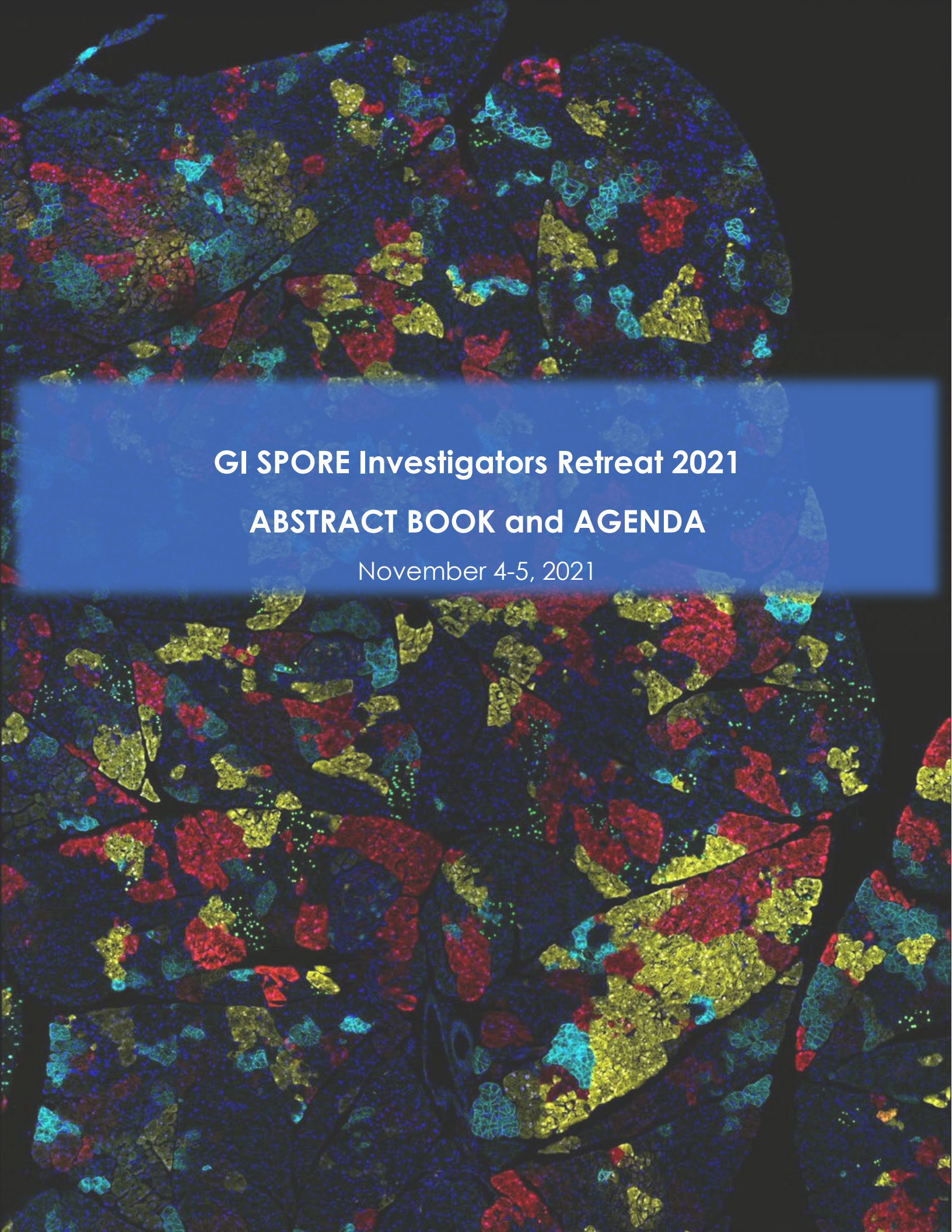

GI SPORE Investigators Retreat 2021

ABSTRACT BOOK and AGENDA

November 4-5, 2021

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GI SPORE Investigators Meeting
Meeting Agenda
November 4-5th, 2021
Virtual Meeting via Zoom

Conference Agenda

Meeting Website: https://www.trpspore.com/

Thursday, November 4th WebEx Meeting Link:
https://cbiit.webex.com/cbiit/j.php?MTID=m4cb6d8900007bd0a08a40966753cc94e

Friday, November 5th WebEx Meeting Link:
https://cbiit.webex.com/cbiit/j.php?MTID=m2a6029e1a7c78cadccce63c0ae6898c6

Eastern Time

Thursday - November 4, 2021	
12:10-12:20 PM EST	Welcome – *Nabeel Bardeesy & Brian Wolpin*
12:20-12:30 PM	Opening Remarks – *Steve Nothwehr*
P20 Cancer Health Disparities SPORE Planning Grant Research – *Moderator: Steve Nothwehr*	
12:30-12:45 PM	Presentation: "Risk Stratification, Risk-Based Surveillance And Precision Screening for Hepatocellular Carcinoma" - *George Ioannou (University of Washington)*
12:45-12:50 PM	Q&A
12:50-1:05 PM	Presentation: "Racial Differences in Host Immune Response And Gastric Carcinogenesis: Translating Underlying Biology To Promote Gastric Cancer Interception" - *Katie Garman(Duke University)*
1:05-1:10 PM	Q&A
Session 1 - Cancer Immunology – *Moderator: Stephanie Dougan (Dana-Farber Cancer Inst.)*	
1:10-1:30 PM	Presentation: "The Role of Neutrophils in Cancer Progression and Metastasis" - *Leah M.Cook (University of Nebraska)*
1:30-1:35 PM	Q&A
1:35-1:55 PM	Presentation: "Optimizing neoantigen-targeted combination immunotherapy" - *Neeha Zaidi (Johns Hopkins University)*

1:55-2:00 PM	Q&A
2:00-2:20 PM	Presentation: “Harnessing HDAC Inhibition to Sensitize PDA to Immunotherapy” - *Marina Baretti (Johns Hopkins University)*
2:20-2:25 PM	Q&A
2:25-2:45 PM	Presentation: “Immune Surveillance of Pancreatic Cancer Metastases” - *StephanieDougan (Dana-Farber Cancer Institute)*
2:45-2:50 PM	Q&A
2:50-3:10 PM	BREAK
Session 2 - Tumor Metabolism – Moderator: *Nada Kalaany (Boston Children’s)*	
3:10-3:30 PM	Presentation: “Ivosidenib – Activity in Treating Pancreas Cancer by Unexpected Targeting of a Metabolic Dependency on Wild-Type IDH1” - *Jordan Winter (Case Western)*
3:30-3:35 PM	Q&A
3:35-3:55 PM	Presentation: “Combined inhibition of EGFR and glutamine metabolism in CRC” - *Charles Manning (MDACC)*
3:55-4:00 PM	Q&A
4:00-4:20 PM	Presentation: “Metabolic vulnerabilities in pancreatic cancer” - *Pankaj Singh (University of Nebraska)*
4:20-4:25 PM	Q&A
4:25-4:45 PM	Presentation: “The Sweet Danger of Sugary Drinks in Colon Cancer Development” - *Jihye Yun (Baylor College of Medicine)*
4:45-4:50 PM	Q&A

Friday - November 5, 2021

Session 3 - Precursor lesions, Early Detection, & Interception
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9:20-9:25 AM	Q&A
9:25-9:45 AM	Presentation: "Human Colorectal Pre-cancer Atlas Identifies Distinct Molecular Programs UnderlyingTwo Major Subclasses of Pre-Malignant Tumors" - *Ken S. Lau (Vanderbilt)*
9:45-9:50 AM	Q&A
9:50-10:10 AM	Presentation: "PTEN Inactivation Initiates an Extrahepatic Cholangitis-Cholangiocarcinoma Continuum in Mice" - *Baoan Ji (Mayo Clinic)*
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10:25-10:45 AM	Presentation: "Identifying Mechanisms Driving Metastatic Dormancy and Outgrowth" – *Christina Ferrer (Mass General Hospital)*
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10:50-11:10 AM	Presentation: "Five Shots at HCC with an Oral Small-Molecule STAT3 Inhibitor" - *David Tweardy (MDACC)*
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11:15-11:35 AM	Presentation: "Recent Advances in Studies of Exosomes and Nanoparticles" - *Bob Coffey (Vanderbilt)*
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Session 4 - Precision Therapy – *Moderator: Andrew Aguirre (Dana-Farber Cancer Inst.)*	
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1:35-1:55 PM	Presentation: “Deciphering treatment vulnerabilities for APOBEC3A and CIN prone PDACs” - *Sonja Woermann (MDACC)*
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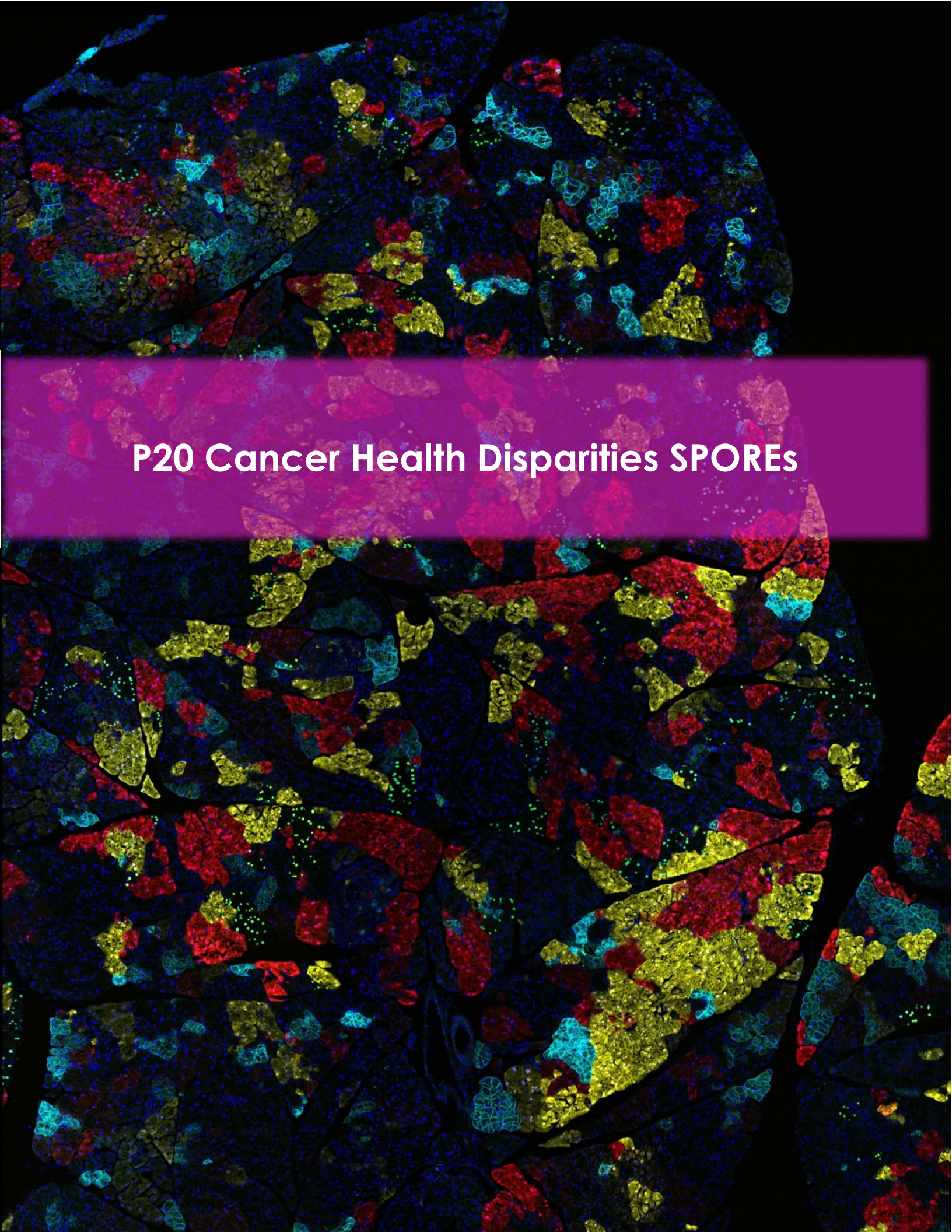
4:00-4:20 PM	Presentation: “Therapeutic Targeting of DKK3 in Pancreatic Cancer and Response to Chemotherapy” - *Rosa Hwang (MDACC)*
4:20-4:25 PM	Q&A
4:25-4:35 PM	Closing Remarks - *Steve Nothwehr, Nabeel Bardeesy, Brian Wolpin*



P20 Cancer Health Disparities SPOREs

P20 Cancer Health Disparities SPORE

Risk Stratification, Risk-Based Surveillance and Precision Screening for Hepatocellular Carcinoma

Abstract Presenter: George Ioannou

University of Washington

We currently have a one-size-fits-all strategy for hepatocellular carcinoma (HCC) screening, whereby the same screening strategy (abdominal ultrasonography ± serum alpha fetoprotein (AFP)) is recommended in patients with cirrhosis or chronic hepatitis B virus (HBV) infection. However, there is wide variability in HCC incidence in this at-risk population. Furthermore, HCC is known to occur in patients with pre-cirrhotic chronic liver disease, albeit at a much lower incidence than in patients with cirrhosis.

An alternative strategy of risk-based surveillance would involve the following steps. First, HCC risk (incidence) needs to be estimated in individual patients using appropriate modeling approaches based on readily available baseline predictor-characteristics. Second, recommendations on whether to screen and what screening strategy to employ are based on an individual's estimated HCC risk. Meaningful risk -based surveillance requires the availability of different screening strategies (e.g. biomarkers, biomarker panels, imaging tests and combinations thereof) that are characterized by increasing effectiveness but also potentially increasing costs or harms.

P20 Cancer Health Disparities SPORE

Racial Differences in Host Immune Response and Gastric Carcinogenesis: Translating Underlying Biology to Promote Gastric Cancer Interception

Abstract Presenter: Katherine Garman

Duke University

Gastric cancer is responsible for the third largest disparity in cancer incidence rates between Non-Hispanic African Americans and whites. More importantly, African Americans are more than twice as likely to die from gastric cancer than whites – the highest mortality disparity of any cancer. As a highly fatal cancer, gastric cancer is the 6th leading cause of death from cancer among African American men. However, the US does not have a strategy for gastric cancer screening, even in high-risk groups. The overarching goal of our P20 gastric cancer disparities pilot project is to identify new opportunities for risk-stratification and gastric cancer interception. Most gastric cancers are caused by Helicobacter pylori (H. pylori) infection, which is more common among African Americans than whites, and this is reflected in our local cohort. Our data suggest that opportunities for gastric cancer interception begin early by addressing disparities related to H. pylori infection, treatment, and eradication. Furthermore, while H. pylori virulence factors are not currently considered in clinical practice, virulence factors, such as cytotoxic associated geneA (CagA) as well as more virulent forms of vacuolating cytotoxin A (VacA), interfere with the host adaptive immune system to allow H. pylori colonization in gastric mucosa. Moreover, certain CagA/VacA genotypes are associated with increased gastric inflammation and epithelial degeneration. Our prior work demonstrates that African Americans have increased antibody responses to CagA and VacA, which correlate with increased risk of gastric metaplasia and dysplasia. Currently, little is known about how racially mediated differences in response to H. pylori infection might result in increased gastric cancer risk. Our current project centers around the hypothesis that H. pylori infection in African Americans is more likely to result in an immune response that increases risk of intestinal metaplasia, dysplasia, and evasion of cytotoxic T cell response, explaining the underlying disparity in stomach cancer incidence and mortality. We have now created a racially diverse retrospective cohort of 600 patients with histologic evidence of H. pylori infection, gastric intestinal metaplasia with H. pylori infection, and gastric cancer. This cohort allows us to test the hypothesis that racial differences in H. pylori virulence factors and related tissue-based immune response will correlate with more advanced disease (Aim 1). In addition to the retrospective cohort, we are enrolling patients in a prospective observational cohort in order to collect data about stress exposures and compare racial differences in host response to H. pylori in fresh serum and tissue samples (Aim 2). We are successfully creating gastric organoids from our diverse prospective cohort to enable mechanistic studies. This translational project aims to develop a risk-stratification strategy that incorporates H. pylori virulence factors and the immune-based signature found in high-risk African Americans as a key step toward reducing the disparity gap in gastric cancer screening, surveillance, and prevention.

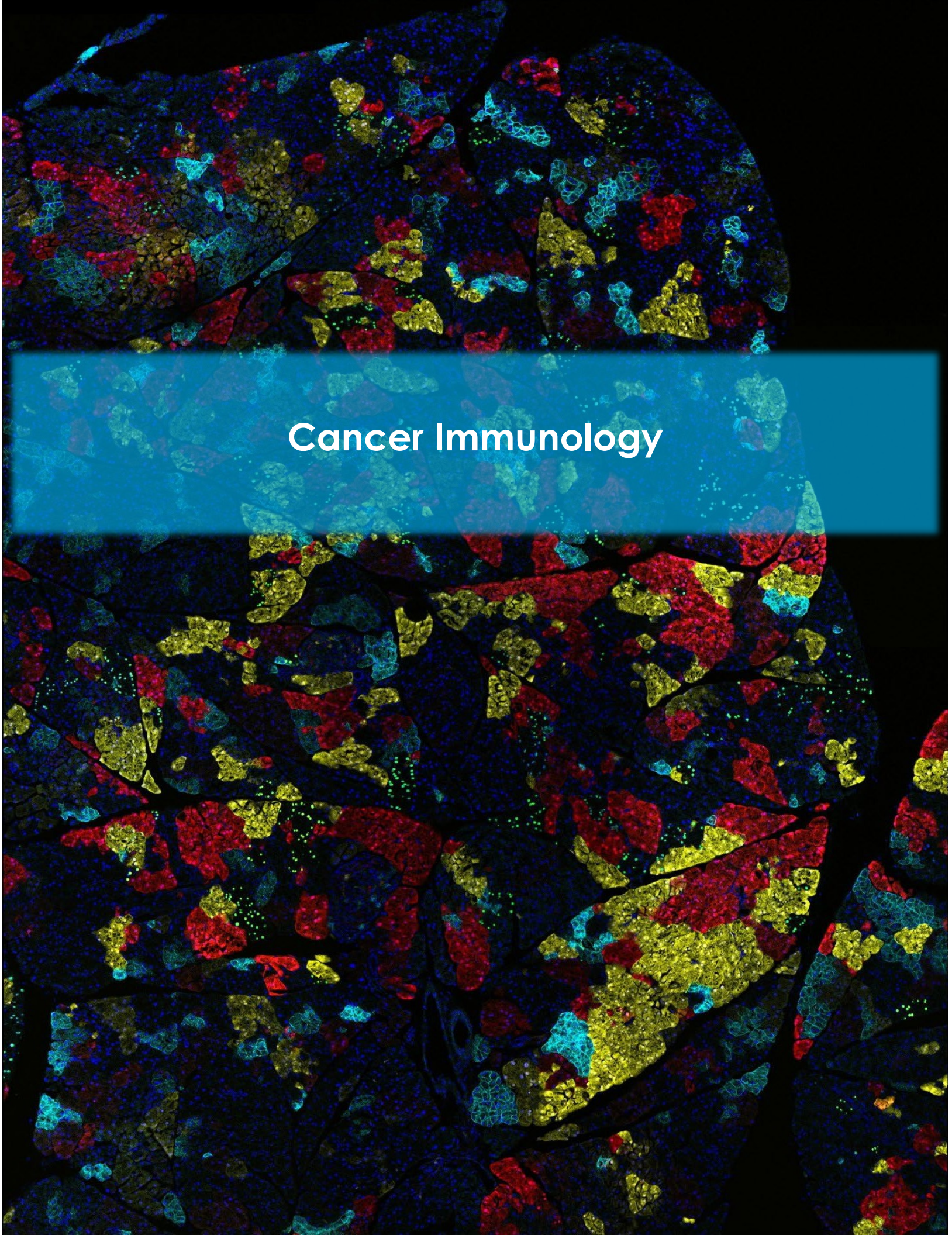
P20 Cancer Health Disparities SPORE Planning Grant Research- Moderator: Steve Nothwehr

George Ioannou (University of Washington)

George Ioannou is a Professor of Medicine at the University of Washington and Director of Hepatology at the Veterans Affairs Puget Sound Healthcare System. He has a broad research program on hepatocellular carcinoma including epidemiological studies, outcomes research, and clinical trials of screening.

Katie Garman and Meira Epplein (Duke University)

Katie Garman is a gastroenterologist and a basic/translational scientist at Duke University where she studies injury, repair and carcinogenesis in the upper GI tract. Dr. Garman co-leads the gastric cancer project in Duke's P20 Health Disparities SPORE with Dr. Meira Epplein, a cancer epidemiologist at Duke University. Dr. Epplein studies modifiable risk factors in under-served populations, with a focus on the association of infection and cancer. Together, Dr. Garman and Dr. Epplein also co-lead Duke Cancer Insitute's new program in Cancer Risk, Detection, and Interception. Dr. Garman will present this introduction of their new P20 gastric cancer project.



Cancer Immunology

Cancer Immunology

The Role of Neutrophils in Cancer Progression and Metastasis

Abstract Presenter: Leah Cook

Massar Alsamraae, Diane Costanzo, Kamiya Mehla, Edson deOliveira, Tyler Keeley, Michael A. (Tony) Hollingsworth, Leah M. Cook

University of Nebraska Medical Center

Pancreatic cancer is currently incurable. Although there have been improvements of therapeutic strategies, impact on patient survival has been dismal. Despite evidence of stromal cell contribution in pancreatic progression, the current of standard care is predominantly chemotherapy-based. Emerging studies have identified significant infiltration of myeloid-derived immune cells, i.e. neutrophils/polymorphonuclear leukocytes (PMNs), into the pancreatic tumor microenvironment where they regulate cancer growth, recruitment of other immune populations, and acquired resistance to chemotherapy. We recently identified that PMNs are protective against metastatic prostate cancer progression in bone (Costanza et al., Cancer Immunology Immunotherapy, Feb. 2020), however, the PMN anti-tumoral immune response diminishes as the tumor progresses but does not switch to a pro-tumor response. Further, we identified several cancer properties that dictate PMN response, including: 1) cancer expression of the transcription factor Signal Transducer 5 (STAT5), and 2) dysregulated NADPH oxidase expression.

To examine the transition of PMNs throughout tumor progression, we examined the killing ability of peripheral blood-derived polymorphonuclear neutrophils (PMNs) from prostate cancer patients of varying disease stage (localized, bone metastatic hormone-sensitive PCa, and bone metastatic castration-resistant PCa (mCRPC); n=20/group) for comparison to healthy donors. Surprisingly, PMNs from mCRPC patients on second-generation androgen deprivation therapy (ADT) including Enzalutamide, a standard-care androgen receptor inhibitor, were significantly less cytotoxic than PMNs from mCRPC patients who only received first-generation ADT, independently of the disease stage. Further, we found that Enzalutamide, increased PMN expression of the serine-threonine kinase receptor 1 of transforming growth factor beta (TBR1), demonstrating the importance of TGFB signaling as a mediator of PMN anti-tumoral response. We verified the impact of TBR1 expression specifically on neutrophils using TBR1-knockout neutrophils. Deletion of TBR1 restored PMN cytotoxicity against prostate cancer. Based on these data and known roles for PMNs in pancreatic cancer, we have begun investigating the interactions of PMNs with pancreatic cancer cells, specifically focusing on differences in metastatic PanCan compared to non-metastatic PanCan.

Preliminary data from my group has shown that pancreatic cancer cells, similar to other cancers, promote survival of PMNs. Further, primary tumor-derived cells, MiaPaCa-2, directly cultured with PMNs, initiated a dramatic PMN cytotoxic response, ~75% PMN-mediated cell death; this finding was confirmed in vivo where PMN depletion resulted in increased MiaPaCa growth. In contrast, liver metastasis-derived cells, Capan-1,

induced a dampened response where only ~25% of Capan-1 cells were killed. PMN cytotoxicity was suppressed by chemo/gemcitabine-resistant MiaPaCa and Capan-1 cells. Treatment of with the immunostimulant and TLR3 antagonist, PolyIC, restored PMN cytotoxicity against chemoresistant PanCan cells, through unknown mechanisms. These findings and others demonstrate the complexity of PMNs in the tumor microenvironment. Further, these findings emphasize the possibility of anti-tumor PMNs that can be manipulated to enhance their cytotoxic potential in a tissue-context manner.

Cancer Immunology

Optimizing Neoantigen–targeted Vaccine Immunotherapy for Immunologically Cold GI Tumors

Abstract Presenter: Neeha Zaidi

Johns Hopkins University

Immune checkpoint inhibitors (ICIs) provide durable clinical responses in about 20% of cancer patients, but have minimal effects in cancers lacking intra–tumoral T cells. Approaches that turn T–cell–deplete cancers into ones that attract high–quality T cells are needed to sensitize these unresponsive cancers to ICIs. Most tumors have somatic mutations that encode for mutant proteins that are tumor–specific and not expressed on normal cells (termed neoantigens). Cancers, such as melanoma, with the highest mutational burdens are more likely to respond to single agent ICIs. However, most cancers, including pancreatic adenocarcinoma (PDAC), have lower mutational loads, resulting in lower antigenicity, weaker endogenous T cell repertoires, and fewer T cells infiltrating the tumor. Our work in a PDAC murine model, Panc02, showed that a neoantigen–targeted vaccine, PancVAX, a mixture of twelve 20–mer neoantigen peptides, when paired with IC modulators (anti-PD-1 and agonist OX40 antibodies) cleared tumors in Panc02–bearing mice (PMID: 30333318). We therefore hypothesize that peptide vaccines targeting either shared ('public') or personalized ('private') neoantigens will trigger high–quality neoantigen–specific effector and memory T cells, which will then become available for further activation by ICIs and result in tumor rejection. Based on this preclinical data, we have developed an "off–the–shelf" pooled long peptide vaccine targeting a public neoantigen, mutant KRAS (mKRAS), a driver mutation expressed in >90% of PDACs and 40% CRCs. Our mKRAS peptide vaccine consists of six 21–mers corresponding to KRAS mutations G12C, G12V, G12D, G12R, G12A, and G13D in combination with immune adjuvant, Poly-ICLC (Hiltonol). Patients with resected PDAC who have completed peri–operative chemotherapy and radiation treatment, as well as metastatic microsatellite–stable (MSS) CRC are eligible for the study and are treated with mKRAS peptide vaccine in combination with ipilimumab and nivolumab (NCT04117087). Preliminary data from our first five vaccinated patients show an induction of interferon–gamma secreting mKRAS specific T cells in the peripheral blood of patients that were not present pre–treatment. Single–cell paired RNA and TCR sequencing of peripheral blood mononuclear cells from both pre– and post–treatment timepoints of the first patient suggests the induction of clonally–expanded, mKRAS–specific clones that are only present at post–treatment timepoints that are phenotypically consistent with effector memory CD8+ T cells. In vitro experiments validating these candidate mKRAS–specific TCRs are currently ongoing. A second study targeting private neoantigens as a "personalized vaccine" in combination with anti-PD-1 antibody is also planned to open for enrollment for patients with newly diagnosed metastatic PDAC and CRC.

Cancer Immunology

Harnessing HDAC Inhibition to Sensitize PDA to Immunotherapy

Abstract Presenter: Marina Baretti

Johns Hopkins University

Immune checkpoint inhibitors (ICI) targeting programmed cell death protein 1 (PD-1) or its ligand have shown unprecedented clinical benefit for some cancers but failed in others, including pancreatic adenocarcinoma (PDA). The tumor microenvironment (TME) in PDA is particularly resistant to ICI therapy, with a dearth of cytotoxic tumor infiltrating lymphocytes but an abundance of immune-suppressive cell populations including myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and tumor-associated macrophages. Our work explored the ability of HDACi to alter the suppressive function of these suppressive immune cells in favor of recruiting T cells into the tumor. Using immunocompetent murine PDA models we recently made the following key preliminary observations: i) HDACi, entinostat, shifted MDSCs from a M-MDSC-dominant population to the less immunosuppressive G-MDSCs and changed the polarity of their immunosuppressive ability to a nonfunctional phenotype; ii) we identified changes STAT3 modulation as a potential driver of the observed G-MDSC dysfunction; iii) combination therapy of entinostat plus anti-PD-1 significantly improved survival as compared with mice treated with either agent alone. Based on these data we hypothesize that the HDAC inhibition will alter the inflammatory TME of PDA and result in clinical benefit to PDA patients when combined with anti-programmed death - 1 (anti-PD-1) inhibition. To test this hypothesis, we have translated these preliminary data into an innovative clinical trial of entinostat and the PD-1 inhibitor nivolumab in advanced PDA patients. In this project, we aim to: Aim 1: Evaluate the safety and clinical activity of entinostat and nivolumab in advanced PDA patients. We are enrolling a single arm, phase II study of this therapy in advanced PDA patients with at least one prior therapy. The primary efficacy endpoint is response rate by RECIST 1.1, with a target response rate of 20% compared to the null hypothesis of 5%. This clinical trial will provide critical biospecimens, including blood and serial biopsy specimens at baseline, on entinostat monotherapy (lead in), and combination therapy, to interrogate the mechanisms of HDAC immunomodulation. Aim 2. Determine the effects of HDAC inhibition on the PDA TME. We will use our unique bank of serial biospecimens to interrogate the mechanisms by which HDAC inhibition impacts the TME in PDA and evaluate changes in immune cell populations and function in the TME using multiple platforms, including single cell analyses with RNA-seq, T cell receptor (TCR)-seq, mass cytometry, and multiplex immunofluorescence (mIF). Metastatic PDA is extremely lethal with limited options for therapy. The proposed research aims to scientifically validate the use of epigenetic modulators agents to prime an immune checkpoint inhibitor insensitive cancer into a sensitive one. If successful, our project will introduce a critically needed new treatment strategy for pancreatic cancer patients and provide important insight about the interplay between epigenetics and the immune system in PDA.

Cancer Immunology

Immune Surveillance of Pancreatic Cancer Metastases

Abstract Presenter: Stephanie Dougan

Dana-Farber Cancer Institute

Pancreatic ductal adenocarcinoma (PDA) is the third most common cause of cancer death in the US with a 10% 5-year survival rate. One of the main contributors to this low survival rate is the early establishment of metastasis which, at diagnosis, leads a dismal 3% overall survival for patients. Dissecting the role of the immune microenvironment and contribution of chemotherapy in the metastatic process will contribute to novel treatments to aid in patient survival. Current metastatic models, such as IV tail vein injection and splenic portal vein injections, are useful to study ability of cells to imbed into the metastatic site of liver and lung. However, these models do not replicate intravasation whereby tumor cells enter circulation consistently over time. To better model the entire metastatic process, we generated a highly metastatic PDA cell line that seeds both inguinal lymph nodes, liver and lungs. Tumors are implanted subcutaneously, allowed to grow and metastasize for 11 days then the subcutaneous tumor is removed, and the animals are monitored for up to 5 weeks then harvested. Metastases commonly occur in the inguinal lymph nodes and lung and less commonly to the liver. With this model in hand, we then evaluated the role of the immune microenvironment as well as chemotherapy on pancreatic cancer metastasis. Despite a proposed role for T cells in immune surveillance, we find little difference of metastasis to lymph nodes or lung with CD4 or CD8 depletion prior to surgery suggesting T-cell surveillance does not meaningfully affect metastatic spread or growth of disseminated tumors. In contrast, with chemotherapy treatment of gemcitabine or FOLFIRINOX of the subcutaneous tumors, two of the most common chemotherapies for PDA, we find little metastasis to the lung or lymph nodes indicating chemotherapy helps to reduce both primary and metastatic burden. We also evaluate the role of several immune modulatory strategies including TGFβ blocking antibodies, depletion of B cells and depletion of eosinophils. In sum, we have developed a novel metastatic model which we have used to study how alterations in the primary tumor microenvironment impact seeding of cells in the metastatic sites.

GI SPORE Meeting Speaker Bios

Session 1-Cancer Immunology- Moderator: Stephanie Dougan

Leah M. Cook (University of Nebraska)

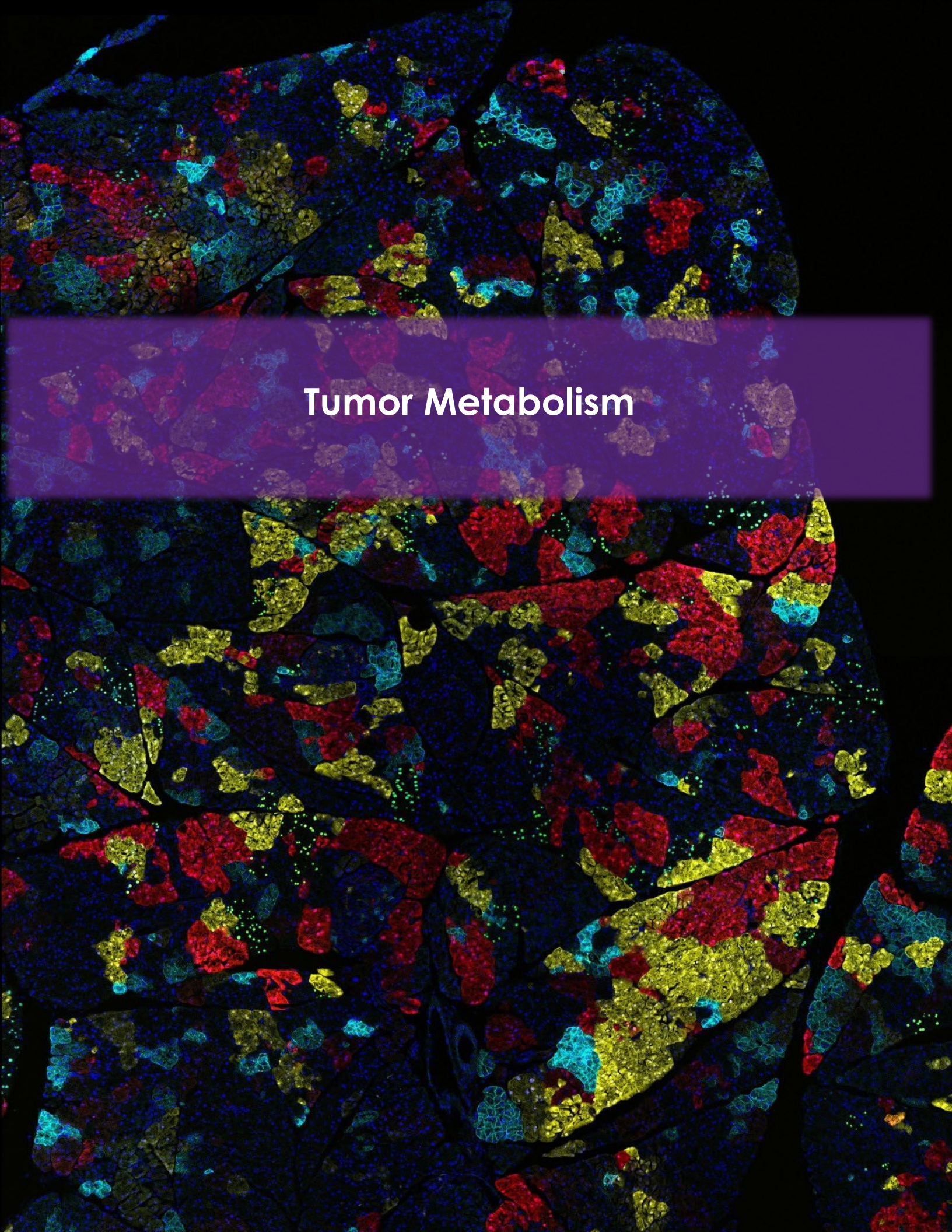
Dr. Leah Cook's goal is to identify novel immunotherapeutic targets for treating and curing metastatic cancer. Dr. Cook received her PhD in Molecular & Cellular Pathology at the University of Alabama at Birmingham (UAB), where she focused on functions of breast cancer metastasis suppressor proteins in transgenic metastasis models. She completed her postdoctoral training at Moffitt Cancer Center where she expanded her metastasis expertise to examining mechanisms associated with progression of bone metastatic prostate cancer. At Moffitt, a hub for cancer immunotherapy research, Dr. Cook was able to hone her skills towards learning more about neutrophil biology and isolation of bone marrow immune cells and has utilized this for her current research program. Dr. Cook joined the University of Nebraska Medical Center Department of Pathology & Microbiology (and the Buffett Cancer Center) in 2017. A major focus of Dr. Cook's lab involves identifying novel immune cell interactions, specifically neutrophils, that contribute to prostate cancer growth in bone and cancer-induced bone disease. A second focus of her lab involves identifying the role of innate immune cells in pancreatic cancer metastasis.

Neeha Zaidi (Johns Hopkins University)

Dr. Neeha Zaidi is a physician-scientist and a GI medical oncologist who focuses on the development of novel precision immunotherapeutic strategies for pancreatic and colon cancers that are generally not responsive to immune checkpoint blockade. She joined the Johns Hopkins faculty in 2019 as Assistant Professor after completing her fellowship under the mentorship of Dr. Liz Jaffee. Her laboratory focuses on developing and testing neoantigen-targeted vaccine approaches for these otherwise immunologically insensitive tumors. Specifically, her work has led to the initiation of clinical trials that utilize neoantigen peptide vaccines in combination with immune checkpoint inhibitors to induce and optimize high-quality neoantigen-specific T cells for a therapeutic advantage. Dr. Zaidi has most recently been awarded a K08 Mentored Clinical Scientist Research Career Development Award, ASCO Career Development Award, and the GI SPORE Career Enhancement Award.

Marina Baretti (Johns Hopkins University)

Marina Baretti , MD, is an assistant professor at Johns Hopkins. She received her medical degree from University of Pisa, in Italy. She completed her internal medicine residency and oncology fellowship at University of Milan. She then went on and completed her Medical oncology fellowship. at the Johns Hopkins University, Baltimore, Maryland. Her academic research is centered on the development of novel agents in gastrointestinal cancers, with particular interest in combinatorial approaches of epigenetic therapies and immunotherapies. She is currently the co-principal investigator on trials in these disease groups at the Johns Hopkins University, working with a collaborative team that incorporates leading experts in cancer immunology, epigenetics and drug development. Her laboratory focus has been on developing and validating a preclinical mouse model of liver cancers to investigate mechanisms underlying their pathogenesis, and will become a critical tool for investigating novel therapeutic strategies



Tumor Metabolism

Ivosidenib – Activity in Treating Pancreas Cancer by Unexpected Targeting of a Metabolic Dependency on Wild-Type IDH1

Abstract Presenter: Jordan Winter

Jordan Winter[1], David Bajor[1], Ali Vaziri-Gohar[1], Mehrdad Zarei[1], JJ Hue[1], 1Omid Hajihassani[1], Halli Graor[1], Rui Wang[1], Joseph Salvino[1], 2Jonathan Brody[2], Henri Brunengraber[1]

[1]Case Western Reserve University, The Wistar Institute, [2]Oregon Health & Science University, Case

Pancreatic cancer is the 3rd leading cause of cancer death in the United States and standard treatments are limited. The tumor microenvironment is austere and nutrient-deprived due to an abundant stroma. Harsh conditions prime protective pro-survival pathways, yet reveal metabolic dependencies which may be less important to normal cells. Isocitrate dehydrogenase 1 (IDH1) is a cytosolic enzyme, and under nutrient-limiting conditions, the enzyme oxidizes isocitrate to yield α-ketoglutarate,and NADPH. These IDH1 products support mitochondrial function and antioxidant defense under metabolic stress, as supported by cell culture studies with IDH1-knockout cells. Moreover, IDH1-knockout cells failed to grow in cell culture under low glucose conditions or proliferate as xenografts. In search of a small molecule inhibitor of wild-type IDH1, compounds developed and presumed to be selective for the mutant IDH1 isoenzyme proved to be potent wild-type IDH1 inhibitors when two specific conditions were met: 1) low magnesium (Mg2+) and 2) low glucose levels. Low Mg2+ enables IDH1 inhibitors to access the allosteric pocket and alter enzyme activity. This is particularly relevant, since we discovered low Mg2+ levels in pancreatic cancer xenografts. IDH1 blockade is lethal to pancreatic cancer cells when glucose is limited due to the importance of mitochondria and antioxidant defense for cancer survival under these conditions. Ivosidenib is a safe, orally administered, and FDA-approved for IDH1-mutant tumors. Experiments reveal that the drug is highly potent against wild-type IDH1 pancreatic cancer in cell culture under glucose withdrawal, as well as in mouse xenograft models. The drug shrinks flank tumors and increases survival by two-fold in an orthotopic pancreatic cancer model. Metabolic effects on cancer cells in culture included impairment of mitochondria and neutralization of reactive oxygen species, similar to IDH1 genetic ablation. Additionally, enhanced glucose uptake was observed in IDH1-knockout or ivosidenib-treated cancer cells. This was validated in animal 18F-FDG-PET studies. Thus, we are conducting a phase 1 neoadjuvant trial of 15 patients with resectable pancreatic cancer to test ivosidenib in combination with standard-of-care FOLFIRINOX. In this proposal, we will demonstrate on-target ivosidenib activity in trial patients through 18F-FDG-PET studies. We anticipate increased SUV after 2 weeks of ivosidenib monotherapy (administered prior to combination therapy). Additionally, we expected changes in tumor metabolites in resected tumors compared to patients treated off-trial. We also expect decreased intra-tumoral Mg2+ levels compared to serum. Pre-clinical studies will show generalizability of ivosidenib activity across pancreatic cancer models (autochthonous pancreatic cancer mice, patient-derived xenografts, metastatic models) through survival and metabolic studies, demonstrate utility of a novel PET tracer (18F-BnTP) to track ivosidenib-related mitochondrial changes, and test ivosidenib in combination with FDA-approved pancreatic cancer treatments including chemotherapy regimens and olaparib. These studies are foundational for future phase 1 and 2 trials.

Combined Inhibition of EGFR and Glutamine Metabolism in CRC

Abstract Presenter: Charles Manning

Allison Cohen[1], Seong-Woo Bae[1], Xiaoxia Wen[1], Gary T. Smith[2], Jennifer G. Whisenant[2], Kristen K. Ciombor[2], Gregory Dan Ayers[2], Lesley Flynt[1], Christine Parseghian[1], Scott Kopetz[1], Peng Wei[1], Robert Coffey[2], Jordan Berlin[2], H. Charles Manning[3]

[1]MD Anderson Cancer Center,[2]Vanderbilt University Medical Center, [3]Vanderbilt University Medical Center/MD Anderson Cancer Center

Precision cancer medicine is tailoring medical treatment to the individual characteristics of each patient. Individual tumors have unique cellular, molecular, and genetic characteristics and we need to understand these characteristics in order to match patients with cancer to ideal therapies. Advances in techniques such as genomics and proteomics have helped advance precision medicine but there remains room for improvement. The role of molecular imaging in precision medicine is increasing; however, critical gaps remain to consistently match patients with cancer and ideal therapies. The Aims of Project 2 of the Vanderbilt GI SPORE are: Aim 1. Conduct a phase II clinical trial combining a GLS1 inhibitor (CB-839) with anti-EGFR mAb therapy (panitumumab) in patients with advanced WT RAS CRC that are refractory to anti-EGFR mAb therapy. Aim 2. Evaluate quantitative Gln PET imaging in patients with WT RAS CRC that are either EGFR-mAb-naïve or refractory to EGFR-mAb therapy. Aim 3. Develop a PET imaging-derived gene signature of Gln avidity to predict responsiveness to pharmacological inhibitors of Gln metabolism.

Glutamine is a critical metabolic substrate leveraged by cancer cells for energy production, biosynthesis, and as a defense against reactive oxygen species. Thus, glutamine metabolism is an emerging area of diagnostic and therapeutic importance. We are utilizing PET tracers of glutamine metabolism in two clinical trials of patients with colorectal cancer (CRC) and in patient-derived xenograft (PDX) mouse models of CRC. 11C-glutamine/18F-4-fluoro-glutamine and (4S)-4-(3-18F-Fluoropropyl)-L-glutamic acid (18F-FSPG) report on unique aspects of glutamine metabolism, glutamine influx and glutamate efflux respectively. We are evaluating these imaging agents as both predictive and prognostic biomarkers of response to treatment.

Clinically, we are conducting a Phase II trial combining an anti-EGFR antibody, panitumumab, with a glutaminase inhibitor, CB-839 (NCT03263429). Patients participating in this trial are imaged pre- and post-treatment with 11C-glutamine and 18F-FSPG PET. We have performed the first-in-human 11C-glutamine scan as part of this trial and recently reported the safety, biodistribution and estimated radiation dosimetry of 11C-glutamine using the baseline PET imaging data (Cohen et al. J Nucl Med. 2021; jnumed.120.261594). Initial imaging results look promising. We have also opened a trial evaluating baseline PET with 11C-glutamine and 18F-FSPG prior to anti-EGFR antibody rechallenge (NCT03275974).

To further elucidate the mechanisms behind drug treatment, we are studying these tracers preclinically using well-annotated PDX mouse models of CRC. PDX-bearing mice have undergone treatment studies using an

anti-EGFR antibody in combination with CB-839 or V-9302, a small molecule inhibitor of the glutamine transporter ASCT2. PET imaging was performed pre- and post-treatment. We are correlating the imaging data to treatment response. In addition, we are using RNA-Seq data from the PDXs to develop imaging-derived gene signatures associated with treatment response. This gene signature could provide rationale of patient selection for treatment with glutaminolysis inhibitors. We have performed preliminary analyses using the PDXs which have been treated with V-9302.

In conclusion, we have identified several PET imaging biomarkers of response to glutamine metabolism-targeted treatments. These biomarkers could serve as a novel imaging approach to select patients who will respond to treatment with these agents as well as predict those patients who are responding to treatment early. These studies could lead to important advances in the diagnosis and treatment of CRC in addition to other cancer types.

Targeting Metabolic Dependencies in Pancreatic Cancer

Abstract Presenter: Pankaj K. Singh

Pankaj K. Singh

University of Nebraska Medical Center

Metabolic dependencies are frequently altered in cancer. We uncovered that SIRT5 loss facilitates selective dependence on non-canonical glutamine metabolism in pancreatic ductal adenocarcinoma (PDAC). SIRT5 negatively regulates tumor cell proliferation and correlates with a favorable prognosis in PDAC patients. Genetic ablation of Sirt5 in PDAC mouse models promotes acinar-to-ductal metaplasia, precursor lesions, and pancreatic tumorigenesis, resulting in poor survival. Mechanistically, SIRT5 loss enhances glutamine and glutathione metabolism via acetylation-mediated activation of GOT1. Our results indicate that SIRT5-mediated deacetylation of GOT1 at K369 acts as a metabolic rheostat that must be turned down by tumor cells to facilitate Kras-induced glutamine addiction. A selective SIRT5 activator, MC3138, phenocopies the effects of SIRT5 overexpression and exhibits anti-tumor effects on human PDAC cells. MC3138 also diminishes nucleotide pools, sensitizing human PDAC cell lines, organoids, and patient-derived xenografts to gemcitabine. Collectively, we identify SIRT5 as a key tumor suppressor in PDAC, whose loss promotes tumorigenesis through increased non-canonical utilization of glutamine via GOT1, and that SIRT5 activation is a novel therapeutic strategy to target PDAC.

The Sweet Danger of Sugary Drinks in Colon Cancer Development

Abstract Presenter: Jihye Yun

Baylor College of Medicine

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in developed countries. Epidemiological studies strongly suggest that diet is the most important environmental factor in CRC development. Diet is known to affect many important aspects of cancer development, such as epigenetics, metabolism, the immune system, and gut microbiota. However, we still lack a clear understanding of the molecular and genetic underpinnings linking diet and CRC. Our laboratory's goals are to identify dietary factors that affect CRC tumorigenesis and to elucidate the molecular basis for the relationship between diet and CRC. We approach these goals using preclinical model systems, such as genetically engineered colon tumor mouse models and ex vivo organoid co-culture systems.

Over the past four decades, an increasing number of studies have suggested a potential link between sugar consumption, especially in the form of sugary drinks, and CRC. However, the direct, causal link between the two has remained controversial. Our lab recently uncoupled the metabolic effects of sugary drinks from other confounding factors such obesity and diabetes by mimicking human consumption of sugary drinks in colon tumor mouse models in which Apc, a tumor suppressor, was deleted. We found that the chronic consumption of a moderate amount of sugar in liquid directly increased both tumor size and number in an Apc-driven mouse model. However, the mechanism by which the sugar treatment influenced CRC development in the mice remained unknown.

Based on our preliminary data, we now hypothesize that sugary drinks contribute to CRC development by altering the composition and function of gut microbiota. To test our hypothesis, our three specific aims are to (1) examine the tumorigenic effects of sugary drinks on an Apc-driven colon tumor mouse model in which a human microbiome has been established through fecal microbiota transplantation; (2) investigate the effects of sugary drinks on gut microbiota and microbial metabolism in this humanized mouse model; and (3) determine the role of sugar-induced gut microbiota in CRC development. Successful completion of this project will uncover the molecular basis of interrelationships among dietary sugar, gut microbiota, and CRC development, a crucial area of study that has yet to be investigated experimentally. Moreover, we will identify sugar-induced metabolites and/or microbes that can serve as new biomarkers and targets for prevention and therapeutic intervention for CRC patients.

Session 2-Tumor Metabolism-Moderator: Nada Kalaany

Jordan Winter (Case Western)

Dr. Jordan M. Winter trained in General Surgery at Johns Hopkins, and spent additional years there as a post-doctoral research fellow in Molecular Oncology. Dr. Winter received specialty fellowship training in Surgical Oncology at the Memorial Sloan-Kettering Cancer Center. In 2011, Dr. Winter was recruited to Thomas Jefferson University as a pancreatic surgeon and research scientist. Dr. Winter assumed the position of Division Chief of Surgical Oncology at University Hospitals and the Director of Surgical Services at the Seidman Cancer Center in 2018. Dr. Winter is a Professor in the Departments of Surgery and Biochemistry at Case Western Reserve University School of Medicine. He is a member of the Developmental Therapeutics Program at the Case Comprehensive Cancer Center. His clinical interest is in the management of pancreatic and related cancers and his basic research program is focused on identifying metabolic vulnerabilities to treat pancreatic cancer.

Charles Manning (Vanderbilt/MDACC)

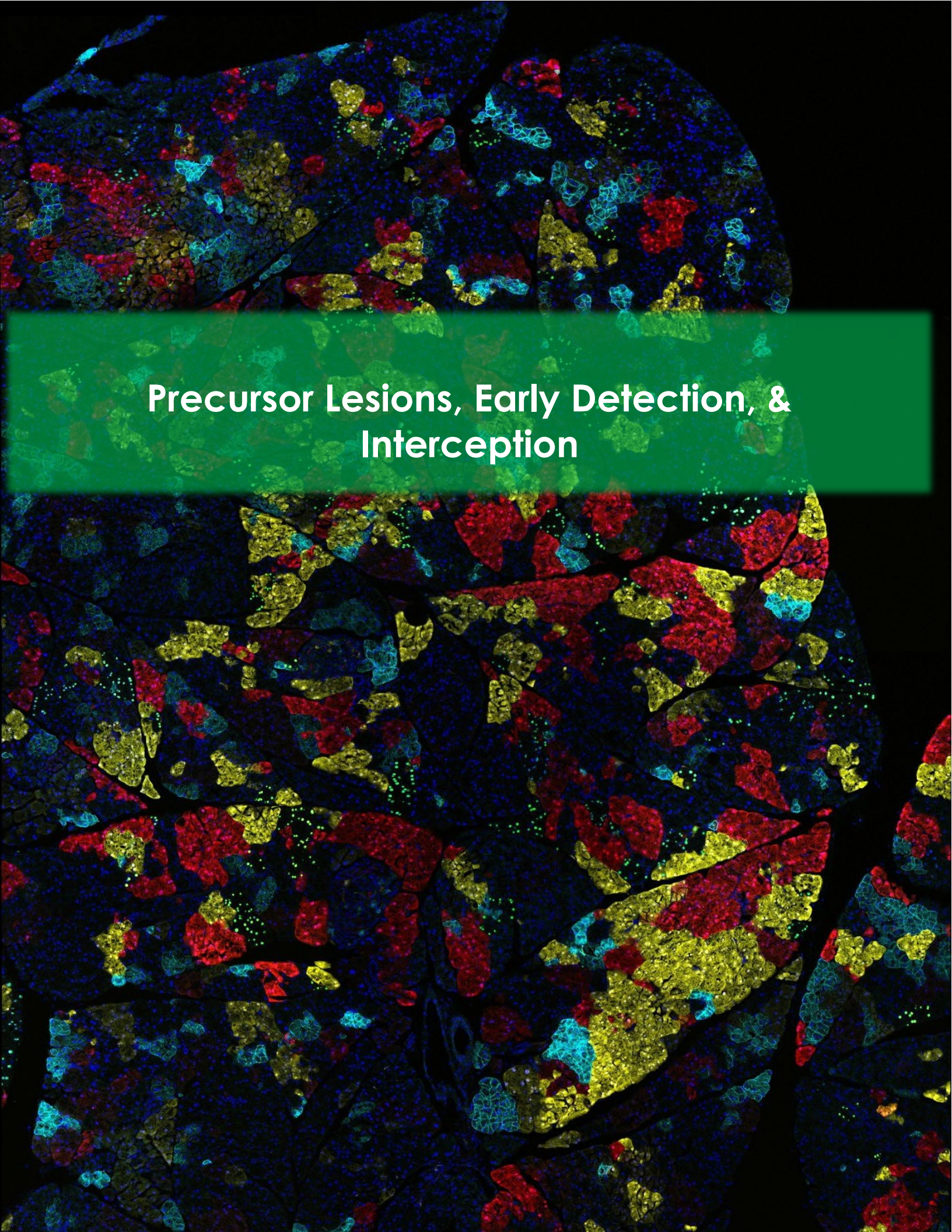
Charles Manning is a chemist with a background in radiochemistry, medicinal chemistry and imaging science. At MD Anderson, Dr. Manning is a Professor in the Department of Cancer Systems Imaging and serves as the Scientific Director of the Center for Advanced Biomedical Imaging (CABI) and Director of the Cyclotron Radiochemistry Facility in the Division of Diagnostic Imaging and co-leads the Institutional Theranostics Program. He is a Cancer Prevention and Research Institute of Texas (CPRIT) Scholar. The current directions of the Manning lab focus on quantifying cellular metabolism non-invasively through the use of high-affinity ligands for receptor-based targets and metabolic substrate transporters elevated in cancer cells.

Pankaj Singh (University of Nebraska)

Dr. Singh received his Ph.D in pancreatic cancer biology from UNMC in 2007. Subsequently, he completed post-doctoral training at the Salk Institute for Biological Studies. Since starting his lab in 2010, Dr. Singh has committed his career to metabolic alterations in pancreatic cancer, with a special emphasis on poor responsiveness to therapy, therapy resistance, and novel therapeutic combinations. Dr. Singh is currently a Professor at the Eppley Institute for Cancer Research and a co-leader of the Cancer Biology Program at the Fred and Pamela Buffett Cancer Center. He has served on numerous review panels at the NIH, VA, DOD, and other granting agencies, and chaired numerous DOD study sections on pancreatic/GI cancer research. Dr. Singh's group was among the first ones to identify the metabolic mechanisms of acquired resistance against fluoropyrimidine analogue-based chemotherapies in pancreatic cancer (Shukla et al., Cancer Cell, 2017). These findings were independently validated by the prospective COMPASS clinical trial. These studies were funded by the SPORE program, and the findings led to a phase IIa clinical trial that is currently recruiting patients (NCT04141995).

Jihye Yung (Baylor College of Medicine)

Dr. Yun received her PhD from Johns Hopkins University, School of Medicine, under the mentorship of Dr. Bert Vogelstein. Then, she joined the Laboratory of Dr. Lewis Cantley at Harvard Medical School and later at Weill Cornell Medicine as a Damon Runyon Postdoctoral Fellow to study cancer metabolism. In 2018, Dr. Yun joined Baylor College of Medicine as an assistant professor. She is also a recipient of prestigious awards such as CPRIT, V and Pew-Steward Scholar. She discovered three important findings in fields of nutrition and cancer that have been translated to human studies. She will talk about one of those findings in today's talk.



Precursor Lesions, Early Detection, & Interception

Interception of Barrett's Esophagus Progression to Adenocarcinoma

Abstract Presenter: Amitabh Chak

Amitabh Chak[1], Sanford Markowitz[1], Joseph Willis[1], Helen Moinova[1], Christopher Douville[2], Nicholas Papadopoulos[2], Chetan Bettegowda[2]

[1]Case Western Reserve University, [2]Johns Hopkins University

This Project aims to reduce mortality from Esophageal Adenocarcinoma (EAC) by pioneering two paradigm changing approaches. First, we will demonstrate the efficacy of non-endoscopic biomarker-based early detection of Barrett's esophagus (BE), in a population without symptoms of gastroesophageal reflux disease (GERD). Second, we will establish a novel molecular technology, dubbed "BAD", for early detection and interception of BE progression toward EAC. BE is the precursor lesion of EAC, a cancer with 80% 5-year mortality. BE is currently detected only when individuals with GERD undergo endoscopic (EGD) screening. Once detected, BE patients undergo triennial surveillance EGD with random biopsies to catch progression to high-grade dysplasia (HGD), that can be eradicated endoscopically to prevent cancer. Weaknesses of the approach include: i) low acceptance of EGD screening among GERD patients; ii) the absence of any recommended screening among non-GERD patients, who fall completely outside of BE screening guidelines, but who account for 40% of EAC; frequent failure of random surveillance biopsies to detect early EAC, with many cancers arising in between surveillance exams and others already metastatic when detected. Our team developed a novel swallowable balloon-based device to enable targeted screening of the distal esophagus (the site of BE origin) in a simple 5-minute office procedure. We mated this device with a methylated DNA biomarker panel that sensitively detects BE. In the GERD population we showed this approach detects non-dysplastic BE (NDBE) with 90% sensitivity and 92% specificity. We now find that non-GERD patients with 3 or more BE risk factors (age, obesity, smoking, male sex, white race) have BE risk similar to GERD patients. Aim 1 of this proposal will conduct a clinical trial demonstrating that our non-endoscopic biomarker-based technology will enable BE detection in this non-GERD population, with positive predictive value greater than that of current guidelines for EGD screening of GERD patients. Second, our group applied methods of deep DNA sequencing and AI analysis, developed for detecting cancer DNA in liquid biopsies, to instead detect abnormal DNA from nascent clones of progressed BE captured in esophageal brushings that comprehensively surveille the full BE disease segment. We showed this method, "BAD", detects as "Very-BAD" 97% of EAC and 68% of HGD. We also showed Very-BAD identifies a 7% subset of non-dysplastic BE, that on retrospective review showed high risk of early progression to HGD or EAC. Aim 2 of this proposal will: i) implement improvements to the BAD methodology aimed at increasing sensitivity for HGD to 85%, while preserving specificity; ii) prospectively demonstrate that Very-BAD NDBE defines a population with high 3-year risk of BE progression to HGD; iii) implement BAD as a method to enable frequent non-endoscopic BE surveillance by adapting BAD to work with samples from our non-endoscopic balloon device. Last, molecular studies will determine the basis of false positive and false negative BE calls in non-GERD subjects, and will also visualize and molecularly interrogate the early progressed BE cells that are detected as Very-BAD.

Human Colorectal Pre-cancer Atlas Identifies Distinct Molecular Programs Underlying Two Major Subclasses of Pre-Malignant Tumors

Abstract Presenter: Ken Lau

Bob Chen[1], Cherie' R. Scurrah[2], Eliot T. McKinley[2], Alan J. Simmons[2], Marisol A. Ramirez-Solano[2], Xiangzhu Zhu[3], Nicholas O. Markham[2], Cody N. Heiser[1], Paige N. Vega[2], Andrea Rolong[2], Hyeyon Kim[2], Quanhu Sheng[2], Julia L. Drewes[4], Yuan Zhou[2], Austin N. Southard-Smit[h2], Yanwen Xu2, James Ro[2], Angela L. Jones[2], Frank Revetta[2], Lynne Berry[2], Hiroaki Niitsu[2], Mirazul Islam[2], Karin Pelka[5], Matan Hofree[5], Jonathan Chen[5], Siranush Sarkizov[a5], Kimmie Ng[6], Marios Giannakis[5], Genevieve M. Boland[7], Andrew J. Aguirre5, Ana C. Anderson[8], Orit Rozenblatt-Rosen[5], Aviv Regev[5], Nir Hacohen[5], Kenta Kawasaki[9], Toshiro Sato[9], Jeremy A. Goettel[2], William M. Grady[10], Wei Zheng[3], M. Kay Washington[2], Qiuyin Cai[3], Cynthia L. Sears[4], James R. Goldenring[2], Jeffrey L. Franklin[2], Timothy Su[2], Won Jae Huh[2], Simon Vandekar[2], Joseph T. Roland[2], Qi Liu, [2] Robert J. Coffey[2], Martha J. Shrubsole[3], Ken S. Lau[1]

[1]Vanderbilt University School of Medicine, [2]Vanderbilt University Medical Center, [3]Vanderbilt Ingram Cancer Center, [4]Johns Hopkins University School of Medicine, [5]Broad Institute of Massachusetts Institute of Technology and Harvard, [6]Dana-Farber Cancer Institute, [7]Harvard Medical School, [8]Harvard Medical School and Brigham and Women's Hospital, [9]Keio University School of Medicine, [10]University of Washington School of Medicine

A comprehensive understanding of the tumor microenvironment and intratumoral heterogeneity in cancer is needed for developing more effective diagnostic and therapeutic strategies. Colorectal cancers (CRCs) arise from precursor polyps whose cellular origins, molecular heterogeneity, and immunogenic potential may reveal valuable clinical insight when analyzed with sufficiently high resolution. Here, we present a single-cell human atlas of the two most common colorectal pre-cancerous polyps, conventional adenomas and serrated polyps, and their resulting CRC counterparts. Using single-cell transcriptomics and multiplex imaging, we report 128 datasets from 62 participants in 2 independent cohorts, and further present bulk data on 66 and 281 polyps using RNA and targeted gene sequencing, respectively. Integrative analysis reveals adenomas arise from dysregulated WNT-driven expansion of stem cells, while serrated polyps are depleted of stem-like populations and are derived from differentiated cells transitioning through a gastric metaplasia program. Mucosal damage associated with metaplasia is coupled to a cytotoxic immune microenvironment that precedes hypermutation. Resulting microsatellite unstable CRCs retain the metaplastic signature and cytotoxic microenvironment, but in distinct non-metaplastic regions, tumor cells acquire stem cell properties, and associated cytotoxic immune cells are relatively depleted. Mouse and organoid experiments validate the importance of the differentiation status of colonic tumor cells in driving cytotoxic immunity partly through increased expression of antigen-presentation machinery. Our multi-omic atlas provides paradigm-shifting insights into malignant progression of colorectal polyps and their microenvironments, and it serves as a framework for precision surveillance and prevention of sporadic CRC.

PTEN Inactivation Initiates an Extrahepatic Cholangitis-Cholangiocarcinoma Continuum in Mice

Abstract Presenter: Baoan Ji

Yan Yang[1], Jianhua Wan[1], Jiale Wang[1], Xiaohui Zhu[1], Ashley N. Haddock[1], Jiaxiang Chen[1], Oliver Wang[1], Kevin Shi[1], Sumera I. Ilyas[2], Zenong Cheng[3], Xueli Zhou[3], Brandy H. Edenfield[1], Liuyan Jiang[1], Michael S. Torbenson[2], Huamin Wang[4], Raouf E. Nakhleh[1], Xuemei Shi[5], Ying Wang[2], Yan Bi[1], Gregory J. Gores2, Tushar C. Patel[1], Baoan Ji[1]

[1]Mayo Clinic, Jacksonville, [2]Mayo Clinic, Rochester, [3]The First Affiliated Hospital of Bengbu Medical College, [4]MD Anderson Cancer Center, [5]8Greenwood Genetic Center

Cholangiocarcinomas (CCA) are a group of relatively rare malignancies that include intrahepatic CCA (iCCA) and extrahepatic CCA (eCCA), two distinctive cancer types that vary in their etiopathogenesis. Understanding the disease pathogenesis has been facilitated by genetic mouse models for iCCA, but similar models are lacking for eCCA. Methods: In this study, targeted Pten gene deletion or expression of active mutant KrasG12D in extrahepatic cholangiocytes and periductal glands were used to study the initiation and progression of eCCA. Results: We observed minimal pathological effects in the extrahepatic biliary tract with KrasG12D expression. In stark contrast, loss of Pten initiated inflammatory changes with enlarged and distorted extrahepatic biliary ducts in mice as early as 4 weeks old. Histologically, sclerosing cholangitis-like changes were observed and characterized by increased epithelial proliferation, inflammatory cell infiltration, and fibrosis. Loss of Pten upregulated p-AKT and caused DNA damage and epithelial-to-mesenchymal transition. Importantly, as the mice aged, the extrahepatic biliary duct became larger and the proliferative epithelial cells progressed to low grade dysplasia, high grade dysplasia, and eventually invasive carcinoma with a long latency. Further study revealed that Pten deletion alone initiated cell senescence, a tumor limiting mechanism. p53 gene deletion abrogated the senescence response and caused rapid CCA tumorigenesis. Conclusion: Pten inactivation in extrahepatic cholangiocytes and periductal glands caused fibro-inflammatory changes and development of invasive eCCA. This novel genetic mouse model for extrahepatic cholangiocarcinogenesis will be valuable to study the mechanisms of the disease progression and aid the development of preventive and therapeutic interventions.

Identifying Mechanisms Driving Metastatic Dormancy and Outgrowth

Abstract Presenter: Christina Ferrer

Christina Ferrer, Ruben Boon, Hyomin Cho, Tiziano Bernasocchi, Lai Ping Wong, Murat Cetinbas, Elizabeth R. Haggerty, Daniel E. McLoughlin, Ruslan Sadreyev, Dejan Juric, Raul Mostoslavasky

Massachusetts General Hospital Cancer Center

Identifying unique, adaptive mechanisms of metastatic cancer cells remains an elusive and central question in the treatment of metastatic disease, particularly in pancreatic cancer (PDA), where the majority of patients present with synchronous metastatic lesions at the time of diagnosis. A loss-of-function shRNA targeted screen in metastatic-derived cells identified Gstt1, a member of the glutathione S-transferase superfamily, as uniquely required for metastasis and dispensable for primary tumor growth. Within established lesions, Gstt1 is expressed exclusively in the non-proliferative compartment, and represents a dormant subpopulation of sustained metastases. Gstt1 is not only expressed in established metastases but also in non-cycling, dormant disseminated tumor cells (DTCs) and is both required and sufficient for dissemination. Mechanistic studies indicate that Gstt1 maintains dormancy by binding to and modifying intracellular fibronectin, influencing fibronectin deposition into the metastatic microenvironment. These findings identify Gstt1 as a novel mediator of metastasis and highlight the relationship between tumor cell dormancy and its influence on the metastatic microenvironment.

Five Shots at HCC with an Oral Small-Molecule STAT3 Inhibitor

Abstract Presenter: David Tweardy

David Tweardy, Moses Kasembeli, Uddalak Bharadwaj, Kwang Jung, Wonbeak Yoo, Apostolia Tsimberidous, Laura Beretta, Ahmed Kaseb

MD Anderson Cancer Center

More than 90% of hepatocellular cancer (HCC) cases arise in the setting of hepatic injury and inflammation, which involve production of several cytokines, notably hepatocyte growth factor (HGF) and interleukin 6 (IL-6), that activate signal transducer and activator of transcription 3 (STAT3) to drive further injury, inflammation, fibrosis, and cancer. STAT3 activation (phosphorylation on Y705, pY-STAT3) promotes tumor cell proliferation and survival, tumor vascularization, and an immunosuppressive tumor microenvironment and occurs in virtually all HCC tumors. Increased STAT3 transcriptional activity within hepatocytes adjacent to tumor was previously shown to predict late HCC recurrence; in a very recent study, we demonstrated that the pY-STAT3 score within tumor cells correlated with early recurrence (p=0.004). Based on these findings, we hypothesized that introduction of a STAT3 inhibitor into current standard-of-care treatment and prevention strategies for HCC will increase response rates, decrease postoperative recurrences, and prevent HCC in patients at high risk. To begin to test these hypothesis, we used computer-based screening of ~4 million compounds, combined with medicinal chemistry, to identify TTI-101, a naphthalene sulfonamide that binds directly to STAT3 with high affinity and potently reduces levels of pY-STAT3 and STAT3-driven cell proliferation. Working with Tvardi Therapeutics, a clinical-phase biopharmaceutical company, we demonstrated that TTI-101 provides excellent plasma exposures following oral administration, concentrates 2-to-6 fold in tissues, and was well-tolerated in patients with solid tumors enrolled in a Phase I study up to the highest dose (DL4; 25.6 mg/kg/d). Importantly, in the dose-escalation phase of the study, TTI-101 demonstrated clinical benefit in 50% of evaluable patients including two HCC patients, who exhibited durable partial responses — one patient had a 42% PR sustained for 10-months and a second patient had a 70% PR sustained for over a year. Also of note, the percent (%) of cells staining positive for pY-STAT3 in post-treatment biopsy samples was 66% lower than in the pre-treatment biopsy samples. Thus, from the perspective of absence of off-target effects, safety, and early efficacy, TTI-101 is the most promising STAT3 inhibitor currently in clinical development for cancer treatment and chemoprevention. Pre-clinical studies are underway to determine the minimum effective dose for preventing HCC in the hepatocyte-specific Pten knock-out, non-alcoholic steatohepatitis (NASH) mouse model of HCC. In addition, Phase II trials are planned to evaluate TTI-101 in HCC patients as first line therapy combined with atezolizumab plus bevacizumab, as second line therapy combined with anti-PD-1, and as third line monotherapy. A Phase I trial also is planned to evaluate TTI-101 in an adjuvant setting following surgical resection of HCC to suppress recurrence by lowering pY-STAT3 levels within residual tumor cells.

Recent Advances in Studies of Exosomes and Nanoparticles

Abstract Presenter: Bob Coffey

Vanderbilt University Medical Center

Exosomes and nanoparticles are under intense investigation as sources of clinically relevant cargo. Exosomes are 40-150 nm endosome-derived, lipid-bilayer enclosed, small extracellular vesicles. A new type of small (< 50 nm), non-membranous, extracellular nanoparticle, termed exomere, recently was identified. We have just discovered a new extracellular nanoparticle, termed supermere (supernatant of exomeres) isolated from the conditioned medium of DiFi cells, a human colorectal cancer (CRC) cell line. These 25 nm nanoparticles are morphologically distinct from exomeres by fluid-phase atomic force microscopy and display a markedly greater biodistribution in vivo compared to exosomes and exomeres. The protein and RNA composition of supermeres differs from exosomes and exomeres. Supermeres are highly enriched with cargo involved in multiple cancers (glycolytic enzymes, TGFBI, miR-1246, and GPC1). In the course of this work, we found that DPEP1 was markedly enriched in a subset of EGFR/CD81 double-bright exosomes using fluorescence-activated vesicle sorting (FAVS). DPEP1 mRNA expression was detected in adenomas and CRC but nor SSLs or normal colon. By immunostaining of separate adenoma and CRC tissue microarrays (TMA), DPEP1 immunoreactivity was detected in 27% of adenomas and 72% of CRCs. In a clinically well-annotated CRC (TMA), diffuse localization of DPEP1 portended a worse outcome. Moreover, by FAVS, DPEP1 was increased in exosomes isolated from the plasma of CRC patients compared to normal individuals. DPEP1 is a GPI-linked glycoprotein that acts as a dipeptidase to convert LTD4 to LTE4. Of interest, a non-enzymatic function of DPEP1 was recently found, that is, to act as a receptor to which neutrophils bind. The implications of these findings will be discussed.

GI SPORE Meeting Speaker Bios

Session 3-Precursor lesions, Early Detection, and Interception- Moderator: Aparna Parikh

Amitabh Chak (Case Western)

Dr. Chak has a broad background in gastroenterology. His endoscopic research in Barrett's Esophagus began as a junior attending at UHC/Case Western Reserve University with the help of the ASGE when he discovered that Barrett's esophagus and cancers aggregated in certain families. His major focus in Barrett's esophagus and esophageal adenocarcinoma has been the epidemiology and genetics of Familial Barrett's Esophagus but this interest has expanded to other aspects of these diseases including early detection, role of obesity specifically adipokines, and genetic biomarkers. Dr. Chak is currently the PI of a BETRNet Center Grant that is developing translational applications by investigating the genetics and genomics of Barrett's esophagus and esophageal adenocarcinoma.

Ken S. Lau (Vanderbilt)

Dr. Lau has expertise in the field of single-cell/spatial -omics and system biology. He is a tenured Associate Professor of Cell and Developmental Biology at Vanderbilt University School of Medicine and a Chancellor Faculty Fellow. Dr. Lau's lab has significant experience in handling human specimens for next-generation high-content technologies, having processed upwards of 500 specimens for scRNA-seq. His lab custom-built an inDrop system for scRNA-seq designed specifically for processing gut tissues, and optimized various tissue handling strategies to ensure high quality data. Dr. Lau's group spans both experimental and computational biology, with significant contributions to development of experimental technologies and computational algorithms for analyzing high content data. Dr. Lau's research is on gut epithelial cell biology, with funded efforts (R01, Helmsley Trust, GI SPORE, HTAN) in the fields of Inflammatory Bowel Disease and colorectal cancer. Dr. Lau served as elected co-chair of Data Collection and Standards Working Group of the Gut Cell Atlas and Molecular Characterization Working Group of the HTAN.

Baoan Ji (Mayo Clinic)

Dr. Baoan Ji is a pancreatologist at Mayo Clinic. He has more than 20 years of experience studying pancreatic biology, pancreatitis, and pancreatic cancer. He has made several fundamental contributions to this field, including mouse models that have been shared with more than 30 laboratories. his research focusing on NF-□B/Ras/trypsin signaling in the development of pancreatitis and pancreatic cancer have been published in JCI, Gastroenterology, Gut, JBC, Oncogene, AJP, etc. Recently, he began to apply his expertise to meet some unmet needs in liver research: using unique in-vivo cholangiocyte-specific system to establish animal models for intra- and extra- hepatic cholangiocarcinomas. Today, he will talk about his eCCA model.

Christina Ferr

Dr. Ferrer completed her PhD in 2015 at Drexel University College of Medicine in the laboratory of Mauricio Reginato where she was working on uncovering molecular mechanisms through which OGT and O-GlcNAcylation contribute to cancer phenotypes, including metabolic reprogramming, survival and metastasis. In 2016, Dr. Ferrer joined the Mostoslavsky group at Massachusetts General Hospital and Harvard Medical School where she is expanding her expertise into understanding how epigenetically driven gene expression changes drive development and cancer progression, including metastasis. er (Mass General Hospital)

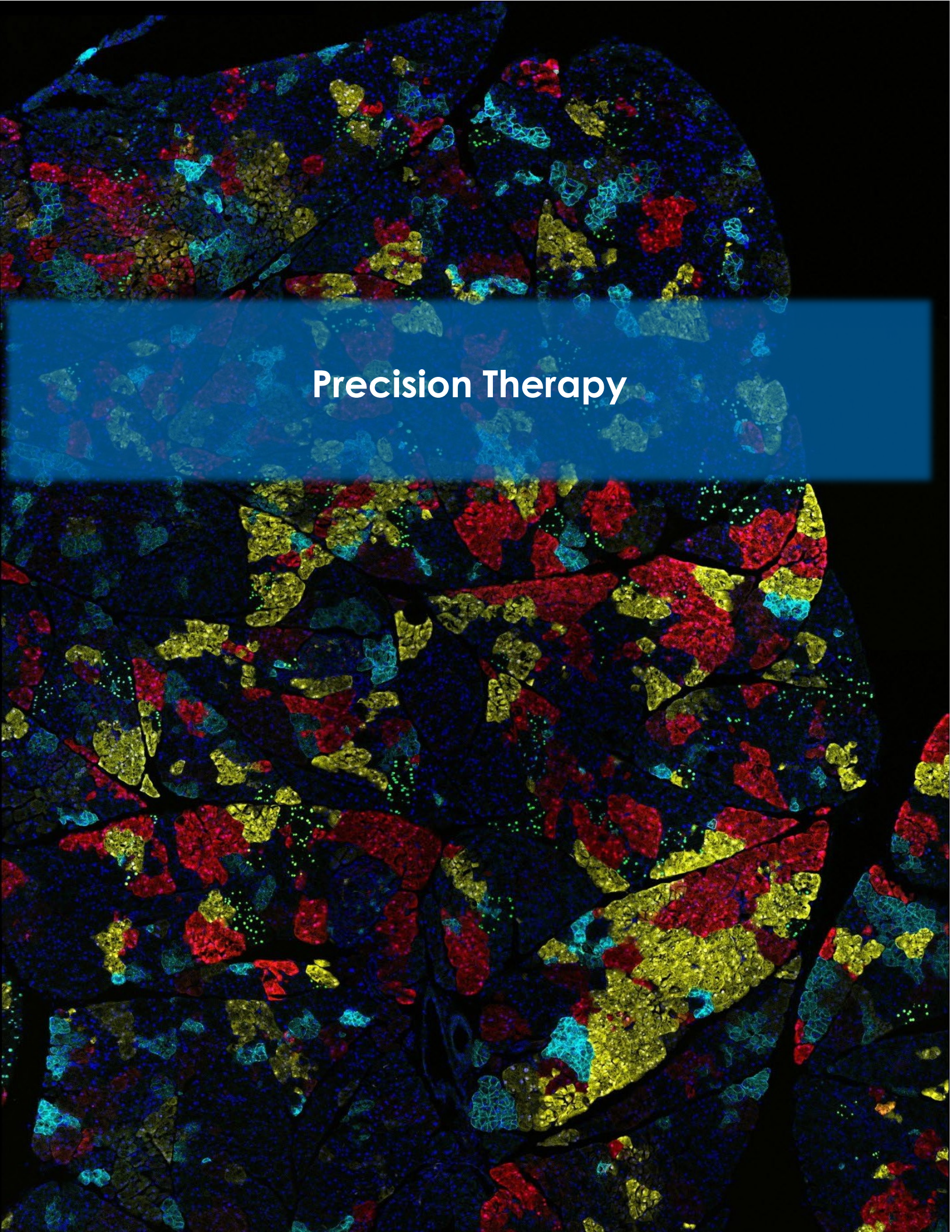
GI SPORE Meeting Speaker Bios

David Tweardy (MDACC)

Dr. David Tweardy is Head of Internal Medicine and Professor of Infectious Diseases, Infection Control and Employee Health at The University of Texas MD Anderson Cancer Center and holds the Dallas/Fort Worth Living Legend Chair for Cancer Research III. He earned his MD from Harvard Medical School and completed his post-graduate clinical training in internal medicine and infectious diseases at Case Western Reserve University in Cleveland and post-doctoral research training in molecular hematology at the Wistar Institute in Philadelphia. Dr. Tweardy's research centers on cytokine signaling and for the past 25 years has focused on signal transducer and activator of transcription 3 (STAT3), a protein whose dysregulation contributes to the development of many diseases. He is a fellow of the American Association for the Advancement of Science and was elected to membership in the Association of American Physicians. He has authored close to 200 original research articles in peer-reviewed journals and is the inventor of 8 patent families and the co-founder of Tvardi Therapeutics, Inc., a clinical-stage biopharmaceutical company based in Houston.

Bob Coffey (Vanderbilt)

Bob Coffey, MD, is John B. Wallace Professor of Medicine, Professor in the Department of Cell and Developmental Biology, and an Ingram Professor of Cancer Research at Vanderbilt University Medical Center in Nashville, TN. He co-directs the Vanderbilt Epithelial Biology Center and is PI of Vanderbilt's long-standing GI SPORE, which focuses on colorectal cancer. He is contact PI of Vanderbilt's Pre-Cancer Atlas Moonshot grant that focuses on the two most common pre-malignant tumors of the colon: adenomas and sessile serrated lesions. He received an NCI Outstanding Investigator Award in 2017. His basic research focuses on 1) spatial compartmentalization of the EGF receptor (EGFR), its cognate ligands and relevant signaling molecules in the context of polarized epithelial cells, and how their dysregulation contributes to cancer, 2) intestinal stem/progenitor cells marked by the pan-ERBB negative regulator, LRIG1, and 3) composition and behavior of extracellular vesicles and nanoparticles.



Precision Therapy

Neoadjuvant Cabozantinib and Nivolumab Convert Locally Advanced HepatocellularCarcinoma into Resectable Disease with Enhanced Antitumor Immunity

Abstract Presenter: Mark Yarchoan

Won Jin, Qingfeng Zhu, Jennifer Durham, Aleksandra Popovic, Stephanie Xavier, James Leatherman, Aditya Mohan, Guanglan Mo, Shu Zhang, Nicole Gross, Soren Charmsaz, Dongxia Lin, Derek Quong, Brad Wilt, Ihab R. Kamel, Matthew Weiss, Benjamin Philosophe, Richard Burkhart, William Burns, Chris Shubert, Aslam Ejaz, AtulDeshpande, Ludmila Danilova, Genevieve Stein-O'Brien, Elizabeth A. Sugar, Daniel A. Laheru, Robert A. Anders,Elana J. Fertig, Elizabeth M. Jaffee, Mark Yarchoan

Johns Hopkins University School of Medicine

Background: Hepatocellular carcinoma (HCC) is the most rapidly rising cause of cancer death in the United States(US) and is anticipated to be the 3rd leading cause of cancer death in the US by 2040. Neoadjuvant studies offer a tremendous opportunity to elucidate mechanisms of immune response and resistance, by enabling in depth profiling of the tumor immune microenvironment (TME) after systemic therapy that is not possible with biopsy specimens. HCC is the ideal tumor to conduct studies of perioperative therapy because no systemic therapy is established as standard of care for resectable patients, and recurrence is common. Here we present the initial results of the first arm of our neoadjuvant HCC platform study, which evaluated the combination of nivolumab (anti-PD1) plus cabozantinib (a multi-kinase inhibitor of VEGFR-2, AXL, and c-MET).

Methods: This open-label, single institution, single arm phase 1b study enrolled patients with HCC outside of traditional resection criteria, including very large tumors, multifocal disease, and tumors with macrovascularinvasion (referred throughout as borderline or locally advanced HCC). Eligible patients received a total of 8 weeks of cabozantinib 40 mg oral daily and nivolumab 240 mg IV every two weeks, followed by surgical re- evaluation.

Results: Of 15 patients enrolled, 12 (80%) underwent successful margin negative resection, and 5/12 (42%) of the resected patients had major pathologic responses. The disease free survival (DFS) was greater than 233 days for all individuals with pathologic responses, whereas 4/7 patients without major or complete pathologic responses developed progression early (between 56 and 155 days). In-depth biospecimen profiling with imagingmass cytometry uncovered key biological parameters of response including an enrichment in T effector cells, as well as tertiary lymphoid structures, CD138+ plasma cells, and a distinct spatial arrangement of B cells in responders as compared to non-responders. Among the myeloid cell clusters, macrophage clusters characterized by lower expression of CD163 and arginase-1 were higher in abundance in the responders.

Conclusion: Neoadjuvant combination therapy with a targeted therapy and systemic immunotherapy is feasible and is associated with a pathologic responses in a subset of HCC patients. Profiling of responders and nonresponders indicated that the observed response was associated with an orchestrated B-cell infiltration, and

a lower degree of myeloid-induced immunosuppression. Ongoing arms of our neoadjuvant platform are enrolling a novel combination of nivolumab plus relatlimab, an anti-LAG3 monoclonal antibody, as well as a control arm of nivolumab monotherapy.

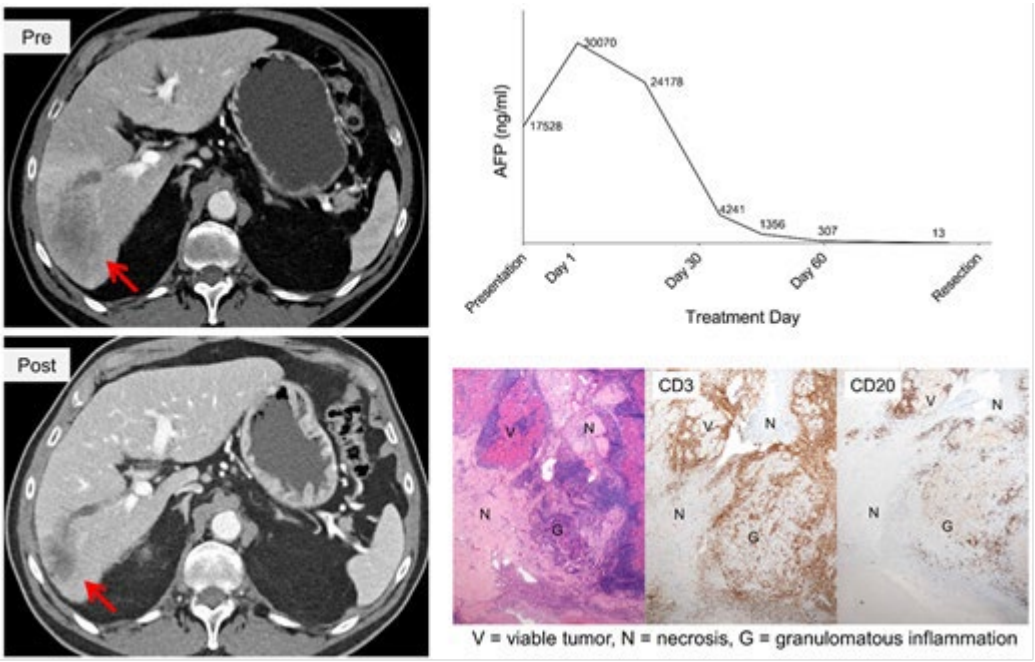


Figure 1: Example of a response to neoadjuvant systemic therapy in our study.

Precision Therapy

Leveraging Distinct Enhancer Connectomes in Targeted Therapy of Pancreatic Cancer

Abstract Presenter: Feda Hamdan

Feda Hamdan[1], Catherine Wegner Wippel[1], Thomas Ekstrom[1], Ana Kutschat[2], Zeynab Najafova[2], Xin Wang[2], Amro Abdelrahman[1], Mark Truty[1], Elisabeth Hessmann[2], Steven Johnsen[1]

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Effective therapy in highly aggressive tumors, such as pancreatic cancer, remains elusive. Almost two-thirds of pancreatic cancer patients are resistant to current therapeutic approaches. This is due to high adaptability of pancreatic cancer driven by aberrant gene transcription. Enhancers are distal regulatory elements that interact with and activate their target genes. Enhancers are deregulated in pancreatic cancer leading to aberrant transcriptional reprogramming, thereby mediating evasion mechanisms to overcome therapy. We utilized cutting-edge molecular techniques, such as HiChIP to detect enhancer-promoter interactions and ChRO-seq to detect enhancer RNA production to characterize the enhancer landscape of resistant pancreatic cancer. Thereby, we uncovered an important function of deregulated enhancer interactions in driving resistance and aggressiveness in pancreatic cancer.

Precision Therapy

Harnessing TNFα and MK2 Signaling to Sensitize Pancreatic Cancer to Genotoxic Stress

Abstract Presenter: Patrick Grierson

Washington University

Cytotoxic chemotherapy remains the foundation of treatment for advanced pancreatic ductal adenocarcinoma (PDAC). Unfortunately, de novo or acquired resistance is nearly uniform. We sought to identify dynamic mechanisms of resistance to cytotoxic chemotherapy in PDAC, focusing on FOLFIRINOX (combination of 5-FU, irinotecan and oxaliplatin). We used a reverse-phase protein array (RPPA) to identify dynamic stress-induced phospho-target changes following FOLFIRINOX challenge. Following FOLFIRINOX treatment of PDAC cells (or treatment with the active metabolite of irinotecan, SN38) we identified activation via phosphorylation of Heat shock protein 27 (Hsp27) as the most significantly upregulated event. Small molecule inhibitor of Hsp27 or Hsp27 silencing by shRNA enhanced apoptosis induced by FOLFIRINOX. FOLFIRINOX upregulated TNFα, and in an autocrine manner thereby led to phosphorylation and activation of TAK1, MK2 (MAPKAPK2) and the direct MK2 target, Hsp27. Targeting MK2 in combination with SN38 prevented Hsp27 activation, sensitized PDAC cells to apoptosis, and suppressed protective autophagy. In the autochthonous KPPC PDAC mouse model, ATI-450 (a novel oral MK2 inhibitor) as a single agent decreased PDAC development and progression. ATI-450 in combination with FOLFIRINOX eliminated most PDAC foci and prolonged survival without additive hematologic or gastrointestinal toxicity. We identified high phospho-MK2 expression in human PDAC tumors to be associated with inferior survival. Taken together, our work identifies genotoxic stress-induced MK2 as a link to the activation of pro-survival pathways following chemotherapy treatment in PDAC thereby providing rationale for combination MK2 inhibition with FOLFIRINOX in advanced pancreatic cancer.

Deciphering Treatment Vulnerabilities for APOBEC3A High and CIN Prone PDACs

Abstract Presenter: Sonja Woermann

Sonja M. Woermann[1], Amy Zhang[2], Fredrik I. Thege[1], Chris Gates[3], Weisheng Wu[3], Reuben S. Harris[4], Faiyaz Notta[5], Susan R. Ross[6], Anirban Maitra[1], Andrew D. Rhim[1], Asha S. Multanis[1], Ya'an Kang[1], Michael P. Kim[1], Melena D. Bellin[7]

[1]MD Anderson Cancer Center, [2]Ontario Institute for Cancer Research, [3]University of Michigan, [4]Howard Hughes Medical Institute, [5]Ontario Institute for Cancer Research, [6]Perelman School of Medicine, [7]University of Minnesota Medical Center

Chromosomal instability (CIN) is a hallmark of cancer and has been associated with acquisition of a metastatic phenotype in numerous cancers. Mechanisms by which these genomic events occur during the lifespan of a tumor have yet to be fully delineated. Recently, large-scale tumor sequencing studies have supported the hypothesis that specific cell intrinsic mechanisms may contribute to genomic instability among cancer cells. One of the most common associations observed across tumor types is single base substitution signatures 2 and 13 (SBS2/13), corresponding to point mutations arising from APOBEC cytidine deaminases, which are upregulated in multiple cancers, and have been identified as key drivers of cancer mutagenesis including pancreatic ductal adenocarcinoma (PDAC).

In our study, we describe for the first time, a tumor promoting role of A3A driving aggressive and metastatic pancreatic cancer. We found that A3A is not routinely detected in non-diseased pancreata; however, expression was detected in the epithelial and stromal compartments from patients with chronic pancreatitis and in precursor lesions of pancreatic cancer and is further significantly increased in invasive neoplasia.

More importantly, we found that A3A expression but not A3A-induced mutagenesis, was associated with a significantly reduced overall survival in PDAC. By employing a variety of genetic tools, we identified a novel function for A3A in initiating CIN, underlining its fundamental role in driving the observed early metastatic propensity in PDAC. Using a series of in vivo and in vitro models, we demonstrate that A3A-induced CIN leads to aggressive cancer, featuring enhanced, STING-dependent, distant organ seeding and metastatic growth. As a consequence of aberrant A3A function and CIN-mediated upregulation of STING, NfkB and Stat3 pathways were activated. More importantly, these effects were independent of the deaminase domain, underscoring a novel role of A3A beyond its established canonical function. Finally, we determined the effect of physiologic deaminase deficient A3A expression in an autochthonous mouse model of PDAC. These experiments showed that A3A expression in the exocrine pancreas led to substantial copy number losses that were independent of deaminase function and reproducible across cohorts. Interestingly, these alterations were reflected in hPDAC tumors, pointing to a causal role of A3A in driving copy number changes frequently seen in patients, but not prevalent in murine GEMMs. Furthermore, we identified a subset of high A3A expressing patient tumors that were enriched for deletions in DNA damage repair genes. While we showed that A3A-expressing PDAC cells do

not fully phenocopy a BRCA mutation-like phenotype, A3A-expressing PDAC cells are exceptionally sensitive to PARP inhibition and DNA crosslinking agents. The combined effect of deletions in these genes has yet to be ascertained, and we hypothesize that these losses further add to ongoing DNA damage in PDAC cells. In summary, our work nominates A3A as a novel initiator of CIN in PDAC, resulting in accelerated tumorigenesis, enhanced metastasis and defined pharmacologic vulnerabilities. Future studies will seek to dissect whether specific vulnerabilities connected to A3A expression can be exploited to improve treatment outcomes for patients with this deadly disease.

Precision Therapy

IgE-based Therapeutic Combination Attenuates Pancreatic Tumor Burden by Activating SMAD1-ID1 axis in NK cells

Abstract Presenter: Kamiya Mehla

University of Nebraska Medical Center

Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer-related deaths in the United States. Late diagnosis and inadequate response to standard chemotherapies contribute to an unfavorable prognosis and an overall 5-year survival rate of 10% in PDAC. To date, studies have focused on IgG-based therapeutic strategies in PDAC. With the recent interest in IgE-based therapies in multiple solid tumors, we explored the efficacy of IgE isotype of MUC1 (chimeric mouse/human anti-MUC1.IgE) antibody against pancreatic tumors in a unique double transgenic (dTg) mice model. These transgenic mice express human MUC1 and human IgE antibody receptor (FcεRIα). Our study demonstrates the notable expression of FcεRI (receptor for IgE antibody) in the tumors from PDAC patients. We show that the administration of anti-MUC1.IgE together with a toll-like receptor 3 agonist (PolyICLC) and anti-PD-L1, produces a robust anti-tumor response that is dependent on NK and CD8 T cells in pancreatic tumor-bearing dTg mice. Besides, our data show that anti-MUC1.IgE-based combination therapy activates the SMAD1-ID1 axis in NK cells. Furthermore, our study shows that antigen specificity of IgE plays a vital role in executing the anti-tumor response. We developed a unique OVA-induced acute asthma-PDAC model and show that OVA-induced IgE fails to restrain tumor growth in preclinical models of pancreatic cancer. Together, our data show the novel tumor protective benefits of anti-MUC1.IgE-based therapeutics in the preclinical models of pancreatic cancer, which can open avenues for future clinical interventions.

Targeting KRAS in GI Malignancies

Abstract Presenter: Andrew Anguirre

Andrew Anguirre, Mark M. Awad, Shengwu Liu, Igor I. Rybkin, Kathryn C. Arbour, Julien Dilly, Viola W. Zhu, Melissa L. Johnson, Rebecca S. Heist, Tejas Patil, Gregory J. Riely, Joseph O. Jacobson, Xiaoping Yang, Nicole S. Persky, David E. Root, Kristen E. Lowder, Hanrong Feng, Shannon S. Zhang, Kevin M. Haigis, Yin P. Hung, Lynette M. Sholl, Brian M. Wolpin, Julie Wiese, Jason Christiansen, Jessica Lee, Alexa B. Schrock, Lee P. Lim, Kavita Garg, Mark Li, Lars D. Engstrom, Laura Waters, J. David Lawson, Peter Olson, Piro Olson, Piro Lito, Sai-Hong Ignatius Ou, James G. Christensen, Pasi A. Jänne

Dana-Farber Cancer Institute

Clinical trials with the KRAS inhibitors adagrasib and sotorasib have shown promising activity in cancers harboring KRAS glycine-to-cysteine amino acid substitutions at codon 12 (KRASG12C). Acquired resistance to these therapies is common, but mechanisms of resistance have not been fully elucidated. Among patients with KRASG12C-mutant cancers treated with adagrasib monotherapy, genomic and histologic analyses were performed comparing pretreatment and post-resistance samples. Cell-based experiments were conducted to study mutations conferring resistance to KRASG12C inhibitors. A total of 38 patients were included in this study: 27 with non-small cell lung cancer (NSCLC), 10 with colorectal cancer (CRC), and 1 with appendiceal cancer. Putative mechanisms of resistance to adagrasib were detected in 17 patients (45% of the cohort), 7 of whom (18% of the cohort) had multiple coincident mechanisms. Acquired KRAS alterations included G12D/R/V/W, G13D, Q61H, R68S, H95D/Q/R, Y96C, and high-level amplification of the KRASG12C allele. Acquired bypass mechanisms of resistance included MET amplification; activating mutations in NRAS, BRAF, MAP2K1, and RET; oncogenic fusions involving ALK, RET, BRAF, RAF1, and FGFR3; and loss-of-function mutations in NF1 and PTEN. In two of nine lung adenocarcinoma cases with paired tissue biopsies, histologic transformation to squamous cell carcinoma was observed without identification of any other resistance mechanisms. Using an in vitro deep mutational scanning screen, we systematically defined the landscape of KRAS mutations that confer resistance to KRASG12C inhibitors. In summary, diverse genomic and histologic mechanisms impart resistance to covalent KRASG12C inhibitors, and novel therapeutic strategies are required to delay and overcome this drug resistance in patients with cancer.

Precision Therapy

Overcoming Radiation-Induced Lymphopenia to Improve Chemoradiation Outcomes for Pancreatic Cancer

Abstract Presenter: Sunil Krishnan

BhanuPrasad Venkatesulu[1], Cheng-En Hsieh[2], Joseph Kim[2], Keith Sanders[2], Amrish Sharma[2], Pankaj Singh[3], Ramesh Tailor[2], Steven Lin[2], Sunil Krishnan[3]

[1]Loyola University, [2]MD Anderson Cancer Center, [3]Mayo Clinic, Jacksonville

Clinical studies have reported radiation-induced lymphopenia (RIL) as an independent predictor of disease-free survival and overall survival in pancreatic cancer. RIL is lower when radiation therapy (RT) utilizes spleen-sparing techniques. However, in our analysis of patients receiving optimal conformal avoidance of the spleen, lymphopenia remains a challenge. Furthermore, this lymphopenia is not associated with a compensatory increase in the homeostatic T cell cytokines IL-7 and IL-15. We recreated the lymphopenia secondary to splenic irradiation in murine models, and observed that peripheral blood CD3, CD4, CD8, and NK cell counts were significantly reduced and this lymphodepletion was associated with inferior tumor control outcomes. Cytokine rescue not only increased the circulating peripheral blood CD3 and CD8 significantly but also improved the tumor control in mice with 75% achieving complete tumor regression. CD3, CD8 and NK cell tumor infiltrating lymphocytes were increased significantly with cytokine supplementation. Lymphodepletion not only affects the primary tumor but also leads to aggressive growth of the secondary non-irradiated tumor. Cytokine rescue leads to improved tumor control outcomes at the primary site as well as at the secondary unirradiated tumor site.

Precision Medicine Targeting of Colorectal Cancer with PIK3CA Helical Domain Mutations

Abstract Presenter: Zhenghe John Wang

Yamu Li[1], David Bajor2

[1]Case Western Reserve University, [2]University Hospitals and Case Comprehensive Cancer Center

PI3Ks consist of p110 catalytic subunits and p85 regulatory subunits. PIK3CA, encoding p110□, is mutated in ~20% human cancers, including 30% colorectal cancer. Most PIK3CA mutations are clustered in the helical domain or the kinase domain. Here, we report that p85β disassociates from p110α helical domain mutant protein and translocates into the nucleus through a nuclear localization sequence (NLS). Nuclear p85β recruits deubiquitinase USP7 to stabilize EZH1 and EZH2 and enhances H3K27 trimethylation. Knockout of p85β or p85β NLS mutant reduces the growth of tumors harboring a PIK3CA helical domain mutation. Our studies illuminate a novel mechanism by which PIK3CA helical domain mutations exert their oncogenic function. Finally, a combination of alpelisib, a p110α-specific inhibitor, and an EZH inhibitor, tazemetostat, induces regression of xenograft tumors harboring a PIK3CA helical domain mutation, but not tumors with either a WT PIK3CA or a PIK3CA kinase domain mutation, suggesting that the drug combination could be an effective therapeutic approach for PIK3CA helical domain mutant tumors. A phase I clinical trial of the combination of alpelisib and tazemetostat is pending.

Precision Therapy

Therapeutic Targeting of DKK3 in Pancreatic Cancer and Response to Chemotherapy

Abstract Presenter: Rosa Hwang

Rosa Hwang, Liran Zhou, Todd Moore, Michael Kim

MD Anderson Cancer Center

Pancreatic adenocarcinoma (PDAC) has a dismal prognosis with a 7% 5-year survival rate. Clearly novel approaches to treatment are urgently needed. The tumor microenvironment (TME) is recognized as an important mediator of tumor progression for many cancers and our lab has recently identified Dickkopf-3 (DKK3) as a pro-tumorigenic factor secreted specifically by the cancer associated fibroblasts in PDAC. Our team has completed preclinical studies demonstrating that DKK3 is an attractive target present in the stroma of PDAC and that treatment with our murine anti-DKK3 monoclonal antibody (mAb) JM6-6-1 significantly inhibits tumor growth and metastasis. Treatment with JM6-6-1 extended survival in relevant PDAC models by at least double and the combination with immune checkpoint inhibitor resulted in a durable improvement in survival. In addition, DKK3 inhibits PDAC response to chemotherapy and suppression of DKK3 with JM6-6-1 improved chemosensitivity in cell culture assays. Our team is actively developing these anti-DKK3 mAb clones towards first-in-human toxicology and feasibility studies. For these studies, preclinical data on the efficacy of anti-DKK3 mAb in combination with chemotherapy in PDAC models will be highly valuable to inform on clinical trial design. The overall hypothesis of our proposal is that DKK3 functions as a tumor promoter in PDAC and contributes to chemoresistance. Specifically in this project, we hypothesize that blockade with anti-DKK3 mAb will be effective to treat PDAC as a single agent and to improve response to chemotherapy. We propose to test our hypothesis with the following specific aims.

Specific Aim 1. To determine the extent to which DKK3 contributes to PDAC chemoresistance. We have previously demonstrated that conditioned media from PSCs, and specifically DKK3, promote resistance of PDAC cells to gemcitabine. Using both in vitro assays and relevant mouse models of PDAC with patient-derived xenograft (PDX) tumors, we will evaluate whether DKK3 contributes to resistance to additional commonly used chemotherapeutic agents and determine whether anti-DKK3 mAb treatment can improve chemosensitivity. We will test multiple chemotherapy combinations with anti-DKK3 mAb using a high-throughput ex vivo PDX live tissue slice assay and the efficacy of anti-DKK3 mAb for chemoresistant PDAC will also be evaluated using PDX from residual tumors pre-treated with chemotherapy.

Specific Aim 2. To identify predictors of response to anti-DKK3 mAb as monotherapy and in combination with chemotherapy. The ability to prospectively identify which patients will respond to treatment is critically important in order to avoid unnecessary toxicity and costs and to deliver therapy to those most likely to benefit. In this aim, we will identify biomarkers (tumor and serum) that predict response to anti-DKK3 mAb and chemotherapy by analyzing PDX tumors and genetically manipulating DKK3 levels in xenograft models of PDAC.

Our team includes translational physician-scientists with expertise in TME biology, relevant mouse models of PDAC, phase I clinical trials for GI malignancies and biostatistics. Together, we are well qualified to complete the studies outlined above which will provide valuable data as we develop DKK3-targeted mAb as a novel treatment for PDAC.

Session 4-Precision Therapy-Moderator: Andrew Aguirre

Mark Yachoan (Johns Hopkins University)

Mark Yarchoan, M.D, is an Assistant Professor of Medical Oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore Maryland. He completed his fellowship in Medical oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, where he received mentorship from Dr. Elizabeth Jaffee. He is focused on developing novel immunotherapy combinations for hepatobiliary cancers, including hepatocellular carcinoma. Using preclinical models of hepatobiliary cancers, he is testing novel therapies that modulate the tumor immune microenvironment, and conducting early stage clinical trials in hepatobiliary cancers. He was the recipient of a GI Spore Career Enhancement Award.

Feda Hamdan (Mayo Clinic)

Dr. Hamdan received her Doctor of Pharmacy degree from the University of Jordan in 2011. Then, she pursued her master's in pharmacology and was awarded a scholarship provided by the German Academic Exchange to pursue her graduate studies in Germany. Dr. Hamdan received her PhD degree with highest honors in molecular medicine from the University Medical Center of Goettingen in 2018. Subsequently, she started her postdoctoral training in Mayo Clinic with a major focus on epigenetic pathways driving aggressiveness of pancreatic cancer. Currently, she is an assistant professor of medicine in the division of Gastroenterology and Hepatology in Mayo Clinic. Her major focus is leveraging high-throughput next generation sequencing data to find novel targeted therapies of pancreatic cancer.

Patrick Grierson (Washington University)

Dr. Grierson is a gastrointestinal medical oncologist. His pre-clinical research focuses on pancreatic ductal adenocarcinoma, which is characterized by frequent mutation of the KRAS oncogene, as well as a desmoplastic stroma. Unfortunately, neither targeting of KRAS nor its downstream effectors has produced meaningful clinical benefit, and the benefits of immunotherapy have not yet been realized in this disease. Further, targeting of the desmoplastic stroma has yielded mixed results, thereby leaving cytotoxic chemotherapy as the standard approach to systemic therapy. Therefore, we aim to identify novel molecular targets, either tumor cell intrinsic or extrinsic, to improve survival in this disease with limited therapeutic options. In an effort to identify novel molecular targets, we employ broad in vitro laboratory techniques as well as in vivo genetically-engineered mouse models of pancreas cancer. Using these approaches, our group has identified stress- and inflammation-mediated MAPK signaling pathways in pancreatic cancer that contribute to treatment resistance, with high potential for clinical translation. Clinically, Dr. Grierson focuses on the care of patients with diverse gastrointestinal malignancies, with a special interest in translating pre-clinical discoveries of novel therapeutics into early-phase clinical trials.

Sonja Woermann (MDACC)

Sonja Woermann received her MD, PhD from Ludwig Maximilians University, Munich. She did her residency and clinical fellowship at Technical University of Munich and worked as a research scientist with Dr. Hana Alguel and Roland Schmid, focusing on inflammation triggered pancreatic carcinogenesis, for which she received the Else-Kröner Fresenius foundation Clinician Scientist Award and the Mildred-

Scheel Postdoctoral Research Fellowship.In 2016 she started a postdoc with Andrew Rhim in the Ahmed Center for Pancreatic Cancer Research at MD Anderson Cancer Center focusing on the role of APOBEC3A in pancreatic cancer oncogenesis and metastasis. She is currently a faculty instructor in the lab of Dr. Anirban Maitra in the Ahmed Center, and she recently received the APA Young investigator in pancreatology research grant and the SPORE career enhancement program research award for her work studying treatment vulnerabilities in A3A and CIN prone PDACs.

Kamiya Mehla (University of Nebraska)

Dr. Mehla is an assistant professor at the University of Nebraska Medical Center. She received her Ph.D. from the Institute of Genomics and Integrative Biology, Delhi, India, in 2012. As a Ph.D. student, she worked on immunological aspects of airway respiratory diseases, including acute lung injury and asthma. She joined Dr. Michael (Tony) A. Hollingsworth at Eppley Institute, UNMC, as a postdoctoral fellow in 2013 and studied immune cell cross-talk at the tumor microenvironment and systemic compartments in PDACs. She also focused on developing novel immunotherapeutic strategies against pancreatic cancer. Currently, she is focused on immunometabolism in pancreatic cancer and pancreatic cancer cachexia.

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