells resulting in local immunosuppression in the TME. Additionally, acidosis of TME through lactate results in local inflammation and angiogenesis by activation of VEGFR signaling. The net result of an increased lactate in TME is that it generates a conducive milieu for tumor growth and metastasis. Although studies show that MCT inhibitors mitigate the effects of lactate and promote immune function, its effect on immune cells in the context of tumor infiltration is yet to be explored. In this study, we used a MCT inhibitor NGY-A to determine the effect of suppressing lactate levels in the TME and restoring the anti-tumor immunity. ([Read more](#))

48/28 - Targeting HDAC6 to reduce the aggressiveness of metastatic breast cancer in immunotherapy

D. Banik, M. Hadley, E. Palmer, V. Gallub, E. Sotomayor, A. Kozikowski, A. Villagra

Poster Session: PO.TB04.01 - Breast Cancer Metastasis

April 15, 1:00 PM - 5:00 PM

Histone modifiers are recognized to perform diverse functions above beyond their conventional roles in remodeling the chromatin landscape. These functionalities range from regulating the outcomes of cellular-health to systemic immune-diseases, e.g., autoimmunity and cancer, positioning the HDAC inhibitors at a crucial junction of immunotherapy. However, the toxicity from the broad-spectrum HDAC-inhibitors has deemed a better focus on inhibitors of individual HDAC-members associated with tumor progression. One such member is HDAC6 which was earlier reported to promote the pro-tumorigenic STAT3 pathway. By using pharmacological inhibitor of HDAC6, the downstream immune-modulatory pathways of STAT3 could be targeted, which directly link to T-cell mediated immunity through the co-stimulatory molecules PD-L1, PD-L2 and B7-H4. This relationship has been established in a wide variety of tumors, including melanoma and breast cancer. HDAC6 has been also involved in a number of structural functions related to cellular motility, shape and intracellular transport through the regulation of the acetylation of numerous targets, including tubulin and cortactin. This function is strongly suggestive of HDAC6 being a key player in metastatic cancer progression. ([Read more](#))

1395/19 - HDAC6 and DNMT inhibition affect immunogenicity of ovarian cancer cells: A rationale for combining epigenetic and immune therapy in ovarian cancer

A. P. Srivastava, S. M. Moufarrij, M. Hadley, S. Chisholm, M. Lopez-Acevedo, A. Villagra, K. B. Chiappinelli

Poster Session: PO.MCB05.02 - Epigenetic Therapy

April 16, 8:00 AM - 12:00 PM

Therapies that activate the immune system to fight cancer have shown robust responses in solid tumors. However, most patients, including those with ovarian cancer, do not respond to these therapies alone. Drugs that inhibit epigenetic modifiers increase immune signaling from cancer cells. Epigenetic modifiers DNA methyltransferase inhibitors (DNMTi) and selective histone deacetylase inhibitors (HDACi), in particular selective HDAC6i, modulate immune-related pathways involved in anti-tumor immune responses. HDAC6i downregulate immunosuppressive ligands PD-L1 and PD-L2 via dephosphorylating pSTAT3 and upregulate tumor associated antigens (TAA) and antigen presentation machinery. Similarly, DNMTi activate anti-viral signaling via expression of Endogenous Retroviruses (ERVs) to trigger the type I interferon response, upregulate tumor antigen processing and presentation, and stimulate pro-inflammatory cytokines. The aim of our study is to test if the combination of epigenetic modulators Nexturastat A (Next A), a selective HDAC6i, and 5-azacytidine (AZA), a DNMTi, can be safely used to increase an immune response in ovarian cancer. We hypothesize that these drugs will enhance tumor immunity alone and when combined with immune checkpoint blockades targeting PD-1. ([Read more](#))

4967 - HDAC11 function as a transcriptional regulator in immature myeloid cells to myeloid-derived suppressor cells transition

J. Chen, F. Cheng, E. Sahakian, J. Powers, Z. Wang, A. Villagra, J. Pinilla-Ibarz, E. M. Sotomayor

Poster Session: MS.IM01.01 - Epigenetic and Metabolic Regulation of Cancer Immunity

April 17, 4:20 PM - 4:35 PM

In normal myelopoiesis, immature myeloid cells (IMCs) differentiate into macrophages, neutrophils or dendritic cells, a process that is tightly controlled by transcription factors and epigenetic regulators. However, under tumor burden, IMCs differentiate into myeloid derived suppressor cells (MDSCs) and with subsequent up-regulation of immune suppressive factors and a pro-tumor effect. In prior studies, we found that MDSCs from HDAC11 KO mice displayed an increased T-cell suppressive activity that was associated with a more aggressive tumor growth as compared to MDSCs from wild type control mice. Unlike MDSC's in which absence of HDAC11 is associated with a suppressive phenotype, T-cell lacking HDAC11 are hyper-reactive and endowed with strong antitumor activity. To assess which phenotype will be the dominant one in vivo, we performed adoptive immune cell transfer experiments of MDSC and/or T-cells from HDAC11 KO mice into C57BL/6 tumor-bearing mice. The transfer of HDAC11KO MDSCs was able to eliminate, at least partially, the anti-tumor effect elicited by the adoptive transfer of HDAC11KO T cells. ([Read more](#))

LB-373/1 - Comprehensive analysis of cancer stemness

T. M. Malta, A. Sokolov, A. J. Gentles, T. Burzykowski, L. Poisson, J. Weinstein, B. Kamińska, J. Huelsken, L. Omberg, O. Gevaert, A. Colaprico, P. Czerwińska, S. Mazurek, L. Mishra, H. Heyn, A. Krasnitz, A. K. Godwin, A. J. Lazar, The Cancer Genome Atlas Research Network, J. M. Stuart, K. Hoadley, P. W. Laird, H. Noushmehr, M. Wiznerowicz

Poster Session: LBPO.MCB03 - Late-Breaking Research: Molecular and Cellular Biology / Genetics 3

April 18, 8:00 AM - 12:00 PM

Abstract embargoed at this time. ([Read more](#))

5459/18 - Regulation of IGF2 by TGF-β signaling in liver cancers and stem cell homeostasis

S. Rao, S. Zaidi, K. Ohshiro, J. Chen, S. Gu, W. Jogunoori, J. White, B. Mishra, S. Li, R. Akbani, L. Mishra

Poster Session: PO.MCB01.07 - Signaling and Therapy

April 18, 8:00 AM - 12:00 PM

Development of hepatocellular carcinoma (HCC), which remains lethal, is associated with alterations in multiple factors including the transforming growth factor beta (TGF-β) signaling pathway. Previously we have uncovered a unique role for TGF-β signaling molecules, Smad3 and its adaptor β2SP, in suppressing stem cell transformation into cancer. Yet, while TGF-β plays a pleiotropic role including regulating stem cell differentiation, proliferation, and inflammation, mechanistic insight into the dichotomy of TGF-β, and its role in stem cell transformation remains poorly understood for these cancers. Here, we took an integrated approach to identify and validate effects of changes in this pathway in HCC and identify potential therapeutic targets such as IGF2. We extended our mechanistic studies associated with the regulation of insulin-like growth factor 2 (IGF2) in the context of the TGF-β-pathway,

by utilizing both human liver cancer cell lines and TGF- β signaling-deficient mice (β 2SP+/- and β 2SP+/-/Smad3+/-) that develop liver cancers. ([Read more](#))

2226/8 - TGF- β and CEACAMs regulated biomarkers detect early colorectal cancer

S. Zaidi, A. Korkut, W. Jogunoori, J. Chen, S. Gu, S. Rao, K. Ohshiro, R. Akbani, C. Deng, B. Mishra, L. Mishra

Poster Session: PO.PR01.03 - Biomarkers, Intervention, and Early Detection for Cancer Prevention

April 16, 1:00 PM - 5:00 PM

Development of colorectal cancer (CRC) is associated with alterations in key driving pathways, which include Wnt (APC- β catenin), TGF- β members, p53 and pathways that regulate Ras activity. Members of the TGF- β superfamily regulate colon inflammation, have both tumor-suppressing and tumor-promoting activities, while colon cancer formation has been observed in TGF- β deficient mouse models. Through earlier studies, using mouse models followed by functional studies in human cell lines and tissues, we identified candidate set of TGF- β regulated biomarkers for early detection of CRC, that were altered in tissues from patients with adenomas, and could represent signs of early cancer stem cell development (J Clin Invest 2016;126(2); PLoS One 2016;11(4)). These markers are CEACAMs 1, 5 and 6; TGFBR2, SMAD4, Smad adaptor, SPTBN1. Here, we took an integrated approach to extend and validate these potential markers for early detection of CRC. ([Read more](#))

3338/5 - BP1 induces an epithelial to mesenchymal transition in breast cancer cells by modulating the Twist/IL6 pathway

F. Vesuna, B-J. Hwang, J. Rheey, M. Giri, M. Gill, S. W. Fu, A. Irving, A. Lisok, Y. Bergman, V. Raman, P. E. Berg

Poster Session: PO.MCB04.03 - Exploring Oncogenic Transcription Factors

April 17, 8:00 AM - 12:00 PM

BP1 (Beta Protein 1) belongs to the Distal-less family of homeobox genes. We have demonstrated that BP1 is activated in over 80% of invasive ductal breast tumors, where it is associated with breast cancer progression. The mechanism(s) of BP1 involvement in breast cancer progression, invasion and metastasis are still not known. Homeobox genes contribute to the epithelial to mesenchymal transition (EMT). During EMT, epithelial cells acquire mesenchymal features which lead to motility, invasiveness and resistance to apoptosis. EMT is also characterized by changes in apico-basal polarity and a dramatic remodeling of the cytoskeleton. During progression toward metastasis, cancer cells acquire a mesenchymal gene expression phenotype and increased motility. This transition allows the tumor cells to metastasize and establish secondary tumors at distant sites. One of the drivers of the EMT is the transcription factor Twist. Twist is a member of highly conserved family of basic helix-loop-helix transcription factors and is involved in the specification and differentiation of mesenchymal tissue in embryos. Twist overexpression can induce EMT, generate cancer stem cells, and promote metastasis in vivo. We hypothesized that BP1 might promote cancer metastasis and invasiveness mediated through Twist and the EMT. ([Read more](#))

1703/28 - The HDAC6 inhibitor Nexturastat A improves in vivo PD-1 immune blockade

T. Knox, E. Sahakian, D. Banik, M. Hadley, E. Palmer, J. Kim, J. Powers, S. Shah, A. Lowe, J. Pinilla, E. Sotomayor, N. Lee, A. Kozikowski, A. V. Villagra

Poster Session: PO.IM02.01 - Immune Checkpoints 1

April 16, 8:00 AM - 12:00 PM

The role of HDACs in cell biology, initially limited to their effects upon histones, now encompasses more complex regulatory functions that vary with their tissue expression, cellular compartmentalization and stage of cellular differentiation. Several recent studies have shown that selective HDAC inhibitors (HDACi) are able to impair in vivo tumor growth. Therefore, there is an emerging interest in the understanding of the molecular mechanisms mediating these anti-tumor properties. In this context, a number of recent publications have demonstrated that the selective inhibition of specific HDACs enhances tumor immunogenicity in a wide variety of tumors, thereby preventing tumor escape and improving immune surveillance. Our group has focused on HDAC6, and shown that both the genetic abrogation and pharmacological inhibition of this HDAC modulates the expression of a variety of immune-regulatory proteins in the tumor microenvironment, including PD-L1, PD-L2, MHC class I, B7-H4 and TRAIL-R1. ([Read more](#))