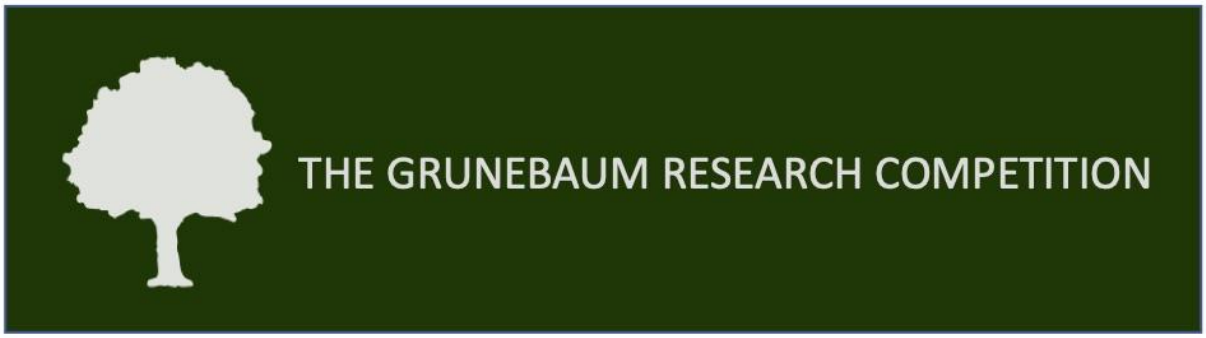

TUESDAY JUNE 30 | 3:30PM
via Zoom

INTRODUCTION

COMPETITION

Nouran Abdelfattah | Breaking tolerance with engineered T-cell receptors for adoptive cell therapies

Sam Barritt | Investigating Dependencies on Coenzyme A Metabolism in Cancer

Priscilla Cheung | Therapeutic reprogramming of the intestinal stem cell state via Hippo signaling

Camille Cushman | Characterization of viral-mediated epigenetic dysregulation in Merkel cell carcinoma

Alissandra Hillis | Identifying synthetic lethal combinations with PI3K/AKT inhibitors in TNBC

Patrick Loi | Investigating EZH2 as an oncogene and therapeutic target in colorectal cancers

Theresa Oei | Understanding Polycomb Phase Separation in Neuroblastoma Epigenetics

Kristin Qian | Elucidating the differential roles of human ATP-dependent chromatin remodeling complexes

Bing Shui | KRas activation induces global down regulation of miRNA function in colorectal cancer

Lisa Situ | Targeting mitochondrial dynamics in melanoma

WINNERS ANNOUCEMENT

Nouran Abdelfattah | G3
Biological and Biomedical Sciences
Elledge lab

Breaking tolerance with engineered T-cell receptors for adoptive cell therapies

Cytotoxic T lymphocytes are potent effector cells of the adaptive immune system and have the ability to recognize and clear tumors. This function serves as the foundation for promising immunotherapies such as adoptive T cell transfer and immune checkpoint blockade. In fact, the clinical success of adoptive T-cell therapy with T-cells expressing CD19-targeted chimeric antigen receptors (CARs) in treating B-cell malignancies has driven FDA approval of both Kymriah and Yescarta. However, CAR-T therapy has proven difficult to translate into solid tumors due to the low number of targetable cell surface antigens, the immunosuppressive microenvironment and the potential for severe systemic toxicity. Genetically engineered T cells with T-cell receptors (TCRs) can overcome some of these challenges because they enable targeting of intracellular antigens presented on major histocompatibility class I (MHC I) molecules increasing tumor antigen breadth and signaling through the physiological CD3 complex, providing more potent signaling. However, TCR therapeutics themselves face two major challenges: isolating effective TCRs to self-antigens and off-target reactivities. Here, I describe an *in vitro*-directed evolution approach to create collections of potent and efficient TCRs that target self-antigens for which central tolerance prevented their production. In this approach, I first raise high-avidity T-cells that recognize a related “foreign” peptide (that differs by one amino acid from the self-peptide) and then modulate the fine specificity of the TCRs by mutagenesis directed to the CDR3 region to engineer self-reactive TCRs. This TCR display system should prove to be a useful strategy for the generation of high-affinity tumor-specific TCRs for adoptive cell therapies.

Sam Barritt | G3
Biological and Biomedical Sciences
Dibble lab

Investigating Dependencies on Coenzyme A Metabolism in Cancer

Highly proliferative cells must meet the metabolic demands of cell growth by promoting the synthesis of macromolecules including lipids, protein, and nucleotides. The accumulation of biomass through central carbon metabolism is dependent on coenzyme A (CoA), a critical cofactor for the TCA cycle, lipid and sterol metabolism, and mitochondrial function. CoA is also necessary for protein acetylation, including that of histones, and redox balance, both of which are important for cancer cell growth. Using stable isotopic labeling and targeted mass spectrometry, we discovered that oncogenic signaling through PI3K stimulates the de novo synthesis of CoA from its precursor vitamin B5. Given the established role of the esterified CoA derivative acetyl-CoA in cell growth and cancer progression, we aim to determine whether cells with oncogenic PI3K signaling are more sensitive to perturbation of CoA metabolism. In addition, we have observed regulation of cell growth and division in response to CoA abundance. Perturbation of CoA metabolism inhibits growth through well-defined tumor suppressor-dependent pathways, suggesting that a similar metabolic vulnerability may exist in tumor suppressor-deficient cancer cells. Overall, we aim to lay the foundation for identifying therapeutic opportunities to target metabolic pathways by investigating the cross-regulation between oncogenic signaling and CoA metabolism.

Priscilla Cheung | G5
Biological and Biomedical Sciences
Camargo lab

Therapeutic reprogramming of the intestinal stem cell state via Hippo signaling

The intestine is intricately regulated by crosstalk between the Hippo and Wnt signaling pathways to control epithelial cell proliferation and differentiation. While the Hippo transcriptional coactivator YAP is considered oncogenic in many tissues, its roles in intestinal homeostasis and colorectal cancer (CRC) remain controversial. Here, we demonstrate that the Hippo kinases LATS1/2 and MST1/2, which inhibit YAP activity, are required for maintaining Wnt signaling and canonical stem cell function. Hippo inhibition induces a distinct epithelial cell state marked by low Wnt signaling, a wound healing response, and transcription factor Klf6 expression. Notably, loss of LATS1/2 or overexpression of YAP is sufficient to reprogram Lgr5+ cancer stem cells to this state and thereby suppress tumor growth in organoids, patient-derived xenografts, and mouse models of primary and metastatic CRC. Finally, we demonstrate that genetic deletion of YAP and its paralog TAZ promotes the growth of these tumors. Collectively, our results establish the role of YAP as a tumor suppressor in the adult colon and implicate Hippo kinases as therapeutic vulnerabilities in colorectal malignancies.

Camille Cushman | G4
Virology
DeCaprio lab

Characterization of viral-mediated epigenetic dysregulation in Merkel cell carcinoma

Merkel cell carcinoma (MCC) is an aggressive neuroendocrine carcinoma of the skin caused by either excessive UV-induced genomic mutations or the integration of the Merkel cell polyomavirus (MCV) genome. Virally-induced MCC is characterized by having a low mutational burden and the primary oncogenic drivers are viral proteins known as small tumor antigen (ST) and large tumor antigen (LT). Previous work has revealed commonalities between virus-positive MCC (VP MCC) and other neuroendocrine carcinomas, including defects in p53 signaling, RB activity, and MYC family hyperactivation. More specifically, our lab determined that ST interacts with the oncogenic transcription factors LMYC/MAX and the Tip60/P400 complex, a large chromatin remodeling complex, to aberrantly activate specific target gene expression. In this study, we aim to further characterize the effect of T antigen expression on the cellular chromatin architecture. Preliminary results suggest that T antigens cause a decrease in chromatin accessibility at genes involved in neuron differentiation, which highlights the role of these viral proteins in promoting a poorly differentiated state. This work serves as a basis towards better understanding the mechanism of epigenetic dysregulation in VP MCC.

Alissandra Hillis | G2
Biological and Biomedical Sciences
Toker lab

Identifying synthetic lethal combinations with PI3K/AKT inhibitors in TNBC

The phosphoinositide-3-kinase (PI3K) pathway is hyperactivated in almost all human cancer types, promoting cell growth and survival. Triple negative breast cancer (TNBC) is a highly heterogeneous disease with poor prognosis and limited targeted therapies. Among the few common genetic features in TNBC is PI3K pathway hyperactivation, which occurs in greater than 50% of TNBC cases. PI3K/AKT inhibitors have been developed to treat PI3K pathway-mutant cancers, but they have been generally ineffective as monotherapies due to the presence of other oncogenic mutations in heterogeneous tumors, the development of acquired resistance, or on-target toxicities. However, in 2019, the PI3K inhibitor, BYL719, was approved, in combination with hormone therapy, for the treatment of estrogen receptor-positive, PIK3CA-mutant breast cancer. This motivates developing additional combination therapies with PI3K/AKT inhibitors in other cancer types. I hypothesize that PI3K/AKT inhibitors can effectively treat PI3K pathway-mutant TNBC, if synthetic lethal drug combinations are identified. With the myriad of potential anti-cancer drug combinations available, it is difficult to predict which combinations will be effective. To identify effective drug combinations, I performed a negative selection CRISPR screen with PI3K/AKT inhibitors in TNBC. This work aims to advance the treatment of TNBC by identifying targetable vulnerabilities in this heterogeneous disease.

Patrick Loi | G3
Biological and Biomedical Sciences
Cichowski lab

Investigating EZH2 as an oncogene and therapeutic target in 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 is found to be overexpressed in multiple solid tumors, including prostate, breast, and colorectal cancer. EZH2 expression levels progressively increase in advanced tumors, and has been functionally shown to drive prostate cancer metastasis. Specifically, EZH2 is overexpressed in 78.5% of colorectal cancers (CRC), which makes it 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. In developing more effective therapies, we have found that EZH2 inhibitors are frequently effective when combined with agents that target other key oncogenic pathways in a given tumor type by clamping down on crucial oncogenic signals at both the kinase level and the transcriptional level. Specifically, I discovered that a combination of EZH2 and MEK inhibitors cooperate to kill KRAS mutant CRC, which reveals a novel approach for treating this advanced disease.

Theresa Oei | G3
Chemical Biology
Kingston lab

Understanding Polycomb Phase Separation in Neuroblastoma Epigenetics

Polycomb group (PcG) proteins are important epigenetic regulators with significant roles in defining developmental pathways and maintaining cell identity. Polycomb Repressive Complex 1 (PRC1) is involved in the formation of PcG bodies - liquid phase separated droplets that appear as puncta in the nucleus. The role of these condensates in PRC1,Äôs function as a regulator of silent chromatin is unknown. Increasingly, phase separation has been shown to play a role in transcriptional activation and silencing by concentrating and compartmentalizing proteins in molecular condensates within the nucleus. PcG bodies may cluster multiple genomic targets and PcG proteins to create and remember a repressed state. The CBX2 subunit has been shown to drive PRC1 phase separation and it is also an essential regulator in neuroblastomas. My research aims to develop chemical and molecular technologies to explore the role of CBX2 condensates in neuroblastoma development. Overall, this project will reveal the role of phase separation in polycomb epigenetics and provide new insights and therapeutic opportunities for cancer.

Kristin Qian | G2
Biological and Biomedical Sciences
Kadoch lab

Elucidating the differential roles of human ATP-dependent chromatin remodeling complexes

ATP-dependent chromatin remodeling complexes (CRCs) play critical roles in the maintenance of tissue- and state-specific chromatin structure and the regulation of gene expression by dynamically positioning nucleosomes along the genome. Importantly, these CRCs are involved in development and differentiation, and mutations in genes encoding CRC protein subunits result in diverse pathologies of cancer and neurodevelopmental disorders. SWI/SNF remodeling complexes, which are mutated in ~20% of cancers, have been extensively studied in our lab. In addition to SWI/SNF, there are three other families of related ATP-dependent CRCs: ISWI, CHD, and INO80. Across these families, there are approximately two dozen CRCs conserved from yeast to human. However, the field lacks an integrative analysis dissecting the roles of these CRCs, and it is unknown how perturbations in each complex family affect the global chromatin landscape. I propose to assess the chromatin localization and remodeling activities of each family of CRCs and their role in regulating accessibility and gene expression at various stages of differentiation and in disease settings driven by CRC mutations. To that end, this study aims to advance our understanding of CRC-directed chromatin changes and to define differential CRC functions in establishing and maintaining chromatin architecture.

Bing Shui | G4
Biological and Biomedical Sciences
Kevin Haigis lab

KRas activation induces global down regulation of miRNA function in colorectal cancer

KRas is frequently mutated in three of the four deadliest human cancers (PDAC, CRC, NSCLC) and regulates miRNAs. miRNAs are immediately actionable therapeutic targets given the large repertoire of miRNA mimics and inhibitors. Investigations of miRNA targets have been dependent on computational algorithms. My thesis project has used newly developed HEAP-CLIP to map physiologic targets of miRNA *in vivo* in murine colorectal cancer +/- oncogenic KRas. Our data suggest that the activation of KRas in tumors greatly expands the miRNA target repertoire and increases miRNA targeting intensity across all major miRNA families. However, this global up-regulation of miRNA targeting paradoxically de-suppresses target expressions. The concordant global increase of miRNA targeting and miRNA targets could be attributed to the down-regulation of Ago2 phosphorylation at S829-S835, regulated by CK1. We hypothesize that KRas activation in colon cancer suppresses CK1 family kinases, subsequently decreases phospho-Ago2 (S829-S835). A recent study reported that the loss of these phosphorylations inhibited the dynamic cycling of Ago2, causing increased miRNA binding to mRNA targets with decreased gene suppression. My work will elucidate a novel interaction between KRas signaling and miRNA machinery and potentially reveal therapeutic vulnerabilities of colorectal cancer, which remains elusive to modern therapies.

Lisa Situ | G2
Biological and Biomedical Sciences
Cichowski lab

Targeting mitochondrial dynamics in melanoma

Although 15-30% of melanomas harbor activating mutations in NRAS, there are currently no approved targeted therapies for this subtype of melanoma. We are interested in developing a novel combination therapy that can improve the clinical efficacy of MEK inhibitors in these tumors. We previously performed a genome-scale CRISPR negative selection screen to identify genes which when suppressed confer sensitization to MEK inhibition. MARCH5 was one of the most significant hits, and our goal is to understand the mechanism by which dual inhibition of MARCH5 and MEK specifically kills NRAS-mutant melanoma cells. MARCH5 is a mitochondrial E3 ubiquitin ligase that has been implicated in the regulation of mitochondrial morphology. We hypothesize that MARCH5 and MEK cooperate to regulate mitochondrial dynamics and that disruption of this axis sensitizes NRAS-mutant melanomas to cell death. While the goal of this research is to advance a potential combination therapy into the clinic for patient benefit, our work will also elucidate novel information about an important but understudied mitochondrial E3 ligase and its interactions with the Ras signaling pathway.

COMPETITION JUDGES

Christian Dibble, Ph.D.
Assistant Professor | BIDMC | HMS

Kevin Haigis, Ph.D.
Chief Research Officer | DFCI
Associate Professor | HMS

Nada Kalaany, Ph.D.
Associate Professor | BCH | HMS

Naama Kanarek, Ph.D.
Assistant Professor | BCH | HMS

Andrea McClatchey, Ph.D.
Professor of Pathology | MGH | HMS

Mohammad Rashidian, Ph.D.
Assistant Professor | DFCI | HMS