Invited Speaker

IA-001 Molecular subtypes and vulnerabilities in pancreatic cancer Andrew Aguirre, Dana-Farber Cancer Institute, Boston, MA.

Pancreatic ductal adenocarcinoma (PDAC) is a deadly disease with few effective treatment options. Understanding the molecular underpinnings of PDAC is critical to developing new biomarker strategies and therapeutic approaches for patients. In this talk, I will review our understanding of the genetics and biology of PDAC, including the major genomic subtypes and transcriptional programs of the disease. I will discuss how single-cell RNA sequencing has refined our understanding of subtype heterogeneity and evolution in the context of therapy and PDAC model systems. Moreover, I will discuss new KRAS inhibitors, their mechanisms of resistance and their potential to impact the treatment landscape for pancreatic cancer patients. Lastly, I will discuss our recent efforts to use functional genetic screening approaches to define new therapeutic targets in pancreatic cancer, highlighting our work on the VPS4A ATPase as a potential new target in tumors with 18q/SMAD4 deletion.

IA-002 Dendritic cell corner stone of tumor immunity in PDAC. David G. DeNardo, Washington University, School of Medicine, St. Louis, MO.

T cell-directed immunotherapies have not been effective for the majority of pancreatic cancer patients, in part, due to our limited understanding of how T cell immunity is subverted in this disease. We sought to identify mechanisms for this failure using spontaneous mouse models. We report that endogenous antigen-specific responses in PDAC are aberrant due to a scarcity of dendritic cells, which favors the expansion of tumor-promoting T_H17 immunity. Restoring cDCs in pancreatic cancer can enhance $CD8^+$ T cell and T_H1 activity to ultimately help control disease. These findings expand our understanding of T cell ineffectiveness in pancreatic cancer, and propose combinatorial strategies to modulate cDCs in conjunction with existing therapies for pancreatic cancer and similar solid malignancies.

IA-003 Proteogenomic characterizations of pancreatic ductal adenocarcinoma. Liwei Cao[1], Chen Huang[2], Daniel Cui Zhou[3], Yingwei Hu[1], Mamie Lih[1], Sara R. Savage[2], Karsten Krug[4], David J. Clark[1], Michael Schnaubelt[1], Lijun Chen[1], Felipe da Veiga Leprevost[5], Rodrigo Vargas Eguez[1], Alexey I. Nesvizhskii[5], D.R. Mani[4], Gilbert S. Omenn[5], Emily S. Boja[6], Mehdi Mesri[6], Ana I. Robles[6], Henry Rodriguez[6], Oliver F. Bathe[7], Daniel W. Chan[1], Ralph H. Hruban[1], Li Ding[3], Bing Zhang[2], Hui Zhang[1], Clinical Proteomic Tumor Analysis Consortium[8]. [1]Department of Pathology, Johns Hopkins University, Baltimore, MD, [2]Lester and Sue Smith Breast Center, Baylor College of Medicine, Houston, TX, [3]Department of Medicine, Washington University in St. Louis, St. Louis, MO, [4]The Broad Institute of MIT and Harvard, Cambridge, MA, [5]Department of Pathology, University of Michigan, Ann Arbor, MI, [6]Office of Cancer Clinical Proteomics Research, National Cancer Institute, Bethesda, MD, [7]Departments of Surgery and Oncology, Cumming School of Medicine, Calgary, AB, Canada[8].

Pancreatic cancer is one of the deadliest cancers and the five-year survival rate is less than 10%. Pancreatic ductal adenocarcinoma (PDAC) represents more than 90% of all pancreatic malignancies, and is responsible for the majority of pancreatic cancer-related deaths. Towards

understanding the underlying molecular alterations that drive PDAC oncogenesis and identify therapeutic targets for personalized treatments, we comprehensively characterized 140 pancreatic cancers and 67 normal adjacent tissues. To ensure robust, downstream analyses, tumor neoplastic cellularity was assessed via multiple, orthogonal strategies using molecular features, and verified via pathological estimation of tumor cellularity based on histological review to select tumors with sufficient tumor cellularity. We also included the analysis of 9 normal pancreatic ductal tissues. Proteomic, phosphoproteomic, and glycoproteomic analyses were used to characterize proteins and their modifications. In addition, whole genome sequencing, whole exome sequencing, methylation, RNA-seq, and miRNA-seq were performed on the same tissues to facilitate an integrated proteogenomic analysis and determine the impact of genomic alterations on protein expression, signaling pathways, and post-translational modifications. These characterizations revealed functional impacts of genomic and epigenomic alterations on proteins and protein modifications, delineated PDAC cell microenvironment compositions and the immune signatures for immunotherapy, also uncovered putative kinase inhibitors that could be tested for therapy. This integrated proteogenomic characterization of PDAC will serve as a valuable resource for the community, paving the way for early detection and identification of novel therapeutic targets.

IA-004 Using an integrative molecular epidemiology approach to battle pancreatic cancer in the era of precision medicine: Hope is on the horizon. Jennifer B Permuth, Moffitt Cancer Center, Tampa, FL.

Pancreatic cancer is the most lethal solid malignancy in the United States, with a 5-year relative survival rate of only 10.8%. Novel strategies are needed to prevent disease and/or detect it as early as possible. There is also an urgent need to study and address biological reasons for the higher pancreatic cancer incidence and mortality rates among African Americans compared to other racial and ethnic groups. Integrative molecular epidemiology is a discipline that brings together epidemiologists, data scientists, basic scientists, and many clinical specialties, to collaboratively study cancer risk and outcomes from different perspectives. This lecture will provide examples of how an integrative molecular epidemiology approach has been used to advance pancreatic cancer early detection and health disparities initiatives. Pancreatic cancer precursor lesions known as intraductal papillary mucinous neoplasms (IPMNs) are cystic lesions increasingly being detected incidentally by imaging, but strategies are lacking to accurately differentiate ‘low risk’ lesions that should be monitored from ‘high-risk’ lesions that should be surgically removed. By leveraging expertise in population, clinical, and data science and informatics and multi-institutional infrastructure known as the Florida Pancreas Collaborative, the investigative team is evaluating the hypothesis that unexplored categories of quantitative ‘radiomic’ features extracted from preoperative computed tomography scans will improve the diagnostic value in predicting malignant IPMN pathology. They further hypothesize that a liquid biopsy that measures microRNAs circulating in blood plasma (a miRNA genomic classifier (MGC)) that they have developed may further enhance diagnostic accuracy. The team ultimately plans to generate prototype clinical decision-making models, or nomograms, that consider radiomic data, the MGC, and other clinical characteristics to aid in predicting IPMN pathology. To improve outcomes and minimize disparities for the diverse population of Floridians affected by pancreatic cancer, the Florida Pancreas Collaborative has also been prospectively building a robust ‘next-generation biobank’ that longitudinally collects blood,

various tissue types, medical images, and clinical, laboratory, epidemiologic, and outcome data. They are also testing the novel hypothesis that biological correlates of cancer cachexia contribute to observed pancreatic cancer disparities. Through these initiatives and an integrative molecular epidemiology approach, the team's long-term goal is to improve survival and quality of life and minimize disparities by personalizing care for individuals with or at risk for pancreatic cancer.

IA-005 Metabolic Stress in Pancreatic Cancer Progression and Therapy, Cosimo Commisso, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA.

Pancreatic ductal adenocarcinoma (PDAC) cells depend on glutamine to meet their unique metabolic needs. The elevated consumption of glutamine leads to intratumoral nutrient depletion, causing metabolic stress that has the potential to impact tumor progression and therapy. We will show that nutrient stress caused by glutamine deprivation leads to the induction of epithelial-mesenchymal transition (EMT) in PDAC cells. Mechanistically, we demonstrate that glutamine deficiency regulates EMT through the upregulation of the EMT master regulator Slug, a process that is dependent on both MEK/ERK signaling and ATF4. We find that Slug is required in PDAC cells for glutamine deprivation-induced EMT, cell motility and nutrient stress survival. Importantly, we decipher that Slug is associated with nutrient stress in PDAC tumors and is required for metastasis. These results delineate a novel role for Slug in the nutrient stress response and provide insight into how nutrient depletion might influence PDAC progression. During the development of a pharmacological *in vivo* system aimed at mimicking glutamine stress, we have serendipitously discovered an approach to profoundly affect PDAC tumor growth and metastasis. We will outline the metabolic mechanisms underlying these effects and discuss additional targeting strategies for PDAC.

IA-007 The KPC model has helped advance pancreatic cancer therapy: Agree. Kenneth P. Olive, Columbia University, New York, NY.

The KPC genetically engineered mouse has been widely utilized within the pancreatic cancer field as a preclinical model system that recapitulates many aspects of human pancreatic ductal adenocarcinoma. The model has proven particularly accurate in replicating many of the etiological, histopathological, and physiological features of the human disease. KPC mouse pancreatic tumors also exhibit the broad chemoresistance phenotype that characterizes human pancreatic cancer, proving to be uniquely resistant to a wide range of cytotoxic, targeted, and immuno-oncology drugs. Nevertheless, the lack of efficacy in several clinical trials that derived from studies initially performed in the KPC model has provoked questions about the clinical predictiveness of the model, and by extension, its preclinical utility. This presentation will summarize the history and lessons learned from using the KPC mouse model and highlight impacts the model has had on pancreatic cancer therapy. We will focus in particular on the appropriate interpretation of preclinical results and understanding the similarities and differences between corresponding trials performed in KPC mice and humans. To date, the model has proven successful both in advancing promising biology-based regimens to the clinic and of dissuading the further clinical development of ineffective regimens. Moreover, by providing a vehicle for the conduct of "post-clinical" trials, the KPC model has enabled the study and understanding of why pancreatic cancer trials can fail, leading to critical lessons that are informing the design of future clinical trials (and the prioritization of candidate therapeutic

agents). Innovative and promising therapeutics approaches developed from studies in the KPC model continue to advance through clinical trials and are bolstered by ongoing co-clinical efforts that iteratively pass from human to mouse and back again.

IA-008 The KPC model has helped advance pancreatic cancer therapy: Disagree.
Phoebe A Phillips, University of New South Wales (UNSW) Sydney, Sydney, NSW, Australia.

Pancreatic cancer researchers have grappled with the difficulty of reproducing the complex tumor microenvironment which holds the key to improving therapeutic treatments for the disease. For decades, murine models of the disease have underpinned all clinically-relevant pancreatic cancer research and indeed, the transgenic KPC mouse model has been touted as our closest *in vivo* model to human disease; reproducing disease progression from early PanIN lesions, extensive fibrosis, metastatic spread and chemoresistance. Numerous clinical studies have been initiated based on the work done in this model. However, most of these trials have failed to successfully improve outcomes for pancreatic cancer patients or to even progress beyond phase 2 clinical trials. A/Prof Phillips will argue that the KPC model, while a useful tool to understand pancreatic cancer biology in the laboratory, has had limited clinical impact due to key differences in mouse and human cell biology as well as inherent limitations of the model. Patient-derived 3D tumor models of pancreatic ductal adenocarcinoma (PDAC) have potential to overcome many limitations associated with the KPC model. Human PDAC organoid and whole-tissue explant cultures may hold the key to precision medicine in their ability to predict patient response to existing treatments, to guide translation of new therapies to the clinic in a technique which is both scalable and provides rapid readout [1,2]. Furthermore, the ability of the human tumor explant model to retain the multicellular microenvironment of patient tumors provides a powerful tool to study the effects of tumor and stromal targeting agents for pancreatic cancer [3]. Coupling this model with the recent explosion of spatial omics techniques also allows us to understand the tumor composition and therapeutic response of individual patient tumors down to the single cell level, negating the need for more homogenous mouse models that require extensive replication and yet make generalized predictions on therapeutic response. Thus, with the advent of these personalized “at-the-bench” 3D human models of pancreatic cancer, perhaps the real question is whether we still require the KPC mouse model? References: 1. Kokkinos, J., Jensen, A., et al., and Phillips, P.A. Does the Microenvironment Hold the Hidden Key for Functional Precision Medicine in Pancreatic Cancer? **Cancers (Basel)**, 2021. 13(10): p. 2427. 2. Kokkinos, J., Sharbeen, G., et al., and Phillips, P.A., Ex vivo culture of intact human patient derived pancreatic tumor tissue. **Sci Rep**, 2021. 11(1): p. 1944. 3. Sharbeen, G., McCarroll, J.A., et al., and Phillips, P.A., Cancer-associated fibroblasts in pancreatic ductal adenocarcinoma determine response to SLC7A11 inhibition. **Cancer Res**, 2021. 81 (13) 3461-3479.