LANDRY
CANCER BIOLOGY
CONSORTIUM

ANNUAL SPRING SYMPOSIUM 2022

THURSDAY JUNE 16
12-6:30pm

featuring
KARIN GRUNEBAUM
CANCER RESEARCH FOUNDATION
POSTER COMPETITION

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LANDRY CANCER BIOLOGY CONSORTIUM – WHO WE ARE

The Landry Cancer Biology Consortium is an educational consortium that aims to bring together the cancer biology community at Harvard and its affiliates. We seek to provide advanced training and opportunities for students to extend their studies and community beyond the classroom and thesis lab. The overarching mission of the Landry Cancer Biology Consortium is **to provide a framework for multidisciplinary approaches to cancer and expose a broader range of minds at every level of training to the challenges of cancer research** and thus achieve a more multidisciplinary perspective – spurring the kind of innovative, non-traditional ideas that often result from recruiting new kinds of expertise.

WE ACHIEVE OUR MISSION –

- By providing **a competitive research fellowship** to graduate students that includes tuition and stipend benefits
- By planning and designing **cancer-related curriculum**
- By planning, organizing, and executing **professional development opportunities** in order to foster the development of the future leaders in cancer biology

This work is made possible by the generous support to Harvard Faculty of Arts and Sciences of the late C. Kevin Landry and his family, colleagues, and friends. This gift represents a transformative investment in some of the best and brightest young minds in cancer biology. Through the Landry Cancer Biology Consortium, Harvard is leveraging the strength of its scientific community to encourage new breakthroughs in cancer research and treatment.

CONNECT WITH US

If you want to learn more about Landry Cancer Biology Consortium, visit our website https://landrycancer.hms.harvard.edu.

Follow us on Twitter @LandryCancerBio

If you have any questions don't hesitate to reach out to Jelena Patrnogić, Jelena_Patrnogic@hms.harvard.edu

KARIN GRUNEBAUM CANCER RESEARCH FOUNDATION

Additional support for cancer biology program at Harvard comes from the Karin Grunebaum Cancer Research Foundation (KGCRF), **established in 1958 in loving memory of Karin Grunebaum** by her husband, Fritz Grunebaum, in order to invest in researchers who have made cancer research their life's work.

KGCRF MISSION

Because Karin Grunebaum died at age 39 from an unknown primary site malignancy, the overriding objective of the Karin Grunebaum Cancer Research Foundation is the eradication of all types of cancer. The Foundation's original Declaration of Trust, written in 1958, mandates that the Foundation's funds be exclusively used for **"...aiding research in and study of the cause, treatment and cure of cancer."**

The Foundation's Trustees firmly believe that the eradication of cancer will only occur through successful research accomplishments which are followed by successful practical/commercial application. Thus, **the Foundation has chosen to invest its funds directly in dedicated cancer researchers in hope of helping them achieve significant accomplishments to eliminate all types of carcinomas and thereby eradicate each and every type of cancer.**

If you want to learn more about the Karin Grunebaum Cancer Research Foundation, visit the website https://www.grunebaumfoundation.org.

KGCRF SUPPORT FOR PROFESSIONAL DEVELOPMENT AT HARVARD

The Foundation's slogan is "*Over 60 years of developing cancer researchers*" and their generous gift to the graduate training at Harvard directly supports professional development of our students. Since 2017, the funds are used for a graduate student poster competition held annually during the Spring Symposium where cancer biology trainees have the opportunity to compete for **KGCRF Professional Development Awards**. In addition to the KGCRF Professional Development Awards, KGCRF's generous gift provides fund to support our newly developed **Karin Grunebaum Career Catalyst Awards** (KGCCA). The KGCCA are designed to support student professional development training by providing opportunities to enhance and expand the scope of their research through new collaborations, skills and knowledge. The KGCCA aim to fund student-conceived proposals that complement, and directly impact their ongoing thesis research, or bring new approaches to the research questions through establishing collaborations.

SYMPOSIUM SCHEDULE

KARIN GRUNEBAUM CANCER RESEARCH FOUNDATION POSTER COMPETITION

Gordon Hall 106 Waterhouse Conference Room

12 – 2pm Poster session

SEMINARS

TMEC 227

2:15 – 2:20pm Introduction & Welcome

2:20 – 2:35pm Spatially mapping T cell receptors and transcriptomes
Sophia Liu, Fei Chen Lab

2:35 – 2:50pm Massively Parallel Profiling of Protein-coding Variants in Transcription Factors with SCAnnEd
Ceejay Lee, Brian Liau Lab

2:50 – 3:05pm Combinatorial strategies to target *NRAS*-mutant melanoma
Lisa Situ, Karen Cichowski Lab

3:05 – 3:20pm Visualizing CD8+ T cell infiltration in a zebrafish model of melanoma
Georgia Stirtz, Leonard Zon Lab

3:20 – 3:35pm A conserved transcription elongation factor mediates DNA replication and genome stability
Catherine Miller, Fred Winston Lab

3:35 – 3:50pm Oncogenic K-Ras suppresses global miRNA function
Bing Shui, Kevin Haigis Lab

3:50 – 4:05pm The Effects of Gly12 KRAS Oncogenes are Mutation and Context Specific
Shikha Sheth, PhD, former graduate student, Kevin Haigis Lab

4:05 – 4:15pm Break

4:15 – 5:15pm **Keynote lecture**
On the evolutionary history of metastatic cancer
Kamila Naxerova, PhD

RECEPTION & KGCRF POSTER COMPETITION WINNERS ANNOUNCEMENT

Gordon Hall 106 Waterhouse Conference Room

5:15 – 6:30pm Reception

KEYNOTE SPEAKER

KAMILA NAXEROVA, PhD

Assistant Professor
Center for Systems Biology
Massachusetts General Hospital
Harvard Medical School

Kamila Naxerova received her B.Sc. in Molecular Biotechnology with a specialization in bioinformatics from Heidelberg University in Germany, and her Ph.D. in Human Biology and Translational Medicine from Harvard University in Cambridge, MA. She completed her postdoctoral training with Dr. Stephen J. Elledge at Harvard Medical School. The Naxerova uses computational and high-throughput experimental approaches to study the evolutionary history of normal and neoplastic tissues. Dr. Naxerova is a recipient of a Breakthrough Award from the U.S. Department of Defense, a NextGen Grant for Transformative Cancer Research from the American Association for Cancer Research, an Early Stage Investigator MERIT Award from the National Cancer Institute, a Howard M. Goodman Fellowship from the MGH Department of Molecular Biology and an Emerging Leader Award from the Mark Foundation for Cancer Research.

KGCRF POSTER COMPETITION – PARTICIPANTS

1. Naya Amoh
   Characterizing The Role of Ring Finger Protein 166 in DNA Damage Response and in Cancer

2. Alice Bertocchi
   B cells facilitate lymph node colonization in pancreatic ductal adenocarcinoma

3. Susanna Dang
   Investigating Differentiation States During Lung Adenocarcinoma Progression

4. Emma Garcia
   Probing Regulatory Mechanisms of the De Novo DNA Methyltransferase DNMT3A

5. Peter Georgiev
   Metabolic regulation of the anti-tumor CD8+ T cell response to PD-1 by asparagine

6. Dennis Grishin
   Allelic imbalance of chromatin accessibility in cancer identifies candidate causal risk variants and their mechanisms

7. Gavin Kuziel
   Functional diversification of plant small molecules by the gut microbiota drives intestinal homeostasis

8. Soo Mi Lee
   Role of MicroRNA-127 in Oncogenic Human Herpesvirus-Induced Transformation and Tumorigenesis

9. Patrick Loi
   Epigenetic based therapeutic strategies for KRAS mutant colorectal cancers

10. Adam Maynard
    Folate Depletion Induces Erythroid Leukemia Differentiation

11. Kelly McGovern

    T cell mediated control of cancer stem cells in colorectal cancer

12. Francesca Nardi

    Co-targeting translation initiation as a therapeutic strategy for KRAS-mutant lung cancers

13. Rhea Sahu

    Co-targeting oncogenic and epigenetic pathways in castration-resistant prostate cancer (CRPC)

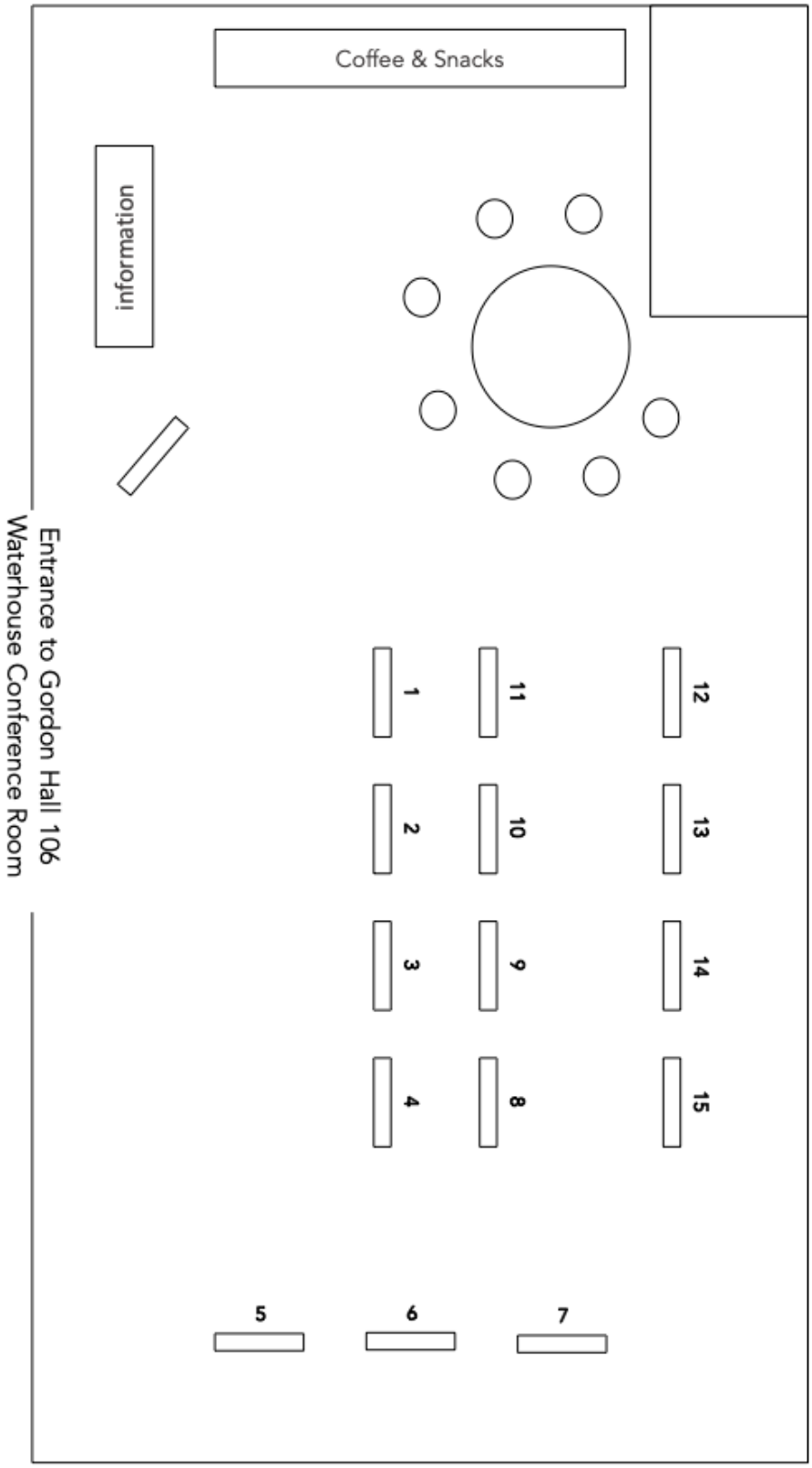
14. Lisa Situ

    Combinatorial strategies to target NRAS-mutant melanoma

15. Kar-Tong Tan

    New Telomeres and Chromosomal Arm Fusions in Cancer Genomes Revealed by Long-Read Genome Sequencing

KGCRF POSTER COMPETITION – POSTER LAYOUT



KGCRF POSTER COMPETITION – JUDGES

Nada Kalaany, PhD
Associate Professor | BCH | HMS

Naama Kanarek, PhD
Assistant Professor | BCH | HMS

Milka Kostic, PhD
Program Director, Chemical Biology | DFCI

Andi McClatchey, PhD
Professor of Pathology | MGH | HMS

Boryana Petrova, Dr. rer. nat.
Instructor | BCH | HMS

Mohammad Rashidian, PhD
Assistant Professor | DFCI | HMS

Nilay Sethi, MD, PhD
Assistant Professor | DFCI | HMS

KGCRF POSTER COMPETITION – ABSTRACTS

NAYA AMOH | G2

Biological and Biomedical Sciences

Raul Mostoslavsky Lab

Characterizing The Role of Ring Finger Protein 166 in DNA Damage Response and in Cancer

Mutations are changes in sequence and structure of DNA. These changes accumulate throughout the lifetime of a cell because of unrepaired DNA damage. Increasing evidence suggests that defects in mammalian DNA repair pathways can contribute to the evolution of the cancer cell genome. Cancer cells generally exhibit genomic instability which leads to activation of oncogenes, cancer suppressor gene inactivation and bypass of DNA damage repair mechanisms and cell cycle checkpoints. DNA damage is repaired by many actors in the cell and an emerging player is the E3 ubiquitin ligase. RING finger E3 ligases are one such group of ligases with known roles in DNA repair. Nonetheless, very few RING finger ligases have been studied in the context of DNA repair. This project aims to characterize the role for RNF166, an E3 ubiquitin ligase we recently identified, in repair of double strand breaks following exogenous and endogenous DNA damage. The proposed experiments will aid in understanding the novel molecular mechanisms underlying the function of RNF166. If successful, this project could provide important new insights into maintenance of cell viability in these basic biological processes, setting the foundation for the discovery of new therapeutics that target dysregulated chromatin factors in cancer.

ALICE BERTOCCHI | G2
Immunology
Stephanie Dougan & Judith Agudo Labs

B cells facilitate lymph node colonization in pancreatic ductal adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) carries a low survival rate. Several factors contribute to its dismal prognosis, including resistance to available therapies and high invasiveness. Lymph nodes act as an early systemic source of circulating malignant cells, allowing their dissemination to distant organs. Lymphatic colonization is linked to worse prognosis, and a better understanding of mechanisms regulating lymph node metastasis is clinically needed. To study each step in the metastatic cascade to the lymph nodes, we have developed a mouse co-clinical model of resectable pancreatic cancer. This model mimics the frequency of human PDAC metastatic recurrence, on a similar time scale relative to the lifespans of mice and humans. In contrast to the established anti-tumor role of T cells, the role of B cells in cancer immunology is more complex. B cells are a predominant immune population in lymph nodes, but their role in relation to lymph node colonization has never been addressed. Using our mouse model of PDAC metastasis, we showed that B cells are required for lymph node metastasis formation. Therefore, our work is investigating the induction of a pro-metastatic phenotype in B cells in PDAC-draining lymph nodes, which we hypothesize facilitates metastasis.

SUSANNA DANG | G2
Biological and Biomedical Sciences
Carla Kim Lab

Investigating Differentiation States During Lung Adenocarcinoma Progression

Lung adenocarcinoma (LUAD), a type of non-small cell lung cancer (NSCLC), is the most common type of lung cancer and arises from alveolar type 2 (AT2) epithelial cells of the distal lung. The most common driver mutations in LUAD are KRAS and EGFR, which remain difficult to target therapeutically due to drug resistance and gaps in knowledge of the specific transcriptional programs activated downstream of KRAS and EGFR driver mutations. This project aims to elucidate how the dysregulation of tumor cell differentiation drives LUAD tumor initiation and metastasis in both KRAS and EGFR mutant backgrounds using in vitro organoid models and in vivo genetically engineered mouse models (GEMMs). I will use KRAS mutant lung cancer organoids to study the regulatory role of transcription factors on tumor growth and differentiation. I will develop an in vivo experimental model of metastasis and utilize lineage tracing technology to identify tumor differentiation states that promote metastasis. Finally, I will establish a novel tumor organoid model of EGFR-driven LUAD and characterize differentiation states that occur upon cancer initiation in an EGFR mutant background of LUAD. Together, this project aims to identify new transcription factors as potential diagnostic and therapeutic targets in LUAD, establish new in vivo models of metastasis, and characterize differentiation states following EGFR-driven cancer initiation in AT2 cells.

EMMA GARCIA | G3
Chemical Biology
Brian Liau Lab

Probing Regulatory Mechanisms of the De Novo DNA Methyltransferase DNMT3A

DNA methyltransferase 3A (DNMT3A) is one of the two human de novo DNA methyltransferases responsible for establishing proper DNA methylation during development. Beyond this role, DNMT3A is frequently mutated in hematopoietic disorders, including clonal hematopoiesis and acute myeloid leukemia (AML). One hotspot mutation, R882H, likely causes a dominant loss-of-function phenotype, but its mechanism of doing so remains controversial. We aim to identify the mechanism by which the R882H mutation causes a dominant negative phenotype and to describe new mechanisms of regulation that might allow for reactivation of the mutant protein. Towards this goal, we have performed a base editing mutagenic screen of DNMT3A in cells with WT DNMT3A as well as in cells harboring a heterozygous DNMT3A R882H mutation and have identified mutations to DNMT3A that boost activity in both WT and R882H DNMT3A. By further characterizing these mutants through crosslinking mass spectrometry, biochemical assays, and reporter-based activity assays in cells, we hope to elucidate novel mechanisms of DNMT3A regulation that could be exploited for the treatment of hematopoietic disorders.

PETER GEORGIEV | G2
Immunology
Arlene Sharpe & Marcia Haigis Labs

Metabolic regulation of the anti-tumor CD8+ T cell response to PD-1 by asparagine

Immune checkpoint blockade (ICB) has revolutionized the way that patients with cancer are being treated by virtue of antagonizing inhibitory immune receptors (e.g PD-1, CTLA-4) that function as endogenous negative regulators of the immune response. To date, no studies have thoroughly examined the metabolic vulnerabilities that govern the degeneration of anti-tumor CD8+ T cells, including the metabolic changes that accompany reinvigoration of dysfunctional CD8+ T cells in the settings of ICB. Herein, we sought to identify and functionally validate novel metabolic regulators of the CD8+ T cell response to ICB therapy with anti-PD-1. Using an unbiased in-vivo loss of function CRISPR/Cas9 screen targeting metabolic enzymes in tumor-specific CD8+ T cells, we identified asparagine synthetase as a novel metabolic regulator of the anti-tumor CD8+ T cell response to anti-PD-1 therapy. Complimentary experiments demonstrated that depletion of extracellular asparagine within the tumor microenvironment through the use of pegylated asparaginase (ONCASPAR) abolished the salutary effects of anti-PD-1 monotherapy in tumor-bearing mice and precipitated the development of a dysfunctional anti-tumor CD8+ T cell response culminating in accelerated tumor growth. Our findings reveal a previously unappreciated role for asparagine metabolism in the regulation of the anti-tumor CD8+ T cell response to anti-PD-1 therapy.

DENNIS GRISHIN | G7+
Biological and Biomedical Sciences
Alexander Gusev Lab

Allelic imbalance of chromatin accessibility in cancer identifies candidate causal risk variants and their mechanisms

While many germline cancer risk variants have been identified through Genome-Wide Association Studies (GWAS), the mechanisms by which these variants operate remain largely unknown. Here we used 406 cancer ATAC-seq samples across 23 cancer types to identify 7,262 germline allele-specific accessibility QTLs (as-aQTLs). Cancer as-aQTLs had stronger enrichment for cancer risk heritability (up to 145-fold) than any other functional annotation across seven cancer GWAS. The majority of cancer as-aQTLs directly altered transcription factor (TF) motifs and exhibited differential TF binding and gene expression in functional screens. To connect as-aQTLs to putative risk mechanisms, we introduced the Regulome-Wide Associations Study (RWAS). RWAS identified genetically associated accessible peaks at >70% of known breast and prostate loci and discovered novel risk loci in all examined cancer types. Integrating as-aQTL discovery, motif analysis, and RWAS identified candidate causal regulatory elements and their likely upstream regulators. Our work establishes cancer as-aQTLs and RWAS analysis as powerful tools to study the genetic architecture of cancer risk.

GAVIN KUZIEL | G5
Chemical Biology
Seth Rakoff-Nahoum Lab

Functional diversification of plant small molecules by the gut microbiota drives intestinal homeostasis

Diet is instrumental in driving the composition and dynamics of the gut microbiome and in the development and prevention of human disease. Plants are broadly composed of carbohydrates, macromolecular building blocks, and phytochemicals, bioactive small molecules with roles in plant defense. Broadly metabolized by diverse members of the gut microbiota, carbohydrates have been established as a strong selective pressure on the evolution of glycan utilization systems across organisms. The products of carbohydrate catabolism by the microbiota, short chain fatty acids, have critically been shown to modulate local immune programs in the gut to maintain homeostasis and prevent the development of intestinal diseases such as colitis and colorectal cancer. In contrast to carbohydrate catabolism, there is a dearth of information as to phytochemical-microbe interactions, whether these abundant and chemically diverse molecules are metabolized by enteric organisms and how products of phytochemical catabolism affect host physiology. Here, we show that diverse gut symbionts leverage distinct genetic and enzymatic systems to bioactivate dietary phytochemicals to immunomodulatory metabolites. Our findings provide new insight into the role of the microbiome in the activation of abundant dietary phytochemicals and the effects of these metabolic transformations on the maintenance of intestinal homeostasis and protection from enteric disease.

SOO MI LEE | G7+
Virology
Frank Slack Lab

Role of MicroRNA-127 in Oncogenic Human Herpesvirus-Induced Transformation and Tumorigenesis

Kaposi's sarcoma-associated herpesvirus (KSHV) causes the endothelial tumor Kaposi's sarcoma (KS), a leading cause of morbidity and mortality in sub-Saharan Africa. KSHV-encoded microRNAs (miRNAs) are known to play an important role in viral oncogenesis; however, the role of host miRNAs in KS tumorigenesis remains largely unknown. Here, high-throughput small RNA sequencing of the cellular transcriptome in a KS xenograft model revealed miR-127-3p as one of the most significantly down-regulated miRNAs, which we validated in KS patient tissues. We show that restoration of miR-127-3p suppresses KSHV-driven cellular transformation and proliferation, and induces G1 cell cycle arrest by directly targeting the oncogene SKP2. This miR-127-3p-induced G1 arrest is rescued by disrupting the miR-127-3p target site in SKP2 messenger RNA (mRNA) using gene editing. Mechanistically, miR-127-3p-mediated SKP2 repression elevates cyclin-dependent kinase (CDK) inhibitor p21Cip1 and downregulates cyclin E, cyclin A and CDK2, leading to activation of the RB protein tumor suppressor pathway and suppression of the transcriptional activities of E2F and Myc, key oncoprotein transcription factors crucial for KSHV tumorigenesis. Consequently, metabolomics analysis during miR-127-3p-induced cell cycle arrest revealed significant depletion of dNTP pools, consistent with RB-mediated repression of key dNTP biosynthesis enzymes. Furthermore, miR-127-3p reconstitution in a KS xenograft mouse model suppresses KSHV-positive tumor growth by targeting SKP2 in vivo. These findings identify a previously unrecognized tumor suppressor function for miR-127-3p in KS and demonstrate that the miR-127-3p/SKP2 axis is a viable therapeutic strategy for KS.

ADAM MAYNARD | G5
Biological and Biomedical Sciences
Naama Kanarek Lab

Folate Depletion Induces Erythroid Leukemia Differentiation

The vitamin folate is essential for rapidly proliferating cells to sustain increased DNA and RNA synthesis. Clinically, folate depletion often manifests as anemia, underlining folate's essentiality for hematopoiesis. In addition, anti-folate therapy is the standard of care in several leukemias. Although folate's necessity in normal and transformed blood cells is known, our understanding of the cellular response to folate depletion is rudimentary. Therefore, we investigated the metabolic changes that occur following folate depletion in erythroid leukemia cells. Surprisingly, we found a significant increase of intracellular heme following folate depletion. In addition, folate depletion induced an upregulation in heme synthesis genes and hemoglobin. Together, these findings suggest folate depletion induces differentiation in erythroid leukemia cells. Through flux analyses of glycine, the only metabolite shared between folate, heme, and nucleotide metabolism, we found that erythroid leukemia cells deprived of folate shifted glycine utilization away from nucleotide synthesis and towards heme synthesis. This metabolic shift suggests a distinct program that favors differentiation over proliferation during folate stress. We are currently studying the metabolic response to folate deprivation in non-transformed, erythroid progenitor cells to identify a shared metabolic response to folate deprivation that has implications for folate-related pathologies in normal and transformed cells.

PATRICK LOI | G5
Biological and Biomedical Sciences
Karen Cichowski Lab

Epigenetic based therapeutic strategies for KRAS mutant colorectal cancers

Polycomb Repressive Complex 2 (PRC2) is a highly conserved developmental regulator that maintains cellular identity by dynamically silencing key genes involved in differentiation. Alterations in PRC2 have been shown to play a driving role in many cancers. EZH2 is the major catalytic methyltransferase of PRC2 and activating mutations in EZH2 have been detected in a subset of cancers, such as melanoma and lymphomas. However, in other solid tumors, EZH2 is more commonly overexpressed rather than mutated. EZH2 expression levels progressively increase in advanced tumors and has been functionally shown to drive prostate cancer metastasis. Nevertheless, the role of EZH2 in other solid tumors, including colorectal cancers (CRC) has not been sufficiently explored. Specifically, EZH2 is overexpressed in 66% of CRC, and its expression appears to inversely correlate with patient survival and advanced disease. This makes EZH2 an attractive therapeutic target, although its role and targets in CRC is unknown. CRC is the is one of the leading causes of cancer deaths worldwide, and advanced metastatic disease is still incurable. Thus, there is a significant unmet clinical need for treatments for CRC, especially those with activating mutations in KRAS. Many drugs that target classic oncogenic kinases are ineffective therapies as single agents, such as MEK inhibitors for KRAS-mutant solid tumors. Therefore, one approach has been to develop more effective combination therapies that might enhance the sensitivity of cells to MEK inhibitors and/or prevent resistance. In a series of studies, our lab has been developing EZH2 inhibitor-based combination therapies with other targeted agents in different solid tumors. Interestingly, we have found that EZH2 inhibitors are frequently effective when combined with agents that target other key oncogenic pathways in each tumor type, such as in breast and prostate cancer. We hypothesize that co-targeting EZH2 along with key oncogenic pathways may lead to cooperative killing of CRC cells by clamping down on crucial oncogenic signals at both the kinase level and the transcriptional level. My preliminary data demonstrates that a combination of EZH2 and MEK inhibitors cooperate to kill KRAS mutant CRC in a variety of in vitro, in vivo xenograft, and organoid models, which reveals a novel approach for treating this advanced disease. Using a combinatorial RNA-seq and ChIP-seq approach, EZH2/MEK inhibitors induce a shift in the differentiation state of the cell by modulating key transcription factors and regulators involved in colonic development. Together, these findings will establish a new paradigm for epigenetic-based combination therapies for advanced diseases that are currently untreatable.

KELLY McGOVERN | G3
Immunology
Judith Agudo Lab

T cell mediated control of cancer stem cells in colorectal cancer

Cancer stem cells (CSCs) are the major drivers of both primary tumor growth and metastasis in colorectal cancer. Current methods to target these rapidly proliferating cell populations include chemotherapy; however, many of these treatments include harsh side effects and do not offer permanent solutions. Therefore, an alternative strategy to target CSCs is needed. Using an antigen engineered to be expressed only in stem cell populations, T cells are able to target and kill CSCs in colorectal cancer. However, other tumor cells are capable of repopulating the CSC niche. The long-term efficacy of T cell-mediated CSC killing on both tumor growth and metastasis is unknown. Thus, the aim of this project is to determine whether and how CSCs are able to escape T cell killing. We propose to use a colorectal cancer model in which CSCs express GFP, the antigen for Jedi T cells, to evaluate T cell and CSC interactions. By understanding the interaction between T cells and CSCs, this strategy will enable us to lay the foundation for the development of new potential T cell-mediated therapeutic strategies to target CSCs. Moreover, understanding potential escape mechanisms from T cell killing can help overcome current immunotherapy resistance. Overall, this work could allow for a new way to efficiently target tumor growth and metastasis without causing detrimental side effects to the patient.

FRANCESCA NARDI | G3
Biological and Biomedical Sciences
Karen Cichowski Lab

Co-targeting translation initiation as a therapeutic strategy for KRAS-mutant lung cancers

Despite the success of KRASG12C inhibitors in non-small cell lung cancer (NSCLC), improved treatments are still needed. Here we show that agents targeting eIF4A, a component of the eIF4F translation initiation complex, potently synergize with KRASG12C inhibitors. When combined, these drugs kill NSCLCs that are only modestly sensitive to single agent KRASG12C inhibitors and dramatically enhance tumor regression in vivo. We further demonstrate that the synergy is mediated by the suppression of multiple BCL-2 family proteins. Accordingly, KRASG12C/eIF4A inhibitors are broadly efficacious in NSCLCs, irrespective of their relative dependency on MCL1, BCL-xL, or BCL-2, which is known to be heterogeneous. Importantly, eIF4A and MEK inhibitors similarly cooperate in tumors harboring other KRAS mutations. Finally, we show that MYC overexpression confers sensitivity to these combinations, by creating a dependency on eIF4A for BCL-2 family protein expression. Together, these studies identify two promising therapeutic strategies for KRAS-mutant NSCLCs, demonstrate that BCL-2 family proteins are critical mediators of the therapeutic response, and uncover a predictive biomarker of sensitivity.

RHEA SAHU | G2
Biological and Biomedical Sciences
Karen Cichowski Lab

Co-targeting oncogenic and epigenetic pathways in castration-resistant prostate cancer (CRPC)

Patients with advanced prostate cancer are treated with medical castration and hormone therapy, but most eventually develop resistance and a lethal form of prostate cancer known as castration-resistant prostate cancer (CRPC). Thus, there is an unmet clinical need to develop more effective therapies for this disease. The epigenetic enzyme EZH2 and the PI3K/AKT signaling pathway have been implicated in the development and progression of CRPC. We show that EZH2 and PI3K/AKT pathway inhibitors cooperate to induce cell death in in vitro and in vivo CRPC models. Moreover, RNA-seq data shows reduced glycolysis and oxidative phosphorylation signatures in combination-treated cells. We hypothesize that dual inhibition of EZH2 and PI3K/AKT pathway decreases glycolysis and oxidative phosphorylation, leading to energy crisis and cell death. My future work will focus on exploring this hypothesis, as well as testing the drug combination in additional pre-clinical models. The results from these studies will help establish a novel therapeutic drug combination for incurable CRPC and broaden our understanding of basic biological mechanisms driving cancer.

LISA SITU | G4
Biological and Biomedical Sciences
Karen Cichowski Lab

Combinatorial strategies to target NRAS-mutant melanoma

Although 15–30% of melanomas harbor activating mutations in *NRAS*, there are currently no approved targeted therapies for this melanoma subtype. When *NRAS*-mutant melanomas are treated with MEK inhibitors that decrease signaling downstream of RAS, progression-free survival increases by only several months, highlighting the clinical need to uncover additional therapeutic targets that may improve the efficacy of single agent MEK inhibition. To address this, we performed a genome-scale CRISPR negative selection screen in an *NRAS*-mutant melanoma cell line to identify genes which, when suppressed, confer sensitization to MEK inhibition. This approach has uncovered a novel combinatorial strategy to elicit melanoma cell death, via inhibition of MEK in combination with suppression of USP7, a deubiquitinating enzyme. Combined inhibition led to cell death *in vitro* and tumor regression *in vivo*, with evidence supporting that the mechanism of cooperative activity may involve disruption of USP7-mediated chromatin remodeling. This work not only suggests that this combination may have the therapeutic potential to cause regression in human tumors, but may also reveal the functional importance of key adaptation pathways in melanoma.

KAR-TONG TAN | G5
Biological and Biomedical Sciences
Matthew Meyerson Lab

New Telomeres and Chromosomal Arm Fusions in Cancer Genomes Revealed by Long-Read Genome Sequencing

Chromosomal rearrangements are widespread features of cancer genomes, and often lead to the generation of both larger and smaller chromosomes that are readily observed by cytogenetics analysis. However, the role of telomeres in these chromosomal-scale rearrangements remains poorly defined. Here, we developed an analytic method (TeloFuse) to identify new telomeres and chromosomal arm fusions which are characterized by telomeric repeats at intra-chromosomal locations. With TeloFuse, we observed new telomeres at sites of terminal deletion with long-reads (telomere length = 2-9 kb); and in 76/326 (23%) of cancer cell lines and 17/97 (18%) of lung adenocarcinoma patient samples with short-reads. Telomere sequence-containing fusions at intra-chromosomal sites were detected in 75/326 (23%) of cancer cell lines and 28/97 (29%) of lung adenocarcinoma patient samples, and confirmed as chromosomal arm fusion events by long-read genome sequencing. Long-read genome sequencing further suggests that new telomeres have similar telomere length as telomeres on normal chromosomal arms (median = 5kb). Conversely, telomeric repeats at chromosomal arm fusion sites were found to be critically short (~200-500bp long). Our results suggest that the formation of new telomeres and chromosomal arm fusions are prevalent events during cancer genome evolution and are likely critical for the stabilization of new chromosomes in human cancers.