THE GRUNEBAUM RESEARCH COMPETITION

MONDAY JUNE 28 | 2:30PM

WELCOME & INTRODUCTION

RESEARCH COMPETITION

Beatrice Awasthi | Interrogating how tissue type influences hyperactive KRAS-induced MAPK signaling

Francisco Fernandez | Protein glycosylation in NF1-related tumors: therapeutic targets and biomarkers

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

Sophia Liu | Spatially mapping T cell receptors and transcriptomes for understanding immune response to cancer

Francesca Nardi | Targeting the eIF4F translation initiation complex as a novel therapeutic strategy for KRAS-mutant lung cancer

Shikha Sheth | Understanding resistance to Kras-G12C inhibitors in colorectal cancer (CRC)

Georgia Stirtz | Tumor Microenvironmental Regulation of T cell Infiltration

SHORT TALKS

Bing Shui | Hyper-activated KRas suppresses global microRNA function in colon and colorectal cancer

Kristin Qian | Elucidating the dynamics and organization of SWI/SNF chromatin remodeling complexes in transcriptional regulation

WINNERS ANNOUNCEMENT

COMPETITION PARTICIPANTS

Beatrice Awasthi | G3

Biological and Biomedical Sciences

Kevin Haigis lab

Interrogating how tissue type influences hyperactive KRAS-induced MAPK signaling

The oncogene KRAS is frequently mutated in two of the deadliest human cancers, pancreatic and colorectal cancer. KRAS activation by mitogenic signals initiates the MAPK phosphorylation cascade that consists of the proteins RAF, MEK, and ERK, the latter of which has hundreds of known substrates, including many transcription factors. In some tissues, like the liver, KRAS-mutant cancers are notably rare. The basis for this is unknown. Understanding differences between tissues with distinct profiles of oncogenic KRAS mutations could aid in the novel identification of targetable vulnerabilities in KRAS-mutant cancers. Phospho-proteomic data from our lab suggests that MAPK-induced signaling networks are tissue-specific. We hypothesize that the basal interactome and epigenome together dictate substrate phosphorylation by ERK and subsequent gene expression changes in tissues downstream of KRAS oncoproteins. Here, I will employ a mutant of ERK2 that can label its substrates to study how the oncogenic allele KRAS-G12D affects ERK substrates in the pancreas, colon, and liver of mice. Simultaneously, I will interrogate the chromatin landscape and identify ERK binding partners in each tissue. My ultimate goal is to understand how basal tissue state affects ERK signaling in response to hyperactive KRAS. This could reveal new therapeutic targets in KRAS-mutant tumors.

Francisco Fernandez | G2
Biological and Biomedical Sciences
James Gusella and James Walker Lab

Protein glycosylation in NF1-related tumors: therapeutic targets and biomarkers

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder affecting 1/3000, caused by mutations in the NF1 gene encoding neurofibromin, a negative regulator of RAS. Patients are predisposed to developing benign peripheral nerve associated tumors including plexiform neurofibromas (PNFs). In about 10% of NF1 patients, PNFs, which are derived from Schwann cells (SCs), transform into malignant peripheral nerve sheath tumors (MPNSTs), which are invariably fatal. Protein glycosylation is a highly regulated post-translational modification playing a critical role in protein structure, function and stability. Changes in glycosylation are a hallmark of cancer with specific glycans driving tumor development and progression. We propose to use mass spectrometry (MS)-based glycoproteomics to identify global glycosylation changes in patient-derived NF1-deficient SCs from PNFs and MPNST cell lines. We will also determine the glycosylation profile of neurofibromin using CRISPR-engineered SC lines in which a FLAG tag has been introduced in-frame with NF1. Modified residues will be compared with our extensive database of pathogenic missense mutations in NF1 to determine if altered glycosylation of neurofibromin itself may play a role in the disease. Profiling and characterization of glycoprotein variations could lead to identification of disease-associated glycan alterations which could be exploited for therapeutic and biomarker potential.

Alissandra Hillis | G3
Biological and Biomedical Sciences
Alex Toker lab

Identifying synthetic lethal combination therapies 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 PI3Kα-selective 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 genome-wide 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.

Sophia Liu | G4
Biophysics
Fei Chen Lab

Spatially mapping T cell receptors and transcriptomes for understanding immune response to cancer

T cells mediate antigen-specific immune responses to disease through the specificity and diversity of their T cell receptors (TCRs). Although determining the spatial distributions of T cell clonotypes in tissues is essential to understanding T cell maturation and behavior, spatial sequencing methods remain unable to profile the TCR repertoire. Here, we develop Slide-TCR-seq, a method to sequence whole transcriptomes and TCRs within intact tissues. We confirmed the ability of Slide-TCR-seq to map the characteristic architecture of T cells and their receptors in mouse spleen. We then spatially profiled T cell clonotypes and their infiltration in renal cell carcinoma specimens before and following immune checkpoint blockade, which identified uniquely distributed T cell clonotypes and transcriptional states. Our method is anticipated to facilitate dissection of the immune microenvironment, yielding insights into the complex spatial relationships between T cell clonotypes, neighboring cell types, and gene expression that drive T cell responses across diseases.

Francesca Nardi | G2
Biological and Biomedical Sciences
Karen Cichowski Lab

Targeting the eIF4F translation initiation complex as a novel therapeutic strategy for KRAS-mutant lung cancer

Although KRAS is the most frequently mutated oncogene in non-small cell lung cancers (NSCLCs), there are currently no effective treatments for KRAS-mutant tumors. We have recently discovered that inhibition of eIF4A, the helicase of the eIF4F translation initiation complex, synergizes with either MEK or KRAS inhibitors and triggers apoptosis of NSCLCs. We further identified several eIF4A-regulated mRNAs in NSCLC including c-Myc, cyclin D1, Bcl-XL, Bcl-2, and Mcl-1. However, using functional genomic studies we found that the therapeutic effects of these drug combinations where mediated by the suppression of the anti-apoptotic bcl-2 family proteins rather than c-Myc or cyclin D1. Importantly, because eIF4A inhibitors suppress the excessive translation of these components in tumors, rather than their biochemical function, this strategy should selectively affect tumor cells while sparing normal tissues. Nevertheless, to complement these studies and gain more insight into the broader functional role of the eIF4F complex in NSCLC, we will perform polysome profiling as an unbiased approach to identify additional translational targets. Together, our studies highlight two promising therapeutic strategies for KRAS-mutant NSCLCs, define the bcl-2 family proteins as critical contributors to the therapeutic response, and will reveal important insight into mechanisms that are required for NSCLC survival and development.

Shikha Sheth I G6
Biological and Biomedical Sciences
Kevin Haigis Lab

Understanding resistance to Kras-G12C inhibitors in colorectal cancer (CRC)

Although mutations in the Kras oncogene are frequent across cancers, they have historically been difficult to target directly. Recent studies have led to the development of inhibitors targeting Kras-G12C mutant cancers (G12Ci), and though these inhibitors are effective against lung tumors, patients with colon tumors do not respond as well. It is not entirely clear what accounts for the differential response in lung and colon tumors, and we believe that the underlying biological processes inherent to colon tumors-but not lung-can contribute to the intrinsic resistance seen in colon tumors. Specifically, loss of Apc and consequent activation of Wnt signaling is very common in colorectal cancer (CRC), and these mutations are rare in lung cancer. We hypothesize that activation of Wnt signaling contributes to intrinsic resistance to G12Ci in colon tumors. Using mouse colon organoids, we evaluate the effect of Apc loss in a Kras-G12C mutant background on response to G12Ci. Our preliminary findings indicate that loss of Apc increases resistance to G12Ci, and that co-treatment of Apc-mutant organoids with a Wnt inhibitor increases sensitivity to G12Ci. Altogether, these studies underscore the importance of understanding tissue context when targeting the same pathway in different tumors, which will hopefully aid in the development of improved drug treatments and combinations.

Georgia Stirtz | G4
Biological and Biomedical Sciences
Leonard Zon Lab

Tumor Microenvironmental Regulation of T cell Infiltration

The advent of immune checkpoint blockade (ICB) has greatly improved survival rates for melanoma patients, yet 40% of patients are unresponsive. Research has demonstrated that tumor-infiltrating lymphocytes are a predictor of response to ICB and increased survival. Therefore, developing strategies to increase T cell infiltration has strong therapeutic potential. Our lab developed a zebrafish reporter that labels CD8+ T cells and used this reporter to visualize tumor-immune interactions in endogenous, nonpigmented melanomas. Using an approach of longitudinal, intravital microscopy to visualize T cell infiltration within the same tumor across development, I identified progressive stages of T cell infiltration and found that CD8+ T cells preferentially infiltrate within clefts in the surface of the tumor. These clefts are commonly adjacent to cxcl12a+ vessels and stromal cells. Single-cell RNA-sequencing of cxcl12a+ stromal cells revealed a cancer-activated stromal population that expresses genes found to correlate with T cell infiltration in human melanomas. I am functionally evaluating these candidate genes in vivo by knockout and overexpression for an effect on T cell infiltration. These experiments will advance understanding of the mechanisms underlying the anti-tumor response to allow for the development of therapeutics to induce T-cell infiltration and expand the population of responders to ICB.

COMPETITION JUDGES

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