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Training the next generation of cancer researchers is one of HCI’s critical missions. This symposium brings cancer center trainees from across the research spectrum together to share their exciting findings. The symposium features a panel of PhD-trained scientists who will share their career paths. A trainee selected speaker, Jeroen Roose, PhD, from the University of California San Francisco, will present his latest work on Ras signaling in autoimmunity and cancer.

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<td>ETV4 is necessary for estrogen signaling and growth in endometrial cancer cells</td>
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<td>Patterns of family communication and preferred resources for sharing information among families with a Lynch syndrome diagnosis</td>
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<td>Intracellular mass generation estimation in cancer cells using quantitative phase imaging</td>
<td>Soorya Pradeep</td>
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<td>Investigating cooperativity between estrogen-responsive enhancers</td>
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CARLETON, JULIA – JASON GERTZ LAB - INVESTIGATING COOPERATIVELY BETWEEN ESTROGEN-RESPONSIVE ENHANCERS

Authors: Julia Carleton, Kristofer Berrett, Jason Gertz

Gene regulatory enhancers play crucial roles in development and disease. The human genome encodes an order of magnitude more enhancers than promoters, suggesting that most genes are regulated by multiple enhancers. Initial studies of enhancer function using reporter assays suggested that these enhancers contribute to gene expression in an independent, additive manner. However, by applying new genome editing technologies to estrogen-responsive enhancers at their endogenous loci, we have found surprising dependencies between neighboring enhancers in the production of a transcriptional response to estrogens. To better understand the mechanisms by which neighboring enhancers affect each other, we generated deletions of individual ER bound enhancers and performed ChIP-seq to analyze the impact on the nearby enhancer. We found that enhancers containing strong estrogen response element (ERE) motifs control ER binding at neighboring sites, while enhancers containing weak ERE motifs contribute to activity and accessibility of their neighboring strong ERE enhancers. Genome engineering revealed that two half ERE enhancers could not compensate for the lack of a full ERE site within a cluster of neighboring enhancers. Two full ERE enhancers produced a transcriptional response greater than the wildtype locus, suggesting that combinations of enhancers are not necessarily configured for a maximal response. Our results demonstrate that clustered enhancers can affect each other in diverse ways despite being thousands of basepairs apart.

ELRICK, ASHLEY – KIM KAPHINGST LAB - FAMILY COMMUNICATION OF MULTI-GENE PANELS: DEVELOPMENT OF STUDY QUESTIONNAIRES

Authors: Ashley Elrick, Wendy Kohlmann, Teneille Brown, Whitney Espinel, Kimberly Kaphingst

Breast cancer survivors are expected to communicate their genetic test results to biological family members, yet this challenging family communication issue often lacks the involvement of communication scholars and legal professionals in shaping theory, research, and policy. This project aims to investigate the application of the goals-plans-action (GPA) model of communication and ethical and legal considerations to the development of measures to assess family communication of genetic information. 10 women with genetic counseling appointments for breast or ovarian cancer risk assessment were recruited for cognitive interviews. Using in-depth cognitive interviewing techniques, we asked participants to think aloud as they read specific questionnaire items and described how and why they would select their answers. Common themes across interviews were identified. The GPA model has five identity goals items on the participants’ communication behaviors based on personal, moral, and ethical standards. Several participants were confused by the term “ethical standards” and did not know how to answer the question. For ethical and legal considerations, we included items on “duty to share the results of genetic testing to your family” and “responsibility to share”. Duty and responsibility were seen as the same concept and said they would respond exactly the same. Data collected from the interviews has been utilized to revise the questionnaires as deemed necessary for the longitudinal phase of this study. Clarifications have been added to questions and directions such as providing additional details to explain terminology.
FORNETTI, JAMIE – ALANA WELM LAB - RON KINASE: A THERAPEUTIC TARGET FOR CANCER-INDUCED BONE DESTRUCTION

Authors: Jaime Fornetti, Alana Welm

Breast cancer most commonly metastasizes to bone and is debilitating for patients. Despite current therapies, many patients progress to develop new skeletal complications, highlighting the need for additional treatments. We previously demonstrated that the macrophage stimulating protein (MSP)/RON tyrosine kinase signaling pathway is elevated in breast cancer and associated with increased bone metastasis. In mice, MSP expression by mammary tumors causes spontaneous bone metastasis and bone destruction through host RON, which is expressed by bone-resorbing osteoclasts. Based on these data, we hypothesize that MSP-expressing tumors promote bone destruction through osteoclast RON, and that MSP/RON signaling may be targetable in breast cancer bone metastasis. To test this hypothesis, RON was depleted in osteoclasts and the effect on tumor-associated osteolysis was assessed using a PyMT intratibial tumor model. RON expression by osteoclasts was also characterized using a mCherry reporter. Data to date confirm RON expression in mature osteoclasts and support a role for osteoclast RON as a mediator of osteolytic metastasis. MSP/RON signaling was also evaluated as a therapeutic target for bone metastasis in humans. Four of six breast cancer bone metastasis samples expressed MSP. Additionally RON inhibitor treatment in cancer patients was associated with a decrease in the bone resorption marker CTX and increase in the bone formation marker BSAP. Altogether, our clinical and preclinical data indicate that RON inhibitors may be effective against osteolytic bone metastasis and provide rationale for the continued investigation of RON inhibitors for use in patients.

GRIESEHOBER, LAURIE – JEN DOHERTY LAB - PRE-DIAGNOSIS NEUTROPHIL-TO-LYMPHOCYTE RATIO AND LUNG CANCER RISK IN HEAVY SMOKERS

Authors: Laurie Grieshober, Stefan Graw, Matt Barnett, Mark Thornquist, Gary Goodman, Chu Chen, Devin Koestler, Carmen Marsit, Jennifer Doherty

The neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammation that is inversely associated with survival for many chronic diseases, including lung cancer. We hypothesize that the inflammatory profile reflected by DNA methylation-derived NLR (mdNLR) may also be associated with lung cancer risk. Within the β-Carotene and Retinol Efficacy Trial (CARET), 319 incident lung cancer cases to controls were matched based on time at risk, age, smoking, sex, race, asbestos, and enrollment year. We computed mdNLR using the ratio of predicted granulocyte and lymphocyte proportions derived from DNA methylation signatures in whole blood samples collected prior to diagnosis. Conditional logistic regression models were adjusted for potential confounders: age, smoking, and body mass index. Each unit increase in mdNLR was associated with a 21% increased risk of lung cancer (Odds Ratio (OR) 1.21, 95% Confidence Interval (CI) 1.01-1.45). There was a 30% increased risk of non-small cell lung cancer (NSCLC; n=240 pairs; 1.30, 1.03-1.63). mdNLR was not associated with small cell lung cancer. The association between mdNLR and NSCLC risk was most pronounced in those with asbestos exposure (3.39, 1.32-8.67; all men). Estimates for NSCLC cases without asbestos exposure were similar for males and females. These results suggest that elevated mdNLR in asbestos-exposed lung cancer cases may indicate an altered inflammatory profile induced by asbestos exposure that is permissive to lung cancer development. A better understanding of the mechanisms conveyed by elevated mdNLR in lung cancer development will inform on whether this marker can be used for prevention and/or early detection.
HOLOWATYJ, ANDREANA – NELI ULRICH LAB - EAVESDROPPING ON THE CROSSTALK BETWEEN VISCERAL ADIPOSE AND TUMOR TISSUES IN COLORECTAL CANCER PATIENTS

Authors: Andreana Holowatyj, Mariam Haffa, Tengda Lin, Dominique Scherer, Biljana Gigic, Jennifer Ose, Christy Warby, Caroline Himbert, Clare Abbenhardt-Martin, Juergen Boehm, Magnus von Knebel-Doeberitz, Nina Habermann, Esther Herpel, Hans-Ulrich Kauczor, Matthias Kloor, Johanna Nattenmüller, Peter Schirmacher, Martin Schneider, Petra Schrotz-King, Thomas Simon, Alexis Ulrich, Laura Bowers, Stephen Hursting, Cornelia Ulrich

Obesity and obesity-driven cancer rates are continuing to rise worldwide. Reprogramming of the adipose microenvironment has emerged as a key driver of obesity-associated cancers. Analysis of tumor-adjacent visceral adipose, tumor, and colorectal mucosa tissue samples among patients diagnosed with colorectal cancer showed a direct bi-directional crosstalk between visceral adipose and tumor tissues. Transcriptomic studies revealed that molecular modulators of adipose-tumor tissue crosstalk activate NF-κB signaling cascades to promote pro-inflammatory interactions and metabolic reprogramming via glycolytic pathways.

Evaluation of systemic inflammatory mediators and gene set enrichment analysis suggested that common mechanistic processes of adipose-tumor tissue crosstalk include NF-κB regulation in response to TNF signaling and the enrichment of proteins involved in glycolysis in the colorectal tumor microenvironment. Development of interventions that interfere with these pro-carcinogenic molecular signals at the nexus of adipose-tumor tissue crosstalk may reduce the burden of obesity-driven colorectal cancers.

KINSEY, CONAN – MARTIN McMAHON LAB - COMBINED INHIBITION OF MEK AND AUTOPHAGY PROMOTES REGRESSION OF PANCREATIC CANCER: BENCH TO BEDSIDE

Authors: Conan Kinsey, Soledad Camolotto, Amelie Boespflug, Katrin Gullien, Mona Foth, Jill Shea, Michael Siepp, Jeff Yap, Lance Burrell, David Lum, Bryan Welm, Courtney Scaife, Eric Snyder, Martin McMahon

Pancreatic ductal adenocarcinoma (PDAC) is a recalcitrant disease responsible for ~43,000 deaths in the USA in 2017. Despite an advanced understanding of the genetics, biochemistry and biology of pancreatic cancer, there is no effective pathway-targeted therapy for PDAC such that the standard of care treatment for most patients remains conventional cytotoxic chemotherapy. Although the clinical picture remains grim, progress has been made in understanding how alterations in tumor suppressors and proto-oncogenes contribute to PDAC initiation and progression. Whereas initiating mutations in KRAS promote the growth of premalignant pancreatic intra-epithelial neoplasia, progression to cancer malignancy requires cooperating alterations of tumor suppressors such as TP53, CDKN2A, and/or SMAD4. Downstream of KRAS oncoproteins, the RAF→MEK→ERK MAP kinase signaling pathway plays a central role in the genesis and maintenance of PDAC. However, to date, pharmacological inhibition of this pathway has demonstrated little clinical benefit in PDAC patients. Here we show that inhibition of KRAS→RAF→MEK→ERK signaling in PDAC cell lines elicits autophagy, a process of cellular recycling, which protects pancreatic cancer cells from the potentially cytotoxic effects of pathway inhibition. Combined inhibition of MEK1/2 and autophagy (with chloroquine) displays synergistic anti-proliferative effects against PDAC cell lines in vitro. Most strikingly, whereas single agent therapy had modest effects, combined treatment of xenografted patient-derived PDAC tumors with trametinib plus chloroquine/hydroxychloroquine elicited striking tumor regression. Finally, the compassionate use treatment of a patient with the combination of trametinib and hydroxychloroquine resulted in dramatic disease response. These data warrant testing this combination therapy in more patients with pancreatic cancer.
MITCHELL, SARANNE – JODY ROSENBLATT LAB - QUANTITATIVE PHASE MICROSCOPY AN EMERGING TECHNIQUE TO EVALUATE EPITHELIAL EXTRUSION

Authors: Saranne Mitchell, Thomas Zangle, Jody Rosenblatt

Epithelial cells function as a barrier that is critical for maintaining organ function, and show some of the highest turnover rates in the body. Cells that are fated for removal from the epithelium are forced out through a mechanism known as cellular extrusion. Regulation of the high turnover rates of epithelia depends on the number of extrusions and cell divisions matching precisely. The mismatch of these rates through increased cell extrusion is associated with a growing number of diseases, including cancer and asthma. Mechanical forces control cell death through a single known stretch-activated ion channel, Piezo1. As the cell ages and/or experiences crowding Piezo1 continuously accumulates into plaques in the cytoplasm of epithelia, leading to extrusion and death. It is unknown how Piezo1 senses this mechanical force. An emerging technique known as quantitative phase microscopy (QPM) can monitor changes in cell mass and mechanical properties of epithelia which may predict cellular extrusion. QPM measures the slowing of light as it passes through a cell. This slowing, or phase shift, is proportional to cell dry mass, allowing label-free biophysical measurement of live cells. Previous work on QPM has focused on measurements of single and sparse cells. In the present work, we are adapting QPM using recent advances in image processing to quantify epithelial monolayer mechanics and extrusion in real time.

MOLLAOGLU, GURKAN – TRUDY OLIVER LAB - LINEAGE SPECIFIERS SOX2 AND NKX2-1 REGULATE NEUTROPHIL RECRUITMENT AND ADENOSQUAMOUS TRANSDIFFERENTIATION IN LUNG CANCER

Authors: Gurkan Mollaoglu, Alex Jones, Sarah Wait, Christopher Conley, Arjun Bhutkar, Jeffery Vahrenkamp, Thomas Lane, Jason Gertz, Kevin Jones, Eric Snyder, Trudy Oliver

Lineage-specific transcription factors are regulators of cell identity in development, homeostasis, and disease. The major types of non-small cell lung cancer are associated with distinct master regulators: SOX2 drives the squamous fate, whereas NKX2-1 governs adenocarcinoma fate. We developed multiple mouse models of lung cancer to interrogate the impact of SOX2 and NKX2-1 on cell fate and innate immune cell recruitment. NKX2-1 potently suppresses SOX2-driven squamous tumorigenesis by repressing adeno-to-squamous transdifferentiation. SOX2 recruits, whereas NKX2-1 suppresses, tumor-associated neutrophils (TANs) at least partly through inverse regulation of the chemoattractant Cxcl5. Tumor-derived CXCL5 is sufficient to recruit TANs. Single-cell RNA sequencing revealed that TANs exhibit tumor-promoting features and distinct gene expression profiles compared to blood neutrophils. These data reveal how lineage specifiers dictate not only cell fate but also distinct immune microenvironments.
STEWART, RACHEL – K-T VARLEY LAB - TRANSLATION OF A GOOD-PROGNOSIS BIOMARKER SIGNATURE IN TRIPLE NEGATIVE BREAST CANCER

Author: Rachel Stewart, Katherine Updike, Rachel Factor, Lynn Henry, Philip Bernard, Katherine Varley

Triple negative breast cancer (TNBC) is an aggressive subtype with disparate outcomes. While 42% of patients experience rapid relapse within three years of diagnosis, the remaining 58% have long-term disease-free survival (DFS). Oncologists cannot currently predict which patients will benefit from standard treatment and which will relapse. In a recent study we reported that expression of the major histocompatibility complex II (MHCII) pathway confers a nearly four-fold improvement in DFS (HR=0.28). In order to translate this discovery into a clinical test, we developed an MHCII gene expression assay on the NanoString platform. We applied this MHCII NanoString assay to RNA from frozen TNBC tumor tissue that we previously analyzed using RNA-seq. Gene expression measurements were highly correlated between the NanoString and RNA-seq assays. The MHCII NanoString assay also confirmed the significant association between MHCII expression and DFS in this cohort. To test whether the MHCII NanoString assay is compatible with degraded RNA from formalin-fixed paraffin embedded tissue (FFPE), we analyzed matched frozen and FFPE samples. The gene expression measurements were highly correlated between sample types. To validate the prognostic significance of the MHCII NanoString assay, we assembled a retrospective institutional cohort of TNBC patients treated at HCI. We macrodissected tumor cells from clinical FFPE specimens, isolated RNA, and performed the MHCII NanoString assay. We observed a significant association between the MHCII signature and DFS in this independent cohort. This study provides the foundation for the development of a clinical test that can be used to predict prognosis in TNBC patients.

VISKOCHIL, RICHARD – NELI ULRICH LAB - THE RELATIONSHIP BETWEEN OBJECTIVELY MEASURED PHYSICAL ACTIVITY, SEDENTARY BEHAVIOR AND OXIDATIVE STRESS IN COLORECTAL CANCER PATIENTS: RESULTS FROM THE COLOCARE STUDY

Authors: Richard Viskochil, Tengda Lin, Stephanie Skender, Jürgen Böhm, Petra Schrotz-King, Biljana Gigic, Karen Steindorf, Robert Owen, Cornelia Ulrich, Jennifer Ose

Physical activity improves quality of life and decreases mortality in colorectal cancer patients. Prior studies have shown an inverse association between subjective measures of physical activity and oxidative stress, however associations between objectively measured physical activity, sedentary behavior and oxidative stress are unknown. The ColoCare study is an ongoing international prospective cohort study (n=1,961) of newly diagnosed stage I-IV colorectal cancer patients. ColoCare participants in Heidelberg, Germany wore an Actigraph GT3x+ accelerometer (Actigraph, Pensacola FL) around the chest for 5 consecutive days during the 6 month and/or 12 month post-surgery time-point. Data was computed using the ActiLife software package (v. 6.6.3). Oxidative stress was determined using urinary 8-hydroxy-2-deoxyguanosine (8-oxo-dG), which was quantified via enzyme immunoassay, log transformed and normalized to creatinine concentrations. Associations between physical activity, sedentary behavior and 8-oxo-dG were determined using Spearman partial correlations adjusting for age, sex, BMI and tumor stage. Seventy-two measurements of accelerometer-derived physical activity and 8-oxo-dG were available at the 6 month (n=42), or 12 month time-point (n=30). Patients accrued 264±180 min/wk of moderate to vigorous physical activity (MVPA), however only 81±126 min/wk were exercise minutes occurring in >10 minute bouts. There were no significant associations between physical activity (MVPA min/wk) and 8-oxo-dG (ng/mg creatinine; r=0.03, p=0.76), or sedentary behavior (%min/day) and 8-oxo-dG (ng/mg creatinine; r=-0.04, p=0.69). As expected, there were significant inverse associations between physical activity and sedentary behavior, including both total MVPA (min/wk) with sedentary time (%min/day, r=-0.51, p<0.001) and exercise MVPA min/wk with sedentary time (%min/day r=-0.26, p=0.036).
Acute myeloid leukemia (AML) is an aggressive and genetically heterogeneous blood cancer with long-term survival rates <20%. Chemotherapy and stem cell transplant-based treatment has not changed for decades, and relapse is common, presumably due to survival of AML stem cells in protective bone marrow (BM) microenvironment. To identify survival-critical genes irrespective of mutational status, I employed an shRNA library screen against 12 primary AML samples grown on BM stroma, to mimic the microenvironment. This analysis revealed that a subset of AML cases are highly dependent on SIRT5, a deacetylase regulating key metabolic pathways, and the only enzyme known with desuccinylase, demalonylase, or deglutarylase activity. Validation studies in 30 patient samples and 24 cell lines revealed that ~2/3 of AML cases are sensitive to SIRT5 knockdown, while normal, healthy blood cells are not. SIRT5 knockdown impaired mitochondrial respiration and glycolysis, and increased reactive oxygen species in SIRT5-dependent, but not -independent cell lines. Metabolomics profiling revealed that many more metabolites were changed in SIRT5-dependent vs. -independent cells upon SIRT5 knockdown, and some changes occurred in opposite directions. SIRT5-/− mice are viable with normal hematopoiesis. However, transformation of SIRT5-/− BM cells by AML-associated oncogenes such as FLT3-ITD and MLL-AF9 is reduced compared to SIRT5+/+ controls. Strikingly, knockdown of SIRT5 completely blocked the development and maintenance of leukemia, and prolonged survival in a xenograft mouse model. Together, these data implicate SIRT5 as a potential therapy target and provide rationale for the development of SIRT5 inhibitors for the treatment of AML.

Sorting nexin (SNXs) proteins have been demonstrated to play fundamental roles in endosomal sorting and signaling. In this study we identified Drosophila SH3PX1, the paralog of human SNX9/18/33, as a cell autonomous regulator of intestinal stem cell (ISC) proliferation. SH3PX1 loss-of-function dramatically increased ISC proliferation mainly though upregulating EGFR signaling. This phenotype can be repressed by the knockdown of EGFR pathway components. Previous study showed that SNX18 controls autophagosome formation. Consistently, knockdown of the autophagy pathway components, atg1, 6, 8a, 16 and Syx17 also increased ISC proliferation. And, knockdown of SH3PX1 in ISCs indeed disrupted autophagosome formation. These data argue that SH3PX1-dependent autophagy restricts ISC proliferation. Based on our current data, we hypothesize that SH3PX1-dependent autophagy controls ISC proliferation through control the endosomal trafficking and degradation of EGFR. Further experiments need to be performed to determine whether endocytosis and degradation of EGFR are controlled by SH3PX1-autophagy pathway, and whether SH3PX1-mediated autophagy is downregulated in stem cells during stress-induced regeneration.
CAMBRON, CHRIS – DAVID WETTER LAB - SOCIOECONOMIC STATUS, SOCIAL CONTEXT, AND SMOKING LAPSE

Authors: Christopher Cambron, Cho Lam, David Wetter

Cigarette smoking is the leading cause of morbidity and mortality in the United States, including accounting for 30% of all cancers and approximately 90% of lung cancer. The majority of individuals who smoke indicate they want to quit, and although half of all smokers make a quit attempt every year, only 6% successfully do so. Factors related to lower socioeconomic status (SES) are powerful predictors of greater difficulty quitting smoking and SES-related tobacco disparities have widened over the last several decades. This project employed ecological momentary assessment data from 375 smokers engaged in a quit attempt to examine real time associations between social context and smoking lapse. Results of multilevel structural equation models suggest that the effects of low-SES on smoking lapse are conferred by exposure to smoking-specific social contexts. Low SES smokers on average spent more time around other smokers and in places that did not restrict smoking which, in turn, increased cigarette availability and, ultimately, smoking lapse in next 8 hours. Results highlight the importance of social contexts in understanding well-established associations between low-SES and difficult quitting smoking.

CHALISHAZAR, MILIND – TRUDY OLIVER LAB - MYC-DRIVEN SMALL CELL LUNG CANCER IS METABOLICALLY DISTINCT AND DEPENDENT UPON ARGinine BIOSYNTHETIC PATHWAYS

Authors: Milind Chalishazar, Fang Huang, Anandaroop Mukhopadhyay, Abbie Ireland, Younjee Lee, Sophia Schuman, Matthew Guthrie, Kristopher Berrett, Jeffery Vahrenkamp, Zeping Hu, Marek Kudla, Nicholas Ingolia, Jason Gertz, Sabina Cosulich, John Bomalaski, Ralph DeBerardinis, Trudy Oliver

Small cell lung cancer (SCLC) has been treated clinically as a homogeneous disease, but recent discoveries suggest that SCLC is heterogeneous. The MYC family of oncogenes including MYC, MYCL and MYCN are expressed in a mutually exclusive manner and impact tumor differentiation and therapeutic vulnerabilities. Whether metabolic differences exist among SCLC subtypes and whether this has therapeutic implications is largely unexplored. Here we show that SCLC subtypes driven by MYC family members have distinct metabolic profiles. MYC-driven SCLC depends on arginine-regulated pathways including polyamine biosynthesis and mTOR pathway activation. Importantly, chemo-resistant SCLC cells exhibit increased MYC expression and similar metabolic liabilities as chemo-naive MYC-driven cells. Inhibition of mTOR in combination with chemotherapy, or arginine depletion alone with ADI-PEG20, suppresses tumor growth and promotes survival of mice with MYC-driven tumors. These data identify metabolic heterogeneity within SCLC subtypes and reveal subtype-specific therapeutic vulnerabilities in SCLC.
DALE, KALI – MARTIN McMAMHON LAB - USING INTEGRIN BETA3 AS A MODEL FOR IDENTIFYING THE MOLECULAR MECHANISMS THAT REGULATE DELAYED EARLY GENE TARGETS OF SUSTAINED MAPK PATHWAY ACTIVATION

Authors: Kali Dale, Martin McMahon

RAS and its downstream effector, BRAF, are commonly mutated proto-oncogenes in many types of human cancer. Mutationally activated RAS or BRAF signal through the MEK→ERK MAP kinase pathway to regulate key cancer cell hallmarks such as progress through the cell division cycle, reduced programmed cell death and enhanced cell motility. Amongst the list of RAS/RAF-regulated genes are those encoding integrins, alpha-beta heterodimeric transmembrane proteins that regulate cell adhesion to extracellular matrix. Altered integrin expression has been linked to the acquisition of more aggressive behavior by melanoma, lung and breast cancer cells leading to diminished survival of cancer patients. We have previously documented the ability of the RAS-activated RAF→MEK→ERK MAP kinase pathway to induce the expression of ITGB3 encoding beta3-integrin in several different cell types. RAS/RAF-mediated induction of ITGB3 mRNA requires sustained, high-level activation of RAF→MEK→ERK signaling mediated by oncogene activation and is classified as “delayed-early”, in that it is sensitive to the protein synthesis inhibitor cycloheximide. However, to date, the regulatory mechanisms that allow for induced ITGB3 downstream of sustained, high-level activation of RAF→MEK→ERK signaling remain obscure. We have identified over 300 genes, including those expressing additional cell surface proteins that display similar regulatory characteristics as ITGB3. We are currently relating altered expression of genes to RAS/RAF-induced changes in chromatin structure to determine if there is an underlying regulatory logic to the observed effects of activated RAS/RAF on delayed-early genes. The work presented from this abstract will help elucidate the regulatory properties of oncogenic progression in BRAF mutated cancers.

GINLEY-HIDINGER, MATTHEW – JASON GERTZ LAB - RECREATION OF COMBINATORIAL GENE EXPRESSION CONTROL BY TARGETING ENHANCERS WITH SYNTHETIC ACTIVATORS

Authors: Matthew Ginley-Hidinger, Julia Carleton, Jason Gertz

Cancer phenotypes can often be determined by subtle differences in gene expression levels. In order to prevent disease, complex transcriptional control strategies are used to fine-tune gene expression. One strategy that is often used in metazoans is combinatorial enhancer control where several gene expression enhancers work in concert to regulate a single gene. However, little is known about how enhancers work together. In order to determine the effects of enhancer combinations on gene expression, we took the approach of recreating enhancer regimes through the recruitment of activators to combinations of enhancers. We activated specific genomic enhancers by fusing dCas9, a Cas9 mutant that does not cut the genome, to protein domains involved in gene activation. We tested this approach on a set of 5 genes with 3 enhancers each and found that these dCas9 constructs significantly activated each gene from enhancers and promoters. We verified specific targeting and activation with ChIP-seq and found that we were able to specifically increase histone H3 lysine 27 acetylation (H3K27ac) at the targeted loci. Activating gene expression from combinations of enhancers revealed complex interactions between these enhancers. In order to better understand these interactions, we developed a thermodynamic model of combinatorial enhancer control. Our modeling results help tease apart whether enhancers are working collaboratively to control gene expression. Overall, our results show that complex patterns of gene expression can be created through the usage of multiple enhancers. The results from this work will help inform the next generation of precision therapeutics.
KALASEKAR, SHARANYA – KIM EVASON LAB - CHARACTERIZING LIVER CANCER MECHANISMS AND THERAPIES IN THE ZEBRAFISH

Authors: Sharanya Kalasekar, Srishti Kotiyal, Richard Smith, Kimberley Evason

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death, and its pathogenesis is incompletely understood. No medications have been shown to prevent HCC in high-risk patients with chronic liver disease, and few effective treatments are available. One of the factors impeding therapy development is the lack of robust animal models for the genetically diverse subsets of HCC. For example, approximately 25% of patient HCCs harbor activating mutations in ctnnb1, the gene encoding the transcriptional activator beta-catenin. However, while activated beta-catenin (ABC) is known to enhance liver tumorigenesis in mouse models, ABC is not sufficient for murine HCC onset. Therefore, mouse models alone may not completely render ABC-specific mechanisms in HCC pathogenesis. Here, we show that hepatocyte-specific ABC can induce HCC in zebrafish, which is highly similar to human HCC with respect to gene expression signatures and morphology, and discuss our ongoing efforts to leverage this zebrafish model to dissect HCC etiology and characterize the mechanisms of potential therapies.

PETERSEN, JENNA – KIM KAPHINGST LAB - PATTERNS OF FAMILY COMMUNICATION AND PREFERRED RESOURCES FOR SHARING INFORMATION AMONG FAMILIES WITH A LYNCH SYNDROME DIAGNOSIS

Authors: Jenna Petersen, Cathryn Koptiuch, Yelena Wu, Ryan Mooney, Ashley Elrick, Kathryn Szczotka, Megan Keener, Sara Johnson, Lisa Pappas, Priyanka Kanth, Andrew Soisson, Wendy Kohlmann, Kimberly Kaphingst

The purpose of this study was to explore patterns of communication among families with a Lynch syndrome diagnosis and understand what resources could facilitate family communication. 127 probands (i.e., first person in family with identified mutation) and family members participated in semi-structured interviews about: how they learned about Lynch syndrome in their family, with whom they shared genetic test results, confidence in sharing results with other family members, and resources that would be helpful when learning about Lynch syndrome. We found that both probands and family members were most likely to share genetic test results with parents and siblings, and least likely to share results with aunts, uncles, and cousins. Most participants felt very confident sharing their test results with family members, but reported that certain topics such as cancer risk were challenging to convey. Probands reported the most helpful resources to be access to a specialty clinic or website, while family members described general printed materials as most helpful. Overall, families affected by Lynch syndrome may experience barriers to communication with more distant relatives, and may benefit from receiving specific resources to facilitate family communication. To help facilitate this process, providers could emphasize the need to share information with more distant family members and provide appropriate supportive resources.
PRADEEP, SOORYA – TOM ZANGLE LAB - INTRACELLULAR MASS GENERATION ESTIMATION IN CANCER CELLS USING QUANTITATIVE PHASE IMAGING

Authors: Soorya Pradeep, Thomas Zangle

Regulation of growth is a core function of the cell. Mass accumulation in healthy cells is tightly controlled. We also expect the location of mass generation inside a cell to be regulated during various stages of the cell cycle. For instance, mass may accumulate in cytoplasm during the G1 phase as the cells grow in size, however, when the cell moves into S phase mass is generated in the nucleus due to DNA replication. Unlike in normal cells, cancer cells exhibit unregulated growth. As a result, the localization of mass generation within cancer cells may vary, providing key data on the mechanisms underlying growth dysregulation in cancer. Our approach to measure changes in cell mass is quantitative phase microscopy (QPM). QPM quantifies the distribution of mass within cells by measuring the slowing down of light as it passes through the cell. Measurements of the same cell over time data reveals changes in mass at a subcellular level. Currently QPM is limited by the inability to distinguish intracellular mass transport from growth. In the present work we aim to develop and test an algorithm to quantify the material velocity inside of single cells with QPM. This will allow us to uncouple mass transport and growth, thus enabling the measurement of localization of mass generation within a single cell. Thus, our method can be used to localize the components inside a cell which contribute to mass generation during unregulated growth of cancer cells as well as the subcellular impacts of prospective therapies.

RODRIGUEZ, CHRISTINA – JAY GERTZ LAB - ETV4 IS NECESSARY FOR ESTROGEN SIGNALING AND GROWTH IN ENDOMETRIAL CANCER CELLS

Authors: Adriana Rodriguez, Jeffery Vahrenkamp, Kristofer Berrett, Kathleen Clark, Katrin Guillen, Bryan Welm, Barbara Graves, Jason Gertz

Estrogen signaling through estrogen receptor alpha (ER) plays a major role in endometrial cancer risk and progression; however, the molecular mechanisms underlying ER’s regulatory role in endometrial cancer are poorly understood. ER genomic binding in breast cancer is enabled by FOXA1 and GATA3, but the transcription factors that control ER genomic binding in endometrial cancer cells remain unknown. We have previously shown that the ETS factor ETV4 binds to similar genomic regions as ER in an endometrial cancer cell line, and recently found the ETV4 binding motif enriched at ER bound sites in endometrial cancer tumor samples. We therefore set out to test ETV4’s potential role in controlling genomic binding of ER in endometrial cancer. Using CRISPR/Cas9 we have created ETV4 knockout clones of Ishikawa, an endometrial cancer cell line. ETV4 knockout causes reduced growth rates, in both 2D and 3D culture with full media that mimic the effect of estrogen-depleted media on the growth of wild-type Ishikawa cells. Loss of ETV4 also causes a striking decrease in ER binding with at least a two-fold reduction in ER binding at 69% of sites, similar to the impact of FOXA1 knock down on ER binding in breast cancer cells. Consistent with the dramatic loss of ER binding, the gene expression response to estradiol was dampened for most genes. Chromatin accessibility was also decreased by ETV4 knockout at a subset of loci. Our results show that ETV4 plays a necessary role in ER genomic binding and gene regulation in endometrial cancer cells.
ARNESEN, SPENCER – JASON GERTZ LAB - EFFECTS OF ERα LIGAND BINDING DOMAIN MUTATIONS IN HORMONE THERAPY RESISTANT ER-POSITIVE BREAST CANCERS

Authors: Spencer Arnesen, Zannel Blanchard, Kristofer Berrett, Jason Gertz

Estrogen receptor α (ER) is expressed in 70% of breast cancers and acts as a key transcription factor driving tumor growth when bound by estrogens. ER-positive breast cancers generally have a good prognosis due to the success of ER-targeted hormone therapies, which function by blocking estrogen production or inhibiting ligand binding. However, resistance to hormone therapies can occur, leading to a 5-year rate of 20-30%. Activating mutations in ER’s ligand binding domain (LBD) have been found in 15% of hormone therapy-resistant metastatic ER-positive breast cancers. Initial studies have shown ligand-independent and novel gene regulation in the context of ER LBD mutations as well as decreased sensitivity to hormone therapies. However, the molecular consequences of mutant ER in terms of gene regulation and hormone therapy resistance are not fully understood. We are investigating the effects of ER mutations through the creation of multiple clones of isogenic breast cancer cell lines that endogenously express mutant ER. Using genome-wide approaches, we have investigated the effects of ER mutations on gene expression, DNA binding, and chromatin accessibility. We find that in addition to ligand-independent gene regulation, mutations in ER also lead to novel ER DNA binding, novel chromatin accessibility, and novel gene expression patterns. The discovery of molecular changes resulting from ER mutations will help us determine mutant ER’s molecular functions and may lead to the identification of treatments that can help patients with ER mutant breast cancer.

BARNARD, MOLLIE – JEN DOHERTY LAB - NSAID USE AND OVARIAN CANCER RISK BY COX1/COX2 LEVELS AND TAM INFILTRATION

Authors: Mollie E. Barnard, Johnathan L. Hecht, Megan S. Rice, Mamta Gupta, Holly Harris, A. Heather Eliassen, Bernard Rosner, Kathryn Terry, Shelley Tworoger

Non-steroidal anti-inflammatory drug (NSAID) use may affect ovarian cancer risk by down-regulating prostaglandin synthesis and reducing macrophage infiltration. We evaluated if the associations between NSAID use and ovarian cancer differed by tumor expression of inflammatory markers COX1 and COX2, or infiltration with macrophages (defined by CD68 and CD163 stains). Our study included cases with immunohistochemistry data for COX1 and COX2 (n=532) or CD68 and CD163(n=530) and matched controls from the Nurses’ Health Study (NHS), NHSII, and New England Case Control Study. We used polytomous logistic regression, adjusted for ovarian cancer risk factors, to estimate odds ratios (OR) for NSAID use and ovarian cancer risk by marker level. We observed a non-significant inverse association for aspirin and no association for non-aspirin NSAIDs with expression. Regular aspirin use was associated with a lower risk of ovarian cancer with high (OR=0.54, 95%CI=0.37-0.78) but not low (OR=1.50, 95%CI=0.97-2.31) CD163 density (p-heterogeneity<0.001). Similar results were observed for aspirin duration and tablets, and for regular NSAID use (CD163-high OR=0.65,95%CI=0.45-0.93; CD163-low OR=2.00, 95%CI=1.32-3.05; p-heterogeneity<0.001). Results did not differ by total macrophages (CD68). In summary, associations between analgesic use and ovarian cancer risk did not differ by COX1 or COX2. Aspirin was associated with a lower risk of ovarian cancer with high but not low infiltration of M2-type macrophages (CD163). Future research should explore prostaglandin-independent mechanisms for the association between NSAIDs and ovarian cancer risk, including immune mechanisms.
Estrogen signaling plays critical roles in the development of endometrial cancer as shown by epidemiological studies and in vivo modeling. Estrogen receptor (ER) is expressed in 95% of type 1 endometrial cancers and induces a pro-growth transcriptional program. Mutations in the ligand binding domain (LBD) of ER have recently been identified in 3.2% of primary endometrial cancers and these mutations are the same changes found in metastatic breast cancers. Functional studies undertaken in breast cancer models indicate the mutations’ ability to promote estrogen-independent ER signaling, which drives ER genomic binding and proliferation in the absence of estrogens while also conferring endocrine therapy resistance. Despite the critical roles that estrogen signaling plays in endometrial cancer, the consequences of ER LBD mutations have not been functionally explored in this disease. We have utilized a CRISPR/Cas9-mediated strategy to introduce a heterozygous D538G ER mutation, while epitope tagging the mutant allele at the endogenous locus. Using chromatin immunoprecipitation sequencing (ChIP-seq) with an anti-FLAG antibody, we have established that mutant ER exhibits ligand-independent genomic binding. RNA sequencing (RNA-seq) experiments indicate mutation-specific gene expression effects, with expression changes of both estradiol-regulated genes and unexpected estradiol-independent genes. ATAC-seq experiments have elucidated the regulatory regions and potentially the transcription factors that are responsible for estradiol-independent gene expression changes caused by the mutation. Together, our results indicate that the D538G mutation causes ligand-independent activity in endometrial cancer cells with some unanticipated gene expression consequences. These studies also provide functional models for further mechanistic and phenotypic investigation.

Oncolytic viruses are promising candidates to enhance the effect of immune checkpoint blockade inhibitors that have recently seen success in clinical trials and have gained FDA approval for treatment of advanced melanoma. These checkpoint inhibitors take advantage of intrinsic host immune surveillance by blocking negative interactions between tumor cells and T cells that would otherwise prevent an immune response to abnormal tumor tissue. Although this strategy has proven to be effective, a subset of patients do not respond and/or develop resistance to these immunotherapies, necessitating alternative interventions to improve patient responses. It is hypothesized that viral infection and oncolysis, coupled with immune checkpoint blockade, will enhance recognition and elimination of tumors via direct destruction of tumor tissue and by promoting tumor-specific adaptive immunity. Coxsackievirus A21 (CVA21/CAVATAK) is a wild-type virus which has a natural tropism for melanoma cells that express its known receptor, ICAM-1, on the cell surface. Cells expressing ICAM-1 can be efficiently infected and lysed by the virus, resulting in tissue destruction and the release of cytokines and tumor antigens that are important for activation of innate and adaptive immune responses. We are developing mouse models to test the efficacy of CVA21 infection in combination with αPD-1 blockade in melanoma. As tumor relapse is expected in a subset of mice, we further look to leverage these models to understand mechanisms of resistance to these therapies in order to develop improved treatment strategies.
Small cell lung cancer (SCLC) has been treated clinically as a homogeneous disease, but recent discoveries suggest that SCLC is heterogeneous. The MYC family of oncogenes including MYC, MYCL and MYCN are expressed in a mutually exclusive manner and impact tumor differentiation and therapeutic vulnerabilities. Whether metabolic differences exist among SCLC subtypes and whether this has therapeutic implications is largely unexplored. Here we show that SCLC subtypes driven by MYC family members have distinct metabolic profiles. MYC-driven SCLC depends on arginine-regulated pathways including polyamine biosynthesis and mTOR pathway activation. Importantly, chemo-resistant SCLC cells exhibit increased MYC expression and similar metabolic liabilities as chemo-naive MYC-driven cells. Inhibition of mTOR in combination with chemotherapy, or arginine depletion alone with ADI-PEG20, suppresses tumor growth and promotes survival of mice with MYC-driven tumors. These data identify metabolic heterogeneity within SCLC subtypes and reveal subtype-specific therapeutic vulnerabilities in SCLC.

Introduction. There were approximately 800,000 thyroid cancer survivors in the United States in 2016. Thyroid cancer has a high 5-year survival rate and is diagnosed among younger patients. Several studies have suggested increased risks of depression among thyroid cancer patients. The aim of our study was to investigate depression and mental health disorders among thyroid cancer survivors. We identified 4,145 thyroid cancer patients and 18,274 individuals in a general population cohort, matched by sex, birth year and birth state. Medical records from multiple statewide resources were used to identify mental health disorders. We used the Cox proportional hazards models to estimate the risk of mental health disorders. Thyroid cancer survivors had higher risks of several mental health diseases during the first year after cancer diagnosis and from 1-5 years after cancer diagnosis. The risk of anxiety disorders (HR=3.42, 95%CI=2.86-4.09; HR=1.30, 95%CI=1.12-1.51), and depression (HR=2.59, 95%CI=2.11-3.19; HR=1.21, 95%CI=1.03-1.42) were increased in the two follow up periods. Hormone therapy treatment, cancer stage, and being overweight at baseline were associated with increased risks of mental illness among thyroid cancer survivors during 0 to 1 years. We did not observe increased mental health disorder risks 5 years after cancer diagnosis. We observed increase risks of developing mental health diseases among thyroid cancer survivors during 0 to 1 and 1 to 5 years, but not for >5 years after cancer diagnosis. Screening for mental health at follow up visits may be beneficial for the thyroid cancer survivor.
DALE, KALI – MARTIN MCMAHON LAB - USING INTEGRIN BETA3 AS A MODEL FOR IDENTIFYING THE MOLECULAR MECHANISMS THAT REGULATE DELAYED EARLY GENE TARGETS OF SUSTAINED MAPK PATHWAY ACTIVATION

Authors: Kali Dale, Martin McMahon

RAS and its downstream effector, BRAF, are commonly mutated proto-oncogenes in many types of human cancer. Mutationally activated RAS or BRAF signal through the MEK→ERK MAP kinase pathway to regulate key cancer cell hallmarks such as progress through the cell division cycle, reduced programmed cell death and enhanced cell motility. Amongst the list of RAS/RAF-regulated genes are those encoding integrins, alpha-beta heterodimeric transmembrane proteins that regulate cell adhesion to extracellular matrix. Altered integrin expression has been linked to the acquisition of more aggressive behavior by melanoma, lung and breast cancer cells leading to diminished survival of cancer patients. We have previously documented the ability of the RAS-activated RAF→MEK→ERK MAP kinase pathway to induce the expression of ITGB3 encoding beta3-integrin in several different cell types. RAS/RAF-mediated induction of ITGB3 mRNA requires sustained, high-level activation of RAF→MEK→ERK signaling mediated by oncogene activation and is classified as “delayed-early”, in that it is sensitive to the protein synthesis inhibitor cycloheximide. However, to date, the regulatory mechanisms that allow for induced ITGB3 downstream of sustained, high-level activation of RAF→MEK→ERK signaling remain obscure. We have identified over 300 genes, including those expressing additional cell surface proteins that display similar regulatory characteristics as ITGB3. We are currently relating altered expression of genes to RAS/RAF-induced changes in chromatin structure to determine if there is an underlying regulatory logic to the observed effects of activated RAS/RAF on delayed-early genes. The work presented from this abstract will help elucidate the regulatory properties of oncogenic progression in BRAF mutated cancers.

DRUMMOND, DANIELLE – LISA ASPINWALL LAB - WHAT MAKES REDUCING CANCER RISK A PRIORITY? UNDERSTANDING THE FACTORS THAT PREDICT PRIORITIZATION OF MELANOMA RISK AMONG HIGH-RISK INDIVIDUALS

Authors: Danielle Drummond, Lisa Aspinwall

Among individuals at high risk of developing melanoma due to family history or a genetic mutation, 48% do not engage in the recommended sun-protection behaviors that would reduce their risk. Priority of risk has been shown to significantly predict engagement in sun-protection behaviors, but little is known about the factors that lead to this prioritization. In the current study, 128 high-risk individuals underwent genetic counseling with or without testing. We then examined the factors that predicted priority of risk before and after genetic counseling, and whether they mediated the impact of a positive test result on priority of risk. Before and after counseling, age, melanoma worry, and understanding of melanoma and melanoma risk predicted greater prioritization of risk. Additionally, these variables mediated the association between a positive test result and greater priority of risk. Thus, better understanding of a disease and one’s personal risk, as well as some degree of negative emotion about that risk (all of which were increased by a positive genetic test result), seem to be important in keeping it at the forefront of one’s attention.
ELRICK, ASHLEY – KIM KAPHINGST LAB - DON’T FORGET ABOUT THE MEN: PARTICIPATION OF MALES IN FAMILY COMMUNICATION ABOUT HEALTH

Authors: Ashley Elrick, Wendy Kohlmann, Teneille Brown, Whitney Espinel, Kimberly Kaphingst

Family communication of health ideally involves all members of the family. Yet prior research has focused on female family members, either due to the health topic of interest (e.g., breast cancer) or study recruitment procedures. This study investigated the perspectives of males on family communication about health. We conducted semi-structured, in-person interviews with 30 family dyads (i.e., siblings and parent-child) with ten dyads from each of three groups: Caucasian, Hispanic, and Pacific Islander. Each family member was interviewed separately and then dyads were interviewed together (average length 90 minutes). 23 males (38.3%) participated representing various dyad types. Some younger males reported little involvement in family communication of health. Most males, regardless of age, were actively engaged in health-related family communication. Males were more engaged in communication with family members when there was a known health concern requiring regular maintenance or preventative measures. Pacific Islander males mentioned diet or exercise as ways to be engaged in family communication. Research on family communication about health has often focused on females. However, we found that there are situations and families where the males are highly involved in family communication about health. Achieving better understanding of the engagement and impact of males in health communication will help future communication interventions target the most appropriate family members.

FORNETTI, JAMIE – ALANA WELM LAB - RON KINASE: A THERAPEUTIC TARGET FOR CANCER-INDUCED BONE DESTRUCTION

Authors: Jaime Fornetti, Alana Welm

Breast cancer most commonly metastasizes to bone and is debilitating for patients. Despite current therapies, many patients progress to develop new skeletal complications, highlighting the need for additional treatments. We previously demonstrated that the macrophage stimulating protein (MSP)/RON tyrosine kinase signaling pathway is elevated in breast cancer and associated with increased bone metastasis. In mice, MSP expression by mammary tumors causes spontaneous bone metastasis and bone destruction through host RON, which is expressed by bone-resorbing osteoclasts. Based on these data, we hypothesize that MSP-expressing tumors promote bone destruction through osteoclast RON, and that MSP/RON signaling may be targetable in breast cancer bone metastasis. To test this hypothesis, RON was depleted in osteoclasts and the effect on tumor-associated osteolysis was assessed using a PyMT intratibial tumor model. RON expression by osteoclasts was also characterized using a mCherry reporter. Data to date confirm RON expression in mature osteoclasts and support a role for osteoclast RON as a mediator of osteolytic metastasis. MSP/RON signaling was also evaluated as a therapeutic target for bone metastasis in humans. Four of six breast cancer bone metastasis samples expressed MSP. Additionally RON inhibitor treatment in cancer patients was associated with a decrease in the bone resorption marker CTX and increase in the bone formation marker BSAP. Altogether, our clinical and preclinical data indicate that RON inhibitors may be effective against osteolytic bone metastasis and provide rationale for the continued investigation of RON inhibitors for use in patients.
FOTH, MONA – MARTIN MCMAHON LAB - MELANOMA CELLS EXPRESSING MUTATIONALLY ACTIVATED RAC1P29S ARE RESISTANT TO BLOCKADE OF PI3K-BETA

Authors: Mona Foth, Martin McMahon

RAC1 mutations are the third most frequently occurring gain-of-function mutation in cutaneous melanoma, with the most frequent alteration encoding for RAC1P29S. RAC1-GTP has pleiotropic regulatory functions in the cell cycle, cell-cell adhesion, motility, tumor angiogenesis, as well as invasion and metastasis. Importantly, the exact mechanism through which mutationally activated RAC1P29S propagates its pro-tumorigenic effects is currently unclear. RAC1-GTP was recently shown to directly regulate the PI3'-kinase isoform PI3K-beta, leading to downstream activation of the AKT protein kinases. Here we sought to investigate whether RAC1P29S propagates its oncogenic signaling through PI3K-beta in melanoma. Given the availability of PI3'-kinase isoform-selective pharmacological inhibitors, we tested whether RAC1P29S-expressing melanoma cells are sensitive to blockade of PI3K-beta. Unexpectedly, RAC1P29S human melanoma cells were resistant to PI3K-beta-selective blockade, suggesting that PI3K-beta-targeted therapy is not a treatment option for melanoma patients expressing mutationally activated RAC1. Furthermore, RAC1P29S melanoma cell lines showed variable sensitivity to pan-class I PI3K inhibition, suggesting that single agent pan-PI3K inhibitors are likely insufficient to prevent cancer progression in melanoma patients expressing RAC1P29S. Lastly, we found that RAC1P29S cell lines also showed variable sensitivity to pharmacological inhibition of the RAC1/PAK1 signaling pathway, questioning the effectiveness of inhibitors of this pathway in RAC1P29S expressing melanoma patients. Our future research efforts will focus on the examination of other potential RAC1P29S downstream effectors, such as WAVE, IQGAP1, Merlin/NF2, mTORC2 and GLUT-4 as possible novel drug targets in RAC1P29S expressing melanomas.

FUJA, DANIEL – MEI KOH LAB - COORDINATED REGULATION OF IRON AND HYPOXIC RESPONSE IN KIDNEY CANCER: A MOONLIGHTING ROLE FOR ISCA2 AND IBA57 IN CLEAR CELL RENAL CELL CARCINOMA

Authors: Daniel Fuja, Mei Koh

One consequence of the precipitous growth rate seen in most solid tumors is the development of hypoxic regions and subsequent activation of hypoxia signaling pathways. Due to the interplay between hypoxia and iron regulation, most tumor types also exhibit changes in iron metabolism and signaling. Alterations in both hypoxia signaling and the regulation of iron metabolism have been linked to tumor progression Clear Cell Renal Cell Carcinoma (CCRCC), the most common and aggressive form of kidney cancer. CCRCC provides a unique opportunity to characterize these hypoxia/iron-associated pathways. Our investigation indicates that—in addition to known mutations, such as pVHL—aberrations in iron-related pathways alter the hypoxic response and iron signaling. Indeed, we show > 20 fold increase in iron accumulation in CCRCC, compared to normal kidney. HIF-2α, a central driver of CCRCC progression is regulated by the binding of iron regulatory protein 1 (IRP-1) to HIF-2α mRNA, which inhibits HIF-2α translation under low-iron conditions. mRNA binding of IRP-1 is prevented by iron-sulfur particle [4Fe4S] presence within the IRP-1 holoenzyme. Intriguingly, silencing of two conserved components of the mitochondrial [4Fe4S] iron sulfur cluster assembly machinery (ISCA2 or IBA57) decreased HIF-2α and HIF-1α. By contrast, silencing of ISCA1—a related component of the [4Fe-4S] iron sulfur cluster assembly machinery—did not similarly affect HIF-2α or HIF-1α protein. ISCA2 knockdown also induced changes in Ferritin and Transferrin Receptor, as might be seen in iron-deprivation. Thus, we identify a novel pathway for coordination of hypoxia response and tumor-specific iron regulation.
FULBRIGHT, ALEXIS – KIM EVASON LAB - DISSECTING THE ROLE OF SEROTONIN IN THE PATHOGENESIS OF HEPATOCELLULAR CARCINOMA

Authors: Liam O'Brien; Alexis Fulbright; Sunita Shankaran; Kimberley Evason

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide. HCC incidence and mortality continue to rise, the pathogenesis of the disease is not well understood, and few effective treatments exist. Due to this, more effective treatment and prevention strategies are critical, which is why we are looking for new therapies targeting HCC. In our studies we use a β-catenin-driven zebrafish model of HCC. This is an ideal system for our studies because zebrafish HCC is histologically similar to human HCC and has similar gene expression profiles. In an unbiased drug screen using this model, we have previously shown that amitriptyline, a tricyclic antidepressant, is able to decrease hepatic hyperproliferation in larvae expressing hepatocyte-specific activated β-catenin. Serotonin has been shown to increase cell proliferation in human HCC cell lines. The aim of our research is to determine the role of serotonin signaling in HCC progression. To do this we use pharmacological and genetic techniques to modulate the level of serotonin and analyze liver size as an indicator of HCC. We have found that decreasing the level of serotonin signaling results in decreased liver size, while increasing serotonin results in increased liver size. Determining the role of serotonin in HCC progression may lead to new treatment options for this deadly disease.

GUNDLAPALLI, HARIKA – ALANA WELM LAB - ROLE OF RON EXPRESSING TISSUE RESIDENT MACROPHAGES IN ENHANCING BREAST CANCER METASTASIS BY IMMUNESUPPRESSION

Authors: Harika Gundlapalli, Atakan Ekiz, Alicia Lai, Alana Welm

Overexpression of the receptor tyrosine kinase Ron is documented in various cancers and is associated with tumor progression and metastasis. Ron is the cell surface receptor for macrophage-stimulating protein (MSP). Independent of its role in tumor cells it was previously shown that host Ron/MSP signaling is essential for conversion of breast cancer micrometastases to overt metastases. Furthermore, CD8+ T-cells are necessary and sufficient to block this conversion, suggesting that inhibiting host Ron promotes an anti-tumor immune response. Interestingly, within the immune system, Ron is expressed only on the terminally differentiated tissue resident macrophages (Mφ), not on bone marrow-derived monocytes or other immune cells. Recent work demonstrates that tissue-resident Mφ are either embryonically-derived or are derived from the adult bone marrow. Embryonically-derived tissue resident Mφ may have distinct functions from bone marrow-derived macrophages in modulating immune responses to cancer; thus, it is important to understand the origin of Ron+ Mφ. Using a Mφ-specific lineage tracing mouse model (Csf1mer-icre-mer/mTmG), we show that at least 50% of Ron-expressing resident Mφ are derived from the embryo. The role of tumor-associated Mφ which come from bone marrow precursors and infiltrate the tumor or metastatic sites via the circulation, have been extensively studied. However, the role of tissue-resident Mφ, which have embryonic origins and reside in the tissue, in modulating immune responses has been understudied. My preliminary data using myeloid-specific Ron knock out mice (LyzM-Cre+/Ronfl/fl), suggest that knocking down Ron specifically on Mφ (Ron TKKOmye) reduces lung metastatic tumor burden.
**HOLOWATYJ, ANDREANA – NELI ULRICH LAB - GUT MICROBIAL COMMUNITY DIVERSITY IS ASSOCIATED WITH SYSTEMIC VASCULAR ENDOTHELIAL GROWTH FACTOR A LEVELS AMONG COLORECTAL CANCER PATIENTS**

**Authors:** Andreana Holowatyj, Zac Stephens, Christy Warby, Kate Buhrke, Biljana Gigic, Tengda Lin, Juergen Boehm, Nina Habermann, Esther Herpel, Jennifer Ose, Martin Schneider, Petra Schrotz-King, Peter Schirmacher, Alexis Ulrich, Adetunji Toriola, June Round, Cornelia Ulrich

Dysbiosis in the gut microbiota and activation of the angiogenic switch in the tumor microenvironment contribute to colorectal carcinogenesis. Analyses of baseline fecal samples via 16S rRNA gene sequencing, and evaluation of angiogenic stimulators, vascular endothelial growth factor (VEGF) A and D, in patient sera among n=125 patients diagnosed with colorectal cancer in the ColoCare Study were used to explore the link between the gut microbiome and systemic biomarkers of angiogenesis. Baseline clinicopathologic and demographic characteristics were evaluated. Relative contributions of taxonomic groups identified through 16S sequencing were examined. Diverse microbial taxa, including previously cancer-associated microbes, were detected in fecal biospecimens. A significant association of gut microbial community diversity was observed by circulating VEGFA (Bray-Curtis metric: $R^2=0.94$, false discovery rate [FDR] q-value=0.007; weighted Unifrac: $R^2=0.95$, FDR q-value=0.026) but not by VEGFD (Bray-Curtis metric: $R^2=0.81$, FDR q-value=0.77; weighted Unifrac: $R^2=0.80$, FDR q-value=0.8) levels. Differences in systemic VEGFA or VEGFD levels were not directly correlated with individual taxa. These findings suggest that microbial community level function is important for driving the association between gut microbial community diversity and circulating VEGFA biomarker levels. Together, profiling of the microbial taxa and systemic angiogenesis biomarkers among colorectal cancer patients demonstrates that circulating levels of angiogenic stimulator VEGFA may reflect changes in the microbial ecosystem of the human gut that influence colorectal carcinogenesis.

**KOTIYAL, SRISHTI – KIM EVASON LAB - AN INDUCIBLE ZEBRAFISH MODEL TO DISSECT THE ROLE OF BETA CATENIN SIGNALING IN HEPATOCELLULAR CARCINOMA**

**Authors:** Srishti Kotiyal, Sharanya Maanasi Kalasekar, Kathryn Davis, Cindy Barba, Annika Young, Kimberley Evason

Hepatocellular carcinoma (HCC) is the third highest contributor to cancer-related mortality in the world. This disease is molecularly heterogeneous in nature, giving rise to the essential and urgent need of delineating HCC mechanisms based on molecular subtypes. Various signaling pathways have been implicated in HCC development. The Wnt/β-catenin pathway remains of particular significance with more than a third of all HCC cases characterized by aberrant activation of the Wnt/β-catenin signaling axis and about 20% of HCC cases presenting activating mutations in β-catenin gene. The need to elucidate the role of aberrant β-catenin gene activation in the development of liver malignancy is thwarted by lack of relevant animal models. To address this bottleneck, we designed a vertebrate model system of activated β-catenin-driven HCC in an inducible background using zebrafish (Danio rerio). Using hepatocyte-specific constitutive/induced Cre-recombinase zebrafish lines together with floxed β-catenin and/or floxed fluorescent reporter lines, we show here that Cre recombinase is successfully able to switch on the expression of floxed transgenes in fish at larval, juvenile and adult stages. Through histology and longitudinal studies, we are determining the ability of our inducible system to increase cellular β-catenin levels and Wnt signaling in the liver and to stimulate HCC when activated β-catenin is turned on at different developmental stages including adulthood. This inducible system will be useful for studying the impact of β-catenin activation on liver size and malignancy at various liver developmental stages and developing treatment strategies.
**LAI, ALICIA – ALANA WELM LAB - RON KINASE INHIBITION TO IMPROVE IMMUNOTHERAPY FOR BREAST CANCER METASTASIS**

**Authors:** Shu-Chin Alicia Lai, Huseyin Atakan Ekiz, Fadi Haroun, Alana Welm

Metastasis is the cause of death for nearly all types of cancer, including breast cancer. An exciting new area of research in metastatic breast cancer centers on immune therapy. Although new immune checkpoint blockade therapies have provided benefit for a fraction of patients tested so far, the majority of patients still do not respond to these drugs. A better understanding of how the immune system can be harnessed against metastatic breast cancer is required in order to improve patient outcomes in this area. We previously discovered that macrophage Ron receptor tyrosine kinase promotes breast cancer metastasis by inhibiting CD8+ cytotoxic T lymphocyte activity. We hypothesized that dual blockade of Ron activity and existing immune checkpoint molecules would unleash a more effective CD8+ T cell response to control or eliminate metastatic breast cancer. Our strategy would simultaneously disable tumor-mediated immune evasion mechanisms on both the innate and adaptive immune systems. To test the potential of combination therapy, the Ron inhibitor BMS-777607 and/or the immune checkpoint blocking agents anti-PD1 or anti-CTLA4, were administrated in our mouse mammary tumor model to examine the effects on breast tumor progression. To examine Ron-specific effects of BMS-777607, we also examined the effect of genetic deletion of host Ron signaling activity in combination with immunotherapy. The anti-tumor immune response was comprehensively examined by multi-color flow cytometry and immunohistochemical staining for tumor-infiltrating lymphocytes (TILs). Our data suggest that the combination of Ron inhibition with immune checkpoint blockade may be an effective therapy in breast cancer.

**MOLLAOGLU, GURKAN – TRUDY OLIVER LAB - LINEAGE SPECIFIERS SOX2 AND NKX2-1 REGULATE NEUTROPHIL RECRUITMENT AND ADENOSQUAMOUS TRANSDIFFERENTIATION IN LUNG CANCER**

**Authors:** Gurkan Mollaoglu, Alex Jones, Sarah Wait, Christopher Conley, Arjun Bhutkar, Jeffery Vahrenkamp, Thomas Lane, Jason Gertz, Kevin Jones, Eric Snyder, Trudy Oliver

Lineage-specific transcription factors are regulators of cell identity in development, homeostasis, and disease. The major types of non-small cell lung cancer are associated with distinct master regulators: SOX2 drives the squamous fate, whereas NKX2-1 governs adenocarcinoma fate. We developed multiple mouse models of lung cancer to interrogate the impact of SOX2 and NKX2-1 on cell fate and innate immune cell recruitment. NKX2-1 potently suppresses SOX2-driven squamous tumorigenesis by repressing adeno-to-squamous transdifferentiation. SOX2 recruits, whereas NKX2-1 suppresses, tumor-associated neutrophils (TANs) at least partly through inverse regulation of the chemoattractant Cxcl5. Tumor-derived CXCL5 is sufficient to recruit TANs. Single-cell RNA sequencing revealed that TANs exhibit tumor-promoting features and distinct gene expression profiles compared to blood neutrophils. These data reveal how lineage specifiers dictate not only cell fate but also distinct immune microenvironments.
MOORE, KRISTINA – JOSHUA SCHIFFMAN LAB - RESTORING DEFICIENT P53 FUNCTION IN LI-FRAUMENI SYNDROME FIBROBLASTS THROUGH ELEPHANT P53 (EP53) EXPRESSION

Authors: Kristina Hodson Moore, Lauren N. Donovan, Cristhian Toruno, Rosann Robinson, Schuyler O’Brien, Tanya Guha, Ana Novokmet, David Malkin, Lisa M. Abegglen, Joshua Schiffman

P53 responds to DNA damage through cell cycle arrest, repair and/or apoptosis. Patients with Li-Fraumeni Syndrome (LFS) have a 90% cancer risk but only 1 functioning TP53 allele, healthy individuals with 2 TP53 alleles have up to 50% lifetime cancer risk, and elephants with 40 TP53 alleles have a low cancer rate of less than 5%. Elephant p53 (EP53) is comprised of two conventional alleles (EP53-anc) and 38 retrogenes (EP53-retro1-19). While fibroblasts from healthy people undergo cell cycle arrest and senescence following ionizing radiation (IR), fibroblasts from people with LFS respond significantly less to IR. To test the hypothesis that EP53 has the ability to restore deficient p53 function in LFS fibroblasts, normal human dermal fibroblasts and LFS fibroblasts were transduced to express flag-tagged EP53-anc, EP53-retro9, or human TP53. Induced and uninduced fibroblasts were treated with 4 Gy IR to cause DNA damage, and response to treatment measured using flow cytometry, senescence-associated-β-galactosidase positivity, and DAPI staining. We observed increased G2/G1 ratio in EP53-anc expressing LFS fibroblasts after IR, consistent with cell cycle arrest. In contrast, human TP53 expressing LFS fibroblasts had decreased G2/G1 ratio after IR. Senescence-associated-β-galactosidase positivity increased in LFS cells expressing EP53-anc after IR compared to untreated control cells. We observed increased apoptosis by DAPI stain after irradiation in EP53-retro9 expressing LFS cells compared to control cells. Our results suggest that EP53 expression can restore deficient p53 function in LFS fibroblasts and support further investigation into the potential for EP53-based therapeutics to modify cancer risk in LFS.

PARK, JIHYE – MIA HASHIBE LAB - RURAL-METROPOLITAN DISPARITIES IN OVARIAN CANCER SURVIVAL: A STATEWIDE POPULATION-BASED STUDY

Authors: Jihye Park, Brenna E. Blackburn, Kerry Rowe, John Snyder, Yuan Wan, Vikrant Deshmukh, Michael Newman, Alison Fraser, Ken Smith, Kim Herget, Lindsay Burt, Theresa Werner, David K. Gaffney, Ana Maria Lopez, Kathi Mooney, Mia Hashibe

To investigate rural-metropolitan disparities in ovarian cancer survival, we assessed ovarian cancer mortality, and differences in prognostic factors by rural-metropolitan residence. The Utah Population Database was used to identify ovarian cancer cases diagnosed between 1997-2012. Residential location information at the time of cancer diagnosis was used to stratify rural-metropolitan residence. All-cause death and ovarian cancer death risks were estimated using Cox proportional hazard regression models. Among 1,661 patients diagnosed with ovarian cancer, 11.8% were living in rural counties of Utah. Ovarian cancer patients residing in rural counties were more likely to be obese, impoverished, and have lower education level. Rural residents were more likely to be diagnosed with advanced cancer stage, and higher histology grade, histology subtype of Endometrioid/non-specific, and receive no treatment or surgery only, although the differences were not statistically significantly different. While ovarian cancer patients residing in rural counties had different characteristics compared to metropolitan residents, we did not observe an association between rural residence and risk of all-cause nor ovarian cancer-specific death after adjusting for confounders. However, among rural residents, ovarian cancer mortality risk was very high in older age at diagnosis and for mucinous carcinoma, and low in overweight at baseline. Rural residence was not significantly associated with the risk of ovarian cancer death. Nevertheless, patients residing in rural-metropolitan areas had different factors affecting the risk of all-cause mortality and cancer-specific death. Further research is needed to quantify how mortality risk can differ by residential location accounting for degree of healthcare access and lifestyle-related factors.
The purpose of this study was to explore patterns of communication among families with a Lynch syndrome diagnosis and understand what resources could facilitate family communication. 127 probands (i.e., first person in family with identified mutation) and family members participated in semi-structured interviews about: how they learned about Lynch syndrome in their family, with whom they shared genetic test results, confidence in sharing results with other family members, and resources that would be helpful when learning about Lynch syndrome. We found that both probands and family members were most likely to share genetic test results with parents and siblings, and least likely to share results with aunts, uncles, and cousins. Most participants felt very confident sharing their test results with family members, but reported that certain topics such as cancer risk were challenging to convey. Probands reported the most helpful resources to be access to a specialty clinic or website, while family members described general printed materials as most helpful. Overall, families affected by Lynch syndrome may experience barriers to communication with more distant relatives, and may benefit from receiving specific resources to facilitate family communication. To help facilitate this process, providers could emphasize the need to share information with more distant family members and provide appropriate supportive resources.

Applying innovations in genetic/genomic medicine to inform individualized cancer therapies is a key focus of precision medicine. Patients are considered crucial collaborators in the discovery and implementation of these new approaches, yet the extent of discussion with patients and the public about gene-based therapies is unknown. We present findings from a scoping review of cancer-related genetic and genomic communication studies published from 2010 to 2017 (N = 513). This body of empirical literature assesses clinical communication, as well as patient or public knowledge, attitudes, and preferences. In this analysis, we describe a subset of studies specific to gene-based cancer therapies and pharmacogenomics within this larger literature landscape. Overall, findings indicate that genomic testing for gene-based cancer drugs and tumor therapies has been largely ignored in genetic and genomic communication research. Studies focused on pharmacogenomics and/or tumor (i.e., somatic) genetic testing comprised only 4% of papers (N = 21). Of these, the majority assessed attitudes among current cancer patients, typically with breast or unnamed cancer. Only one study measured outcomes of direct-to-consumer pharmacogenomic testing. Two papers examined whether risk information format affected patient understanding. Nonwhite patients were less open to testing than white patients. Overall, findings indicate that most patients have low knowledge of genetic or genomic testing to inform cancer therapeutic decisions, and the potential exists for disparities in underserved and minority patient populations. We conclude by highlighting research gaps, including the need for studies that can inform effective and inclusive communication about therapeutic applications of genomic medicine.
SCHERZER, MICHAEL – MARTIN McMAMHON LAB - LOSS OF BIM DIMINISHES CELL DEATH FOLLOWING PATHWAY-TARGETED THERAPY IN BRAF(V600E) LUNG CANCER

Authors: Michael Scherzer, Martin McMahon

Activation of the MAPK pathway is central to the initiation and progression of lung adenocarcinoma. Importantly, small molecule inhibitors against MAPK pathway constituents can provide patients with a therapeutic benefit. However, it has been shown previously in BCL-ABL AML and in EGFR-mutated lung adenocarcinoma that patients with deletion-polymorphisms in the BIM gene are refractory to pathway targeted therapy. This ~2000 bp deletion polymorphism leads to the pro-apoptotic BIM protein being non-responsive to MAPK-directed degradation. Therefore, activation of intrinsic apoptosis seems critical for MAPK-addicted cancer cell death. BRAF, a central kinase in the MAPK pathway, is commonly mutated in lung adenocarcinoma and can be successfully targeted with small molecule inhibitors for a therapeutic benefit in patients with BRAF\textsuperscript{V600E} mutations. However, the role of BIM in cell death of BRAF(V600E)-addicted lung cancer cells has not been explored. Here, we genetically ablate the BIM gene in both human and mouse BRAF (V600E) lung cancer cells and show that it is required for the cell death phenomenon caused by small molecule inhibitors against BRAF and its downstream effector MEK.

TRUONG, AMANDA – MARTIN McMAMHON LAB - EVALUATION OF SKIN CANCER DIAGNOSES IN DERMATOLOGY PATIENTS SEEN IN A HOMELESS CLINIC

Authors: Amanda Truong, Caroline Laggis, Laura Gardner, Brayden Forbes, Douglas Powell, Chelsey Vranes, Trevor Annis, Tiffiny Gregory, Christopher Hull, Bethany Lewis

Dermatologic conditions are a common cause of morbidity in homeless persons and can be attributed to poor healthcare access and harsh environmental exposures. To examine common skin diagnoses, risk factors, and obstacles to prevent or treat these conditions, we performed a retrospective chart review of patients seen from 2009-2017 in a free monthly referral-based dermatology clinic serving the homeless population in Salt Lake City, Utah. 147 patients [average age 50.6 years (Range: 21-83), 66.2% male, 75.5% Caucasian] were included with an average of 1.9 (Range: 1-7) skin diagnoses per patient. After benign growths (31%), the most common diagnoses were non-melanoma skin cancer (13.2%), dermatitis (9.2%), and actinic damage (8.6%). Notably, more than half of patients followed-up as recommended and only 10.2% of those with ultraviolet associated diagnoses (UVAD; actinic damage and skin cancers) had documented counseling on sun protection during their appointment. A subsequent in-clinic survey of dermatology patients (n=50) found that 62% believed their skin health to be fair or poor and 68% believed that skin exams from providers are too expensive. Most reported sun protection as important to them, but 52% rarely or never use sunscreen. In particular, those diagnosed with UVAD were more likely to report never wearing sunscreen (p=0.02). Most (>70%) reported being unable to afford basic skin care items. Our results highlight the importance of skin cancer prevention in the homeless, particularly the need for accessibility to dermatologic resources, such as sunscreen, better adherence to follow-up, and improved patient education.
UPDIKE, KATHERINE (KATE) – K-T VARLEY LAB - MHCII EXPRESSION IN TNBC TUMOR CELLS ACTIVATES TUMOR INFILTRATING LYMPHOCYTES AND IS ASSOCIATED WITH GOOD PROGNOSIS

Authors: Katherine Updike, K-T Varley

Triple Negative Breast Cancer (TNBC) is an aggressive disease with disparate patient outcomes. There are no approved targeted therapies for TNBC, and patients are treated with surgery, radiation, and cytotoxic chemotherapy. After treatment, 42% of patients relapse within five years. We performed RNA-seq on patient tumors and found that expression of the major histocompatibility complex II (MHCII) pathway in tumor cells was significantly associated with long-term disease-free survival. The MHCII pathway is normally expressed by professional antigen presenting cells that activate T cells to fight infection. We hypothesize that MHCII expression in TNBC tumor cells activates T cells that prevent metastasis. To test the functional role of MHCII expression in tumor cells, we utilize a syngeneic mouse model of TNBC that we engineered to contain a doxycycline inducible driver of MHCII pathway expression. When tumor cells are induced to express the MHCII pathway in vivo, we observe a significant increase in activated CD4+ T cells in tumors. We are currently testing whether inducing MHCII expression in tumor cells leads to reduced metastatic burden in mice. Additionally, recent studies in melanoma report that MHCII expression correlates with response to PD-1 inhibitor therapy. We observe a significant increase in PD-1 positive T cells in TNBC tumors that express MHCII in mice and patients. We are testing whether neoadjuvant PD-1 inhibitor therapy improves outcomes in mice with tumors that express MHCII. This study will reveal whether MHCII expression in TNBC tumor cells activates an anti-tumor immune response that can be enhanced with immunotherapy.

VISKOCHIL, RICHARD – NELI ULRICH LAB - EXERCISE TRAINING LOWERS POSTMEAL INSULIN BUT MAY NOT IMPROVE OTHER METRICS OF DIABETES RISK IN BREAST CANCER SURVIVORS

Authors: Richard Viskochil, Jennifer Blankenship, John Staudenmayer, Susan Hankinson, Patty Freedson, Barry Braun

Elevated insulin concentrations may influence cancer and cardiometabolic disease prognosis, however the effect of exercise on insulin supply and demand in breast cancer survivors is unclear. The objective of this study was to evaluate the effects of exercise training on postmeal insulin concentrations and mechanisms responsible for changes to insulin supply and demand in breast cancer survivors. Fifteen postmenopausal breast cancer survivors underwent a supervised 12-week aerobic exercise program (60 min/day, 3-4 days/week). Changes in fitness and body composition were determined by estimating VO2peak from a submaximal exercise test and dual energy X-ray absorptiometry (DEXA) respectively. Postmeal insulin was determined by peak insulin and area under the insulin curve (iAUC) during a five-sample oral glucose tolerance test. Insulin sensitivity was estimated using the Matsuda composite insulin sensitivity index (C-ISI). Participants averaged 156.8±16.6 minutes/week of supervised exercise training at an intensity of 81.4±6.2% HRmax over the 12-week intervention period. Estimated VO2peak significantly increased (+2.8±1.4 ml/kg/min, p<0.05) and body weight significantly decreased (-1.1±0.8 kg, p<0.05) following the intervention. There were no differences in fasting insulin, iAUC, C-ISI or peak insulin. Postmeal insulin concentrations were lower only at 120 minutes following glucose consumption (68.8 ± 34.5 vs. 56.2 ± 31.9 uU/ml, p<0.05), and there was a significant interaction with past/present aromatase inhibitor (AI) use for peak insulin (-11.99 (non-AI) vs +13.91 (AI) uU/ml) and iAUC (-24.03 (non-AI) vs +32.73 (AI) uU/mL). Exercise training had limited benefits on postmeal insulin concentrations in breast cancer survivors, and this relationship may be influenced by AI use.
WARNER, RICHARD – MATTHEW VAN BROCKLIN LAB - RECEPTOR IDENTIFICATION METHOD FOR DISCOVERY OF NOVEL RECEPTORS FOR IMMUNE CO-SIGNALING MOLECULE, B7H3

Authors: Richard Warner, Vaishnathi Thiraviyarajah, Valeria Ortiz, William Burnett, David Burnett, Matthew VanBrocklin

Recently, immunotherapies have shown great promise for melanoma patients. Many immunotherapies include immune checkpoint inhibitor antibodies which reactivate immune responses by removing malfunctioning brakes on immunity. For example, CTLA4 and PD1-targeting antibodies given together in Phase III clinical trials have resulted in tumor diminishing responses in up to 60% of patients. Although combined blockade of CTLA4 and PD1 antibodies has been fruitful, up to 40% of patients do not respond and additional means for immune activation are needed. Our goal is to develop tools to study the immune nature of B7H3, a PD-L1-related signaling molecule, and identify B7H3 receptors involved in immune suppression as additional targets for immunotherapy blockade. B7H3 is in the same family as PD-L1 (aka. B7H1), which is a ligand of the PD1 checkpoint receptor, hence, B7H3 is a likely candidate for successful immune checkpoint blockade. We observed B7H3 as a marker with high expression in microarray analysis of melanoma tumor lines and high protein expression in many human and mouse melanoma cell lines, regardless of oncogenic BRAF or NRAS status. We seek to identify immune populations to which B7H3 can bind, identify receptors, and functional effects of B7H3. We’ve tested peripheral blood fractions and activated T-cells for demonstrable binding to exogenous B7H3. We’ve employed protein cross linkers to trap B7H3-bound proteins for pull-down and identification by mass spectrometry. Taken together, we conclude that B7H3 mediates immune regulation through interactions on T-cells, NK cells, and/or macrophages. Currently, we are testing probable candidates toward identification of its receptor.

YAN, DONGQING – MICHAEL DEININGER LAB - SELECTIVE INHIBITION OF NUCLEAR CYTOPLASMIC TRANSPORT AS A NEW TREATMENT PARADIGM IN MYELOFIBROSIS

Authors: Dongqing Yan, Anthony Pomicter, Srinivas Tantravahi, Clinton Mason, Anna Senina, Jonathan Ahmann, Ami Patel, William Heaton, Anna Eiring, Phillip Clair, Sabina Swierczek, Erkan Baloglu, Jamshid Khorashad, Josef Prchal, Thomas O'Hare, Michael Deininger

Myelofibrosis (MF) is a fatal hematopoietic stem cell neoplasm characterized by constitutive activation of JAK/STAT signaling due to mutations in JAK2, calreticulin or MPL. JAK inhibitors such as ruxolitinib reduce symptoms and improve quality of life, but are not curative. We therefore sought to identify new therapeutic targets in MF by performing an shRNA library screen on JAK2V617F-mutant HEL cells, and identified Nuclear-cytoplasmic transport (NCT) genes including RAN and RANBP2 as the top candidates. Validation experiments show that JAK2V617F-mutant HEL, SET-2, and HEL resistant to JAK inhibition cells are exquisitely sensitive to knockdown of RAN or pharmacologic inhibition of NCT by selective inhibitors of nuclear export (SINE) compounds KPT-330 or KPT-8602. Inhibition of NCT selectively decreased viable cells and colony formation by MF compared to cord blood CD34+ cells and enhanced ruxolitinib-mediated growth inhibition and apoptosis, both in newly-diagnosed and ruxolitinib-resistant/refractory MF cells. Inhibition of NCT in MF CD34+ cells led to nuclear accumulation of p53 and NPM1. KPT-330 in combination with JAK inhibitor normalized white blood cells, hematocrit, spleen size and splenic architecture and delayed emergency of ruxolitinib resistance in an MPN mouse model, with selective reduction of JAK2V617F expressing cells. Our data implicate NCT as a potential therapeutic target in MF and provide a rationale for clinical evaluation in relapse and ruxolitinib-refractory MF patients.
YOUNG, ERIN – JOSHUA SCHIFFMAN LAB - GERMLINE CONTRIBUTION TO THE GENOMIC INSTABILITY IN EWING SARCOMA

Authors: Erin Young, Diana Abbot, Schuyler O’Brien, Jamie Gardiner, Trent Fowler, Rosann Robinson, Lisa Abeggen, Barry Moore, Matthew Velinder, Nathan Pankratz, Spencer Kelley, Brent Pedersen, Lucy Hayes, Wendy Kohlmann, Kinley Garfield, Cathryn Koptiuch, Stephen Lessnick, Lor Randall, Gabor Marth, Aaron Quinlan, Mark Yandell, Kevin B. Jones, Angelica Putnam, Jennifer Wright, Lisa Cannon-Albright, Holly Spraker–Perlman, Logan Spector, Philip Lupo, Joshua Schiffman

Ewing sarcoma (ES) is the second most common bone cancer in children and adolescents. Chromosomal translocations resulting in EWS-ETS transcription factor fusion proteins are considered the major driver of ES. The Genetics of Ewing Sarcoma International Study (Project Genesis) is one of the largest ES epidemiology studies, combining whole-genome sequencing (WGS) with clinical information and family history. ES probands and family members were recruited into Project Genesis. This resulted with 344 kindreds (228 full trios) with both self-reported family history and WGS. Out of 407 kindreds with ES, 58 (14.3%) had at least one first and/or second degree relative who met current genetic testing guidelines for Chompret (n=10), hereditary breast and ovarian cancer (HBOC, n=44), Lynch syndrome (n=8), hereditary melanoma (n=3), hereditary prostate (n=4), and Cowden’s syndrome (n=1), and 14 (3.4%) had at least one first or second degree relative diagnosed with cancer under 25 years of age. 18.3% of ES probands carried a P/LP variant in a Fanconi anemia or cancer predisposition gene. Grouping together Fanconi anemia and other genomic stability genes, a significant burden was observed in ES probands (p=1.879e-05). In conclusion, 14.7% of ES probands harbor deleterious variants in genes with roles in genome maintenance. No single gene explained a large portion of ES incidence, but combined there is evidence of an increased burden of deleterious variants in genomic stability genes which may prime the cell for chromosomal translocations.

ZHANG, PENG – BRUCE EDGAR LAB - SH3PX1-DEPENDENT AUTOPHAGY REGULATES INTESTINAL STEM CELL PROLIFERATION THROUGH CONTROLLING THE ENDOSONAL TRAFFICKING OF EGFR

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Sorting nexin (SNXs) proteins have been demonstrated to play fundamental roles in endosomal sorting and signaling. In this study we identified Drosophila SH3PX1, the paralog of human SNX9/18/33, as a cell autonomous regulator of intestinal stem cell (ISC) proliferation. SH3PX1 loss-of-function dramatically increased ISC proliferation mainly though upregulating EGFR signaling. This phenotype can be repressed by the knockdown of EGFR pathway components. Previous study showed that SNX18 controls autophagosome formation. Consistently, knockdown of the autophagy pathway components, atg1, 6, 8a, 16 and Syx17 also increased ISC proliferation. And, knockdown of SH3PX1 in ISCs indeed disrupted autophagosome formation. These data argue that SH3PX1-dependent autophagy restricts ISC proliferation. Based on our current data, we hypothesize that SH3PX1-dependent autophagy controls ISC proliferation through control the endosomal trafficking and degradation of EGFR. Further experiments need to be performed to determine whether endocytosis and degradation of EGFR are controlled by SH3PX1-autophagy pathway, and whether SH3PX1-mediated autophagy is downregulated in stem cells during stress-induced regeneration.
Melanoma is the deadliest form of skin cancer. Screening through skin self-exams (SSEs) could aid in early detection, when treatment is more effective. Regular SSEs with the help of parents or caregivers could help children establish habits around regular screening and facilitate future early detection of melanoma. There have been few studies examining frequency of SSE among children who have a family history of melanoma, as well as whether SSE implementation is related to other melanoma preventive behaviors, such as sunscreen use. The current study examined the frequency of children’s implementation of SSE, and potential relationships between SSE frequency and other melanoma preventive behaviors. Children (n=63) and their parents (n=69) were asked to complete a questionnaire that included items on self-reported frequency of engagement in melanoma preventive and screening behaviors. Parents reported that their children engaged in SSE less (74%) or more (16%) than once per month. Children report that they performed SSE less (53%) or more (33%) frequently than one time per month. There were no significant associations between children’s SSE frequency and their reported engagement in any melanoma preventive behaviors (p’s = .20-.96). Even among children at elevated risk for melanoma, the majority are not performing monthly SSE. Future studies could examine potential barriers to SSE implementation in this population. Interestingly, SSE implementation was not correlated with engagement in melanoma preventive behaviors. These findings suggest that interventions to promote engagement in melanoma prevention and screening behaviors may require targeted strategies for screening, separate from those for preventive behaviors.