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Poster Board **#1**

Gregory L. Beatty, MD, PhD

2020 AACR-The Mark Foundation for Cancer Research "Science of the Patient" SOP Grant

Impact of Liver Biology on Cancer Immunity

Liver metastasis and inflammation are correlated with poor clinical responses to immunotherapy and cytotoxic therapies. Given that the liver is a lymphoid organ central to peripheral immune tolerance, we hypothesized that cancer immunosurveillance may be regulated by the liver. To test this hypothesis, we have studied the impact of liver inflammation on immune responses and treatment outcomes in mice and humans. Our findings reveal that STAT3 activation in the liver and the release of acute phase reactants, namely serum amyloid A proteins 1 and 2 (SAA), restrict T cell infiltration into tumors. Conversely, loss of STAT3 or genetic deletion of SAA promotes the entry of CD8+ T cells into tumors. Mechanistically, IL-6, released by non-malignant cells in the tumor microenvironment, activates hepatocytes via the STAT3 pathway to release SAA. These proteins then engage Toll-like receptor 2 (TLR2) to reduce the number of intratumoral dendritic cells, thereby inhibiting T cell infiltration. Genetic deletion of SAA improves survival after tumor resection in a T cell-dependent manner in mice. Similarly, in patients with pancreatic cancer, lower serum levels of SAA correlate with longer survival after surgery. Collectively, these results identify a key link between liver function and cancer immunity, wherein hepatocytes act as an immune checkpoint. These findings open new therapeutic opportunities aimed at targeting liver biology for broadening the potential efficacy of immunotherapy as well as cytotoxic therapies.

Poster Board **#2**

Kristopher R. Bosse, MD

AACR-AstraZeneca Career Development Award for Physician-Scientists, in Honor of José Baselga

Murine GPC2 CAR T Cells to Define Mechanisms of Immune Escape

Children with high-risk neuroblastoma have a significant risk of death. Our laboratory discovered that glypican 2 (GPC2) is a differentially expressed neuroblastoma oncoprotein, developed both murine (m) and human (h) GPC2 CARs from our prioritized D3-GPC2 antibody, and opened a first-in-human Phase 1 GPC2 CAR T cell clinical trial. To understand the role of the neuroblastoma tumor microenvironment in GPC2 CAR efficacy, we performed murine neuroblastoma allograft studies where we nominated limited CAR T cell tumor trafficking and enhanced tumor infiltration of immunosuppressive myeloid-derived suppressor cells (MDSC) as mechanisms of neuroblastoma GPC2 CAR immune escape. Notably, this significant and persistent post-CAR MDSC tumor infiltration was accompanied by high levels of MDSC-associated cytokines (e.g., CXCL1, CXCL2).

We now show that MDSCs directly inhibit mGPC2 CAR T cell proliferation, activation, and cytotoxicity with in vitro co-incubation studies. We also generated a CXCR2-armored mGPC2 CAR which we hypothesized would both increase CAR T cell tumor homing and suppress MDSC tumor infiltration by co-opting CXCL1/2. In vitro, CXCR2-GPC2 CARs migrated in response to CXCL1/2 in transwell assays. In vivo, CXCR2-GPC2 CARs were significantly more potent against neuroblastoma allografts compared to either mGPC2 alone or control CARs. Clinically, in dose-level 1 (n=3 patients) of our GPC2 CAR trial we observed that peripheral MDSC levels robustly correlated with CAR T cell expansion and that clinical responses are associated with lower levels of pre-infusion MDSCs and post-infusion levels of MDSC-associated cytokines. Collectively, MDSCs may modulate GPC2 CAR efficacy both in neuroblastoma preclinical models and patients.

Poster Board **#3**
Mariana Bustamante Eduardo, PhD
AACR-Pfizer Breast Cancer Research Fellowship

Medium Chain Fatty Acids Shift Metabolism Towards the De Novo Serine Pathway Fostering Epigenetic Plasticity and Oxidative DNA Damage

Introduction. Fatty acid (FA) exposure alters histone methylation, gene expression and increases flux through the de novo serine synthesis pathway (SSP). We proposed that FA induces a metabolic shift towards the SSP, increasing S-adenosylmethionine, altering histone methylation, gene expression, and promoting estrogen receptor-negative breast cancer (ERnegBC).

Methods. Proteomics, metabolomics, Reactive Oxygen Species (ROS) measurement, comet assay and H3K4me3 CUT&RUN were performed in MCF-10A cells exposed to octanoic acid (OA). Single-cell RNA-seq was performed in breast tissue derived microstructures exposed to OA.
Results. OA increased the SSP enzyme PHGDH, as well as S-adenosylmethionine, glutathione and 2-hydroxyglutarate. Blocking PHGDH, prevented these increases. The SSP transcription factor ATF3 and genes PHGDH and PSAT1 increased with OA in microstructures. Basal BSL1, hormone sensing HS1 and luminal progenitor LP3 subtypes showed an increased flux through the SSP. The SSP transcription factors ATF3/4 ($p < 0.05$) motifs were enriched at H3K4me3 peaks. After 5 min OA exposure, mitochondrial and nuclear ROS increased significantly ($p < 0.01$), peaking at 15 min. OA exposure triggered DNA damage likely due to ROS increase in the nucleus. OA increased glutathione metabolism and ROS detoxification in BSL1.

Conclusions. PHGDH is elevated in 70% of ERnegBCs, despite its gene being amplified in only 6% of all BCs, implying other mechanisms are involved in PHGDH dysregulation. One possibility involves the FA-induced metabolic shift towards the SSP increasing S-adenosylmethionine, 2-hydroxyglutarate and glutathione. This promotes epigenetic phenotypic plasticity and controls ROS, thereby supporting the survival of cells that acquire DNA damage and potentially facilitating carcinogenesis.

Poster Board #4

Yves Chiswili Chabu, PhD

AACR Career Development Award to Further Diversity, Equity, and Inclusion in Cancer Research

Tolerogenic Mechanisms of KRAS/STK11 Co-mutated Non-Small Cell Lung Cancer

Oncogenic KRAS mutations and STK1 loss of function alleles cooperate to give rise to aggressive lung cancers that are resistant to immunotherapy. The underlying mechanisms are not fully understood. We found that oncogenic KRAS and STK11 loss of function mutations cooperatively stimulate the small G-protein ARF6.In turn, ARF6 activation triggers the release of immunosuppressive extracellular vesicles that potently promote tumor immune evasion in a mouse model of KRAS/STK11 co-mutated Non-Small Cell Lung Cancer (KS-NSCLC). Inhibition of ARF6, reprograms the tumor immune microenvironment into an active state and correspondingly suppresses tumor size. These findings suggest that ARF6 plays a key role in KS-NSCLC immune escape and that targeting ARF6 will sensitize KS-NSCLC to immunotherapy.

Poster Board **#5**

Jennifer C. Coleman, PhD

AACR-Pediatric Brain Tumor Foundation Medulloblastoma Research Fellowship

Examining Life-or-Death Stress Responses in DEAD-box Helicase X-linked (DDX3X)-mutated Medulloblastomas

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Medulloblastoma (MB) is the most common primary brain tumor in children, contributing significantly to death and morbidity. DDX3X, an ATP-driven helicase, is the second most frequently mutated gene in MB and acts to coordinate developmental programs and suppresses MB by restricting expansion of tumor cell lineages that. Brain tumor treatments have not changed significantly in 20 years, therefore furthering our mechanistic understanding of how mutated DDX3X (mutDDX3X) contributes to these pathologies is critical to identify new curative treatments for children. MutDDX3X induces hyper-assembly of stress granules (SGs) – phase-separated organelles that enhance cell survival through translation stalling and pro-survival signalling. Abnormal SG dynamics promote oncogenesis, tipping the balance between cell death and survival. As such, SGs present currently unexplored novel therapeutic strategies, yet there is a lack of pharmacological candidates to treat SG-related pathologies. In this fellowship, I aim to advance our knowledge of how mutDDX3X-driven SG hyperassembly arises by developing in vitro models to profile protein and RNA targets of SGenriched wildtype and mut-DDX3X. Extrinsic regulators of SG assembly will be used in alongside microscopy, cell survival and protein synthesis assays to understand mutDDX3X SG phenotypes, if they can be circumvented through pharmacological intervention and whether this impacts cancer cell survival. We are also acquiring a compound library to develop a high-throughput screening assay to identify drugs that present as viable options for treating DDX3X-driven MB. Using this combinatorial approach, I aim to accelerate discovery of novel drug treatments to improve therapies for patients with DDX3X-driven MB.

Poster Board **#6**

Brehima Diakite, MD, PhD

Beginning Investigator Grant for Catalytic Research (BIG Cat)

Pharmacogenetics of Hormonal Breast Cancer Treatment

Background: Breast cancer is a multifactorial disease resulting from a complex interaction between genetic and non-genetic factors. Polymorphisms in the Glutathione S-transferase (GST) genes affect the detoxification of xenobiotics. The aim of our study was to evaluate the role of GSTM1 and GSTT1 genes in breast cancer outcomes in Malian women.

Methods: We conducted a case-control study involving 109 breast cancer patients matched with 116 unrelated healthy controls. GSTM1 and GSTT1 genotypes were determined using multiplex PCR.

Results: The frequency of the GSTM1 null genotype was slightly higher in patients than in controls (24.8% vs 19.0%), but it was not associated with breast cancer (OR: 1.40, 95% CI = 0.74-2.65; p= 0.29). This null GST genotype does not protect patients against breast cancer risk. Additionally, the frequency of the GSTT1 null genotype showed a similar trend between patients and controls (43.1% for both) with a neutral association with breast cancer (OR: 1.0, 95% CI = 0.59-1.69; p= 0.99). Although patients with combined GSTM1 present/GSTT1 null (OR: 1.12, 95% CI = 0.61-2.04; p= 0.70), GSTM1 null/GSTT1 present (OR: 1.94, 95% CI = 0.80-4.70; p= 0.13), and GSTM1 null/GSTT1 null (OR: 1.21, 95% CI = 0.49-2.96; p= 0.66) genotypes were not associated, individuals carrying these combinations were not protected against the risk of breast cancer.

Conclusion: Our results showed that the GSTM1 gene could be a significant risk factor for breast cancer, while GSTT1 may have a neutral effect.

Poster Board **#7**

Madelyn Espinosa-Cotton, PhD

AACR Fellowship to Further Diversity, Equity, and Inclusion in Cancer Research

HER2 Pretargeted Alpha Particle Radioimmunotherapy for Desmoplastic Small Round Cell Tumor

Radioimmunotherapy is an effective treatment modality for desmoplastic small round cell tumor. Compartmental 131-I-8H9 (targeting B7-H3) prevents peritoneal relapse, but extra-peritoneal relapse remains an issue. Our goal is to determine if the alpha emitter 225-Ac can be delivered systemically to eradicate DSRCT using a HER2-directed self-assembling, disassembling (SADA) antibody platform for pretargeted radioimmunotherapy (PRIT). Immunohistochemistry (IHC) was performed to evaluate binding of our HER2 Ab to a panel of DSRCT surgical specimens, DSRCT cell lines, and normal tissues. Xenograft tumors were established on the flanks of male BRG mice. SADA antibodies were injected iv 48-168 hours before administration of 225-Ac. Tumors were measured twice weekly using calipers. Mice were weighed twice weekly and evaluated for signs of gross toxicity (weight loss, petechiae, lethargy, etc). Blood was collected weekly for CBC and biweekly for serum chemistry to monitor kidney function. Blood was also collected 30 minutes after administration of SADA and immediately preceding administration of 225-Ac. ELISAs were performed on the serum from this blood to determine the peak (30 min post injection of SADA Abs) and trough (immediately preceding administration of 225-Ac) levels of circulating SADA antibodies. IHC shows strong binding of our HER2 Ab to a majority of DSRCT surgical specimens and cell lines and extremely limited binding to normal tissues. Xenograft mouse experiments show that HER2 SADA + 225-Ac (2 uCi) can eliminate DSRCT xenografts ranging from 200 to more than 1000 mm3. We propose that HER2-directed SADA PRIT is a promising strategy for DSRCT and should be further investigated.

Poster Board **#8**

Javiera Garrido, MSc, PhD

AACR Maximizing Opportunity for New Advancements in Research in Cancer (MONARCA) Grants for Latin America

Tumor Genomic Heterogeneity in Non-Small Cell Lung Cancer (NSCLC) Patients from Latin America

Motivation: Life prospects of non-small cell lung cancer (NSCLC) patients have greatly improved over the last decades with the adoption of tumor genomic profiling. However, tumors present a widespread heterogeneity, and many challenges remain to fully comprehend the influencing factors. Of particular importance is the Latin America population which i) is commonly underrepresented in clinical trials and epidemiological studies, ii) presents higher incidence and mortality rates in comparison to the developed world, and iii) is constituted by a genetically admixed population. This research attempts to close this knowledge gap.

Methodology: The study population is derived from the NIRVANA study, a cross-sectional multicenter observational study aiming to characterize and validate molecular diagnostic technologies for NSCLC patients in Chile, Brazil, and Peru. Next Generation Sequencing (NSG) genomics profiles were obtained using the Oncomine Focus Assay (OFA). Covariates of interest, including sociodemographic, clinical, and lifestyle factors, were assessed at enrollment. QC-approved genomic profiles were obtained for 1864 participants.

Results and Conclusions: The prevalence of mutations and fusions in the eight most relevant NSCLC genes (EGFR, KRAS, ALK, MET, RET, BRAF, ROS1 and ERBB2) varies based on sociodemographic, clinical and lifestyle characteristics. Clear distinctions emerged in the prevalence of EGFR, KRAS and ERBB2 mutations among the three countries. Furthermore, distinct association patterns were identified between the prevalence of genetic alterations and the studied factors. These findings provide novel insights into NSCLC studies among Latin-American patients, potentially serving as guidelines for more tailored strategies in the overall management of this underrepresented population.

Poster Board **#9**
Jenny M. Hogstrom-Stakem, PhD
AACR-AstraZeneca Breast Cancer Research Fellowship

Mechanisms of Succinate-Mediated Resistance to CDK4/6-Inhibitors in HR+ Breast Cancer

Breast cancer is the most prevalent cancer among women worldwide with estrogen receptor-positive (ER+) cancer constituting 70% of all breast cancers. Although ER+ breast cancers initially respond well to ER-targeted therapies and CDK4/6 inhibitors, approximately 30% patients acquire resistance to targeted therapies. In addition to intrinsic resistance that tumors develop, cancer-associated fibroblasts (CAFs) residing in the tumor microenvironment, also contribute to treatment-resistance and poor survival. Therefore, to investigate the mechanism of stroma-mediated resistance to CDK4/6 inhibitors, we propagated patient-derived organoids (PDOs) and matching CAFs from ER+ breast tumors. Our data shows that the polar metabolite containing fraction of CAF-conditioned media stimulate resistance to CDK4/6 inhibitors. To identify metabolites that drive resistance, we performed metabolomics on CAF-conditioned media. We observed that the CAF-conditioned media was enriched for TCA cycle intermediates and identified succinate as a driver of resistance. Succinate is an oncometabolite that has an essential function in energy metabolism and perform other various biological processes such as epigenetic modifications and pseudohypoxia. Furthermore, extracellular succinate can bind to the succinate receptor SUCNR1 and induce GPCR-mediated signal transduction. To assess the mechanism of resistance, we treated PDOs with a SUCNR1 agonist and observed that the agonist stimulated treatment-resistance. Furthermore, the resistance phenotype was rescued with a SUCNR1 antagonist, showing that succinate mediated resistance is conveyed via SUCNR1. This suggests that CAF-secreted succinate plays a role in supporting a pro-tumor environment by promoting drug resistance. Defining this mechanism of resistance will elucidate potential therapeutic targets to augment patient response to therapy.

Poster Board **#10**

Abram Kamiza, PhD

Beginning Investigator Grant for Catalytic Research (BIG Cat)

Evolving Genetic Factors for Cervical Cancer in Women of African Ancestry

Cervical cancer is the second most common cause of cancer deaths among women worldwide. Genome-wide association studies (GWAS) have identified genetic variants associated with cervical cancer. However, these discoveries have been limited by the small sample sizes of individual cohorts. To identify additional novel loci associated with cervical cancer, we performed a multi-ethnic meta-analysis of GWASs, fine mapping and then developed polygenic risk scores. GWAS summary data were obtained from women of European, African and Asian ancestries. Meta-analyses were performed using fixed effect inverse variance weighted method implemented in GWAMA. To localize putative genomic loci associated with cervical cancer, we performed fine mapping using the Bayesian approach by calculating the marginal posterior probability of causality for each single nucleotide polymorphisms (SNPs) and 99% credible set size. We also developed and assessed the performance of polygenic scores using PRSice-2. We identified 25 independent loci associated with cervical cancer. Of these loci, nine were novel. These include rs111611884, rs41560220, rs9266265, rs188481108, rs1200371217, rs763308335, rs12660769, rs2854260, and rs461807. These loci are implicated in various carcinogenic pathways. Our Bayesian fine mapping identified five loci with a marginal posterior probability of causality > 0.99 and reduced the 99% credible set sizes for genomic loci. Moreover, our PRS derived from multi-ancestry summary data performed and predicted better than the PRSs derived from ancestry-specific data. In conclusion, we identified additional novel loci associated with cervical cancer and our fine mapping identified genomic loci with a high posterior probability of being causal

Poster Board **#11**

Lindsay M. LaFave, PhD
AACR Career Development Award in Lung Cancer Research

Loss of CEBPA Accelerates Lung Cancer Progression by Disrupting Immunity

Lung adenocarcinoma (LUAD) remains one of the leading causes of cancer-related mortality. Recent work using single-cell technologies has demonstrated the expansive heterogeneity and plasticity of lung cancer cells. Yet, there is a limited understanding of the mechanisms that drive lung cancer heterogeneity and therapeutic vulnerabilities introduced during this cellular diversification process. Our previous work showed that transformation of alveolar type 2 (AT2) cells, a predicted LUAD cell-of-origin, with KrasG12D and deletion of p53 leads to increased heterogeneity during lung cancer progression. This cellular plasticity is associated with chromatin reorganization and atypical activity of transcription factors involved in AT2 lineage identity, including loss of CEBPA activity. In this project, we aimed to investigate how CEBPA loss contributed to lung cancer heterogeneity using new CEBPA loss-of-function organoid and murine models. Depletion of CEBPA in AT2 organoids led to changes in genome-wide chromatin accessibility and gene expression as demonstrated with ATAC-seq and RNA-seq, and strikingly, included many genes which mediate immune regulation and antigen processing. Similarly, depletion of CEBPA in LUAD organoid and murine models led to exacerbation of lung cancer development, and increased heterogeneity as evidenced by single-cell ATAC-seq. Chromatin changes corresponded with distinct immune phenotypes, including altered macrophage infiltration. We identified other CEBP family proteins which modulate the epithelial-immune crosstalk in these models. Ongoing work will explore if these immune pathways are specific to KRAS-mutated malignancies, which are more commonly associated with prior smoking history, and if these pathways can be leveraged or targeted to improve immunotherapy response in LUAD patients.

Poster Board **#13**

Edwin R. Manuel, PhD

Lustgarten Foundation-AACR Pancreatic Cancer Career Development Award, In Honor of John Robert Lewis

Bacterial-Based Approaches to Target Heparan Sulfates in Pancreatic Tumors

Pancreatic ductal adenocarcinoma currently has the lowest 5-year survival rate among all major cancer types. Thus, novel treatment strategies are needed to improve patient survival. Heparan sulfonated proteoglycans (HSPGs) can be found in the tumor extracellular matrix (TEM) and play a significant role in pancreatic cancer growth, resistance and metastasis. The pro-tumor attributes of HSPGs are intimately tied to their cleavage by human heparanases. In contrast, several studies have reported that the use of bacterial heparanase III (HepIII) results in modification of tumor HSPGs that results in decreased tumor growth, invasion and metastasis. In this project, we have engineered tumor-colonizing bacterial vectors (attenuated Salmonella typhimurium) that express HepIII anchored to their outer membrane (ST-HepIII). We have performed in vitro studies that confirm the ability of ST-HepIII to cleave heparan sulfates and reduce their presence on the surface of pancreatic cancer cells, resulting in reduced proliferation and invasion. We have also confirmed the therapeutic potential of ST-HepIII in vivo and are currently performing metabolomic and spatial gene analysis studies to determine the effects of ST-HepIII treatment on tumor cell metabolism and survival. We hypothesize that ST-HepIII treatment reduces the ability of pancreatic cancer cells to obtain nutrients and that combinatorial approaches may help improve efficacy of currently available anabolic inhibitors.

Poster Board **#14**

Yehoda M. Martei, MD, MSCE

Breast Cancer Research Foundation-AACR Career Development Awards to Promote Diversity and Inclusion

Effectiveness of Community Health Workers on Access to Breast Cancer Care

Purpose: We aimed to 1) evaluate cancer outcomes in patients enrolled in a standardized Penn Medicine community health worker (CHW) from 2013-2023; 2) implement a pilot study to evaluate implementation outcomes of utilizing CHWs for breast cancer care delivery.

Methods: For Aim 1, participants who completed a standardized Penn Medicine CHW program, will be analyzed to identify an analytic cohort of participants who developed cancer using the Penn electronic medical records. Case control analysis will be conducted matching age, year of diagnosis, primary malignancy, zipcode and insurance. We will test for differences in cancer stage, no-show appointment rates and treatment completion. For Aim 2, eligible patients will include women, ≥18yo with breast cancer, residing in zipcodes with ≥20% poverty rates in Philadelphia. Effectiveness and implementation outcomes of the CHW program will be conducted.

Results: For Aim 1, 3111 patients enrolled in a CHW program from 2013-2017, of those 2696 (86.7%) successfully completed a standardized CHW program. Cancer outcomes will be reported later. For Aim 2, 9 patients have completed enrollment. Preliminary results show, 100% self-identified as Black, 80% as non-Hispanic. 75% screened positive for moderate-high cancer distress, and identified multiple barriers to care. Formal analysis will be completed at the end of enrollment.

Conclusions: Preliminary results show a high engagement rate of patients previously enrolled in a standardized CHW program. Final analysis will show how this impacts cancer outcomes. Breast cancer patients meeting our inclusion criteria may have higher than average reported cancer distress scores and multiple barriers to care.

Poster Board **#15**

Ryan H. Moy, MD, PhD

AACR-Debbie's Dream Foundation Innovation and Discovery Grant

Targeting CCNE1 Amplification in Gastric Cancer

Cyclin E1 (CCNE1) amplifications are found in ~10% of gastric cancers and drive DNA replication stress and chromosomal instability. In addition to promoting resistance to targeted therapy, CCNE1 amplification is also associated with immune cell exclusion. Recent synthetic lethality studies found that CCNE1-amplified tumors are vulnerable to loss of PKYMT1 kinase, a member of the Wee1 G2 checkpoint family that negatively regulates CDK1. However, the role of PKMYT1 inhibition in CCNE1-amplified gastric cancer and potential interactions with immunotherapy are not defined. Lunresertib (RP-6306) is a selective, first-in-class, oral PKMYT1 inhibitor that is currently in phase 1 clinical trials. PKMYT1 inhibition leads to unscheduled mitotic entry and chromosome pulverization selectively in CCNE1 overexpressing cells. Therefore, we hypothesized that DNA damage induced by PKMYT1 inhibition can trigger innate immune responses and synergize with immune checkpoint blockade. Using mouse three-dimensional organoids and patient-derived models of gastric cancer, we found that lunresertib induces robust DNA damage and cytotoxicity in CCNE1-amplified but not wild type models. In a syngeneic tumor xenograft mouse model of CCNE1 overexpressing gastric cancer, lunresertib or anti-PD1 monotherapy modestly reduced tumor growth, whereas the combination of lunresertib and anti-PD1 resulted in marked tumor regression suggesting potential synergy. Current studies are underway to define the effect of PKMYT1 inhibition on the tumor microenvironment and mechanism by which PKMYT1 inhibition modulates anti-tumor immunity. Overall, these studies will define CCNE1 amplification as an important biomarker and drug target in gastric cancer, providing rationale for clinical development of PKMYT1 inhibitor and immunotherapy combinations.

Poster Board **#16**

Mary M. Mullen, MD, MSCI

Victoria's Secret Global Fund for Women's Cancers Career Development Award, in partnership with Pelotonia & AACR

Targeting COPS5 and COPS6 to Overcome Platinum Chemotherapy Resistance

To identify potential candidates to enhance sensitivity to platinum chemotherapy, we conducted a high-throughput screen using short-interfering RNA to knock down 108 deubiquitinases in a chemotherapy-resistant ovarian cancer cell line, treated the cells with cisplatin, and stained for γH2AX, a DNA damage marker. COP9 signalosome complex subunit 6 (COPS6) was a top candidate. Depletion of COPS6 using CRISPR-Cas9 reduced cell viability by 60-70% in two additional platinum-resistant ovarian cancer cell lines. In an in vivo model, genetic depletion of COPS6 significantly decreased tumor burden in response to platinum chemotherapy ($P<0.001$). COPS6-deficient cells were more sensitive to PARP inhibitors, formaldehyde, and UV damage, indicating a role in nucleotide excision repair (NER). COPS5 depletion downregulated key NER proteins, but did not affect functional homologous recombination. In primary ovarian cancer cell lines, COPS6 expression was significantly associated with in vitro platinum resistance (Pearson $r=0.96$, $P=0.03$). Additionally, patients with high COPS6 expressing tumors ($n=41$) had decreased overall survival ($P = 0.11$). COPS5 is the enzymatic binding partner of COPS6. Inhibition of COPS5 with CSN5i-3 improved platinum sensitivity up to 90-fold in four established and three patient-derived ovarian cancer cell lines. CSN5i-3 synergized with platinum chemotherapy in eleven ovarian cancer cell lines (Loewe Synergy Score >10). A novel platinum-resistant syngeneic mouse model showed CSN5i-3 significantly improved tumor response and survival when combined with platinum chemotherapy compared to chemotherapy alone ($P=0.03$). Our work establishes COPS6 as a target and CSN5i-3 as a potential therapeutic to improve platinum sensitivity and improve outcomes for patients with cancer.

Poster Board **#17**

Chemtai Mungo, MD, MPH

Victoria's Secret Global Fund for Women's Cancers Career Development Award, in Partnership with Pelotonia & AACR

Cervical Cancer Prevention in Low-and Middle-Income Countries

BACKGROUND: Innovative strategies are needed to improve cervical intraepithelial neoplasia grade 2/3 (CIN2/3) treatment among women living with HIV (WLWH) in Sub-Saharan Africa (SSA), where recurrence rates reach 30%. While studies in high-income countries have demonstrated that 5-Fluorouracil (5FU) can reduce recurrence rates, no studies have investigated its use in SSA, despite the regions high burden of cervical cancer.

METHODS: A Phase I trial in Kenya evaluated the safety, tolerance and adherence to self-administered 5FU among 12 WLWH. Participants self-administered 2g of 5% 5FU intravaginally every other week for 8 applications. Safety was assessed with a standardized scale, and adherence was measured through self-report and objective methods.

RESULTS: The mean age and CD4 count were 43.9 years and 781 cells/mm3, respectively. The majority, 7 (58%) had an 8th-grade education or less. All participants reported at least one grade I adverse event (AE), 1 (8.3%) reported a grade 2 AE, and no grade 3 or 4 AEs were reported. Increased vaginal discharge 9 (75.0%) and irritation 5 (41.6%) were the most commonly reported AEs. Provider-observed AEs included grade 1 cervical erythema and superficial, minor epithelial disruptions. All participants tolerated eight 5FU doses, and 96% adherence was demonstrated.

CONCLUSION: Self-administered intravaginal 5FU was safe, tolerable, and had high adherence among women living with HIV in Kenya. Randomized trials are needed to determine if 5FU can improve CIN2/3 outcomes or serve as primary therapy in Africa. Such a treatment could significantly increase access and help achieve WHO elimination targets.

Poster Board **#18**

Mya L. Roberson, MSPH, PhD

Victoria's Secret Global Fund for Women's Cancers Career Development Award, in partnership with Pelotonia & AACR

Factors Affecting Cancer Germline Testing among Black Women

Introduction: The objective of this study was to evaluate patterns in breast cancer treatment by genetic testing and results among young Black women with breast cancer.

Methods: Study participants were a population-based sample of self-identified Black females diagnosed with invasive breast cancer ≤ age 50, recruited through two state cancer registries. Using survey data, participants were categorized three germline testing status groups: 1. Not tested; 2. Tested and not positive; and 3. Tested and positive for BRCA1/2. Using crude and adjusted logistic regression, we evaluated the impact of receipt of testing and on treatment received.

Results: A total of 350 Black women with testing status and completion of baseline questionnaire were included in the analysis. Median age of diagnosis was 44. For germline testing, 51 (14.6%) were not tested, 233 (66.7%) tested but were not BRCA+ positive, and 66 (18.9%) tested and were BRCA+. In fully adjusted models, women who received germline testing before their treatment began and were BRCA positive had substantially higher likelihood (aOR 22.01, 95% CI 5.94, 81.55) of receiving a bilateral mastectomy compared to untested women. BRCA+ participants were also more likely to receive chemotherapy and there was no association with receipt of radiation.

Conclusion: Our findings suggest that genetic testing may help support guideline-concordant cancer treatment decisions. Higher rates of chemotherapy among those with HR- and/or younger-onset disease are consistent with current best practices, and prior studies have suggested potential benefits in survival among those with positive test results, particularly regarding BRCA1 and BRCA2.

Poster Board **#19**

Rizine Robert Mzikamanda, MBBS, MMED

Beginning Investigator Grant for Catalytic Research (BIG Cat)

Acute Leukemia Diagnostics In Malawian Children

Introduction: Risk stratification and molecular targeting have been key to increasing cure rates for pediatric leukemia in high-resourced settings. Unfortunately, most children with leukemia live in low-resourced settings where insufficient pathology infrastructure leads to imprecise diagnosis and much poorer outcomes. This study aimed to assess the feasibility of implementing molecular assays to improve leukemia diagnoses in SSA.

Methods: Retrospective molecular testing was performed on 126 RNA samples from children with suspected leukemia. After validation with characterized samples in the US, a custom assay designed to detect gene fusions associated with leukemias was introduced at two SSA sites using the NanoString nCounter platform. Fusion results were analyzed blindly and then compared to morphology and flow cytometry results.

Results: Gene fusions were detected in B-ALL(33/56), AML(31/46), T-ALL(2/7), and CML(1/1) cases. No fusions were detected in nine non-leukemic samples. Thirteen cases failed for background or RNA quality. All results were consistent with flow-based immunophenotypes, including 6 PML::RARA fusions in known APL cases. Common B-ALL fusions were ETV6::RUNX1(9), BCR::ABL1 or Ph-like(6), and TCF3::PBX1(9). AML fusions were RUNX1::RUNX1T1(23), with NUP98, KMT2A, CBFB fusions also detected.

Conclusions: Initial results in SSA suggest gene fusion testing will define a more precise type of leukemia in greater than 60% of cases, allowing treatment centers in SSA to move toward incorporating risk stratification for optimized therapy and maximizing chances of a cure in children with leukemia. The 6 BCR::ABL1/Ph-like cases, if identified at diagnosis, could have been treated with a tyrosine kinase inhibitor available at the sites.

Poster Board **#20**

Carolina Reduzzi, PhD

2024 AACR-Lobular Breast Cancer Alliance-Deborah Mueller Foundation Fund Invasive Lobular Carcinoma Innovation and Discovery Grant

Investigating Differences in the Composition of Circulating Tumor Cells (CTCs) Clusters in Invasive Lobular and Ductal Carcinoma to Decipher Lobular Breast Cancer Metastasis

Background: Invasive lobular carcinoma (ILC) has distinctive clinical/genomic features compared with invasive ductal carcinoma (IDC); however, they are treated the same way. Better characterization of ILC is an unmet need. Liquid biopsy is a useful tool to achieve this. Previous studies showed that, compared to IDC, ILC has specific circulating tumor DNA alterations and higher counts of circulating tumor cells (CTCs) and CTC-clusters (CTC-CL, considered the main seed of metastasis). Here, we investigated differences in CTC-CLs according to the breast cancer histotype.

Methods: Blood samples collected from patients with metastatic breast cancer were processed with the CellSearch system. CTCs and CTC-CL were manually enumerated. The size of CTC-CL and presence of white blood cells (WBCs) in CTC-CL (heterotypic) were assessed.

Results: Of 351 included patients, 73% had IDC while 13% ILC. The presence of CTC-CL was higher in ILC (27% vs 11%, p=0.004) but the number of clustered-CTCs was lower (median=4.5 vs 9.5, p=0.039), suggesting a smaller cluster size in ILC. Indeed, the median and maximum number of CTCs/CTC-CL was numerically lower in ILC than IDC. Heterotypic CTC-CL were identified in 50% and 36% of ILC and IDC pts, with a trend for higher median (0 vs 2, p=0.37) and maximum WBC number (2.5 vs 3.5, p=0.26) in CTC-CL in ILC.

Conclusion: CTC-CLs in ILC appear to be different from IDC, being more numerous, smaller but more frequently containing WBCs. This suggests a possible different biology for CTC-CL formation in ILC, which should be further investigated in future studies.

Poster Board **#21**
Zuen Ren, MD, PhD
AACR-Pfizer Breast Cancer Research Fellowship

Molecular Analysis of BRCA1/2 Genetic Carriers Revealed the Early Pathogenesis of Hereditary Breast Cancer Development

Women who harbor germline heterozygous mutations of BRCA1 or BRCA2 have a high risk of hereditary breast cancer. We have shown that age-associated expansion of BRCA2mut/+ luminal progenitors (LPs), the suspected cancer cells of origin, are more prone to exhibit subchromosomal copy number variations and associated DNA damage. The clinically assessable biomarkers for early pathological alterations of BRCA1/2 mutation in LPs remain unmet need. Single-cell RNA sequencing revealed enrichment of KIT expression (KIT+) and subsequent transcriptional factor activations were observed in LPs of BRCA1/2mut/+ carriers relative to non-carriers. Gene set enrichment analysis (GSEA) revealed that KIT+ BRCA mut/+ LPs were abundantly enriched in pathways involving DNA binding transcription activator activity and oxidative phosphorylation. In vitro modeling of CRISPR knock-in of BRCA1/2 mutation in MCF10A cells revealed that BRCA1/2 mutation promotes single stranded DNA gap formation in stalled DNA fork which is one source of DNA replication stress. Moreover, whole genome sequencing of MCF10A BRCA1 mut/+ cells uncovered significantly high percentage of single base substitutions particularly with cytosine (C) to adenine (A) (C>A) alteration due to reactive oxygen species insulting from oxidative phosphorylation that may be a potential mechanistic link to DNA gap formation. Collectively, our study may identify potential biomarkers of the risk prediction for early pathogenesis of BRCA1/2 mut/+ carriers. Following validation of our findings via tissue microassay analysis and clinical trials, we expect to ultimately assist clinicians in their decision making of prophylactic surgeries for BRCA1/2 mutation carriers.

Poster Board **#22**

Evanthia Roussos Torres, MD, PhD

Breast Cancer Research Foundation-AACR Career Development Awards to Promote Diversity and Inclusion

Suppressing Suppression: A Myeloid Centric Approach to an Anti-Tumor Immune Response in Breast Cancer

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In our Phase Ib trial (NCI-9844) we found that the combination of histone deacetylase inhibitor, entinostat, with dual ICI (anti-PD1 and anti-CTLA4), led to a 25% objective response rate in patients with metastatic HER2 negative breast cancer. Our preclinical studies also support response in mouse models and show decreased infiltration or suppression of myeloid derived suppressor cells (MDSCs) by entinostat as a potential mechanism of action. Here, we examined breast-to lung metastases to gain a comprehensive understanding of changes to the tumor immune microenvironment within the metastatic niche induced by treatment with entinostat and perpetuated after treatment with dual ICI. Single cell RNA sequencing of treated lung metastasis revealed significant shifts in macrophages, dendritic cells, and some T and B cell populations. Entinostat treatment increased stemness in tumor cells and decreased mesenchymal gene expression. Cell circuit and CellChat analysis revealed significant effects on MDSC- CD8-T cell, macrophage- CD8-T cell and NK- G-MDSC/ CD8-T cell interactions. Ligand receptor pair analysis revealed signaling pathways controlling chemokine secretion, and cell adhesion are significantly decreased following treatment with entinostat and are preserved with dual ICI therapy. We are investigating 6 candidate targets on MDSCs and macrophages using ex-vivo suppression assays to determine the contribution of these signaling axes in decreasing immunosuppressive function within the TME. Evaluation of patient samples via CyTOF suggests a significant decrease in MDSC-CD8-T cell and Macrophage-CD8-T cell interaction in responders. Overall, entinostat decreases immune suppression via interference of MDSC and macrophage interaction with CD8-T cells.

Poster Board **#23**

Lia C. Scott, PhD

AACR Career Development Award to Further Diversity, Equity, and Inclusion in Cancer Research

Disparities in Breast Cancer Incidence by Hormone Receptor Status Among US Women from 2016-2020, a Population-Based Study

Breast cancer diagnoses differ by hormone receptor status between racial and ethnic groups, age and stage, with Black women and younger women experiencing a higher frequency of adverse histological features. Using a cross-sectional approach and data from the National Program of Cancer Registries restricted-access dataset, we aimed to identify population-level differences in breast cancer incidence among women age 20 to 84 by race and ethnicity, age, stage and hormone receptor status. Multivariable adjusted polytomous regression was used to evaluate joint hormone receptor status distribution by age, race and ethnicity and stage at diagnosis.

Of the 1,168,176 cases of female invasive, malignant breast cancer diagnosed from 2016-2020, most were classified as Luminal A (73.3%), followed by triple-negative (13.1%), Luminal B (9.7%) and ERRB2-enriched (3.9%). Most cases were age 50 to 64 (37.0%), White (82.4%) and local stage (67.9%). Compared to Luminal A cases, triple-negative and Luminal B cases were more likely to be under the age of 50, while ERRB2-enriched cases were more likely to be age 20 to 39. Triple-negative cases were more likely to be Black, American Indian/Alaskan Native, or diagnosed at regional or distant stage, with cases age 20 to 39, Black and distant stage having more than twice the odds of diagnosis. Luminal B cases were 20% more likely to be Black or Asian/Pacific Islander and ERRB2-enriched cases were more likely to be Black, American Indian/Alaskan Native or Asian/Pacific Islander with the highest odds for the latter group. Triple-negative and Luminal B were more than twice as likely to be diagnosed at distant stage and ERRB2-enriched was over 3 times as likely to be diagnosed at distant stage.

This data highlights stark differences in age, stage and race by hormone receptor status. Future work can continue to explore additional clinicopathologic characteristics that characterize these differences that serve as a foundation for breast cancer disparity research.

Poster Board **#24**

Stuart J. Smith, PhD

AACR-Novocure Tumor Treating Fields Research Grant

Combining Tumor Treating Fields with Ion Channel Blockade

Glioblastoma (GBM) is a leading cause of cancer-related death in adults under 40. Electrophysiological activity mediated by conductive ion channels plays a crucial role in the progression of brain tumors. Using bioinformatic analysis of publicly available genomic datasets we have identified ion channel targets that seem to be particularly crucial in GBM and response to Tumor Treating Fields, including BK channels and the SCNN sodium channel family.

We have validated the expression levels of these channels in low passage patient derived GBM cell lines and tissue specimens of high- and low-grade gliomas, with strong support for a role for SCNN1D in particular. We observe upregulation of SCNN1D at RNA and protein levels in GBM compared to normal astrocytes.

Inhibitors of SCNN ion channels have been tested against GBM cell lines, demonstrating antiproliferative effects, both alone and in combination with temozolomide. We also demonstrate potentiation of Tumor Treating Fields in combination with inhibitors of SCNN channels, suggesting possible future therapeutic strategy.

Electrophysiological studies have also been conducted to evaluate the functional contribution of different ion channels to the cellular membrane potential. We demonstrate that GBM cells exist at a significantly more depolarized membrane potential than normal astrocytes, a change that has previously been associated with elevated cell cycling and malignant potential. BK potassium channels seem to be the dominant influence in GBM cells.

Our study suggests a potential novel mechanism for the electrical field based Optune treatment, with antiproliferative effects mediated via alterations to membrane potential and ion channel conductivity.

Poster Board **#25**

Timothy Spear, MD, PhD

Friends of the AACR Foundation Early Career Investigator Award

Targeting Neuroblastoma Intracellular Oncoprotein PHOX2B with Peptide-Centric CAR-T Cells and mRNA-LNP Vaccination Boost

We recently described a novel class of “peptide-centric” chimeric antigen receptors (PC-CARs), where antigen specificity is directed against a peptide presented by MHC rather than a plasma membrane protein (Yarmarkovich, Nature 2023). We showed that a PC-CAR targeting a peptide from the intracellular neuroblastoma (NB) oncogenic driver PHOX2B presented by HLA-A*24:02 showed promising anti-tumor efficacy against patient-derived xenografts (PDXs). This CAR is planned for clinical trials for relapsed/refractory high-risk NB in Q1 2025. While PC-CAR T cells induced PDX remission, CAR T cells rapidly disappear without antigenic stimulus, allowing for late relapses in some mice. To address these limitations, we developed a first-in-class immunocompetent murine model to study PC-CARs. Our TH-MYCNTg/Tg, TH-Cre, Sdhbfl/wt genetically engineered mouse model (GEMM) develops spontaneous NB tumors fully penetrant in CB57BL/6 and with tumors transplantable as allografts. TH-MYCN BL/6 GEMM crossed with HLA-A-A*24:02 transgenic mice and syngeneic allografts engineered with a novel single chain trimer (SCT) chimeric human/mouse pMHC (PHOX2B/A24/H-2Kb) provide two immunocompetent systems for PC-CARs. GEMM-derived A24+ allografts are killed by an orthogonal second-generation murine (m)PC-CAR containing scFv conserved to our clinical product, conjoined to murine 4-1BB and CD3ζ. To address waning CAR T cell persistence, we developed an mRNA-lipid nanoparticle vaccine encoding 9mer antigen, which is presented by A24+/H-2Kb-engineered murine DCs and induces expansion of mPC-CAR T cells. Validation in autologously-matched HLA-A*24:02 human products are ongoing. Our first-in-class model to study CAR T cells targeting HLA-presented oncogenic drivers with vaccination boost has potential to transform CAR T cell therapy for pediatric solid malignancies.

Poster Board **#26**

Peter M. Westcott, PhD

AACR Gertrude B. Elion Cancer Research Award

Deconstructing Benign-to-Malignant Transition at Spatiotemporal Resolution

Colorectal cancer (CRC) is now the first and second leading cause of cancer-related deaths in men and women under 50, respectively, upending prior predictions. While many risk factors have been identified, the etiology of early onset disease is poorly understood and it is unclear why some benign polyps progress to CRC while most do not. The genetic drivers of colon tumor initiation and progression to malignancy are likely insufficient to drive disease on their own, as evidenced by the near ubiquitous presence of oncogenic mutations within morphologically “normal” adult tissues like the colon. This raises a number of fundamental questions: 1) what are the pioneering molecular and cellular events underlying benign-to-malignant transition following oncogenic mutation? 2) Is this sequence of events predetermined by cancer genetics or are additional (micro)environmental stimuli necessary? 3) How does the benign-to-malignant transition reshape tumor clonal architecture and is this immunogenic? We propose to address these questions using a combination of rare human colon polyps with evidence of early cancer (intramucosal carcinoma) and new autochthonous mouse models of stepwise colon cancer progression we developed. Preliminary spatial transcriptomic analyses of two human specimens revealed distinct gene programs of early progression and a unique immune infiltrate associated with intramucosal carcinoma. We also observed a restructuring of the colonic stem cell niche within the early carcinoma, which we validated in our mouse model. By delineating the earliest events underlying cancer progression, the proposed work may inform new strategies for early detection and prevention.

Poster Board **#27**

Kipp Weiskopf, MD, PhD

AACR-AstraZeneca Career Development Award for Physician-Scientists, in Honor of José Baselga

Unbiased Discovery of Novel Antibody Therapies to Stimulate Macrophage-Mediated Destruction of Aggressive B-Cell Lymphomas

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Macrophages are critical innate effectors of antibody therapies for lymphoma, but their phagocytic capacity is limited by the CD47/SIRPa interaction, a macrophage immune checkpoint. Here, we sought to define a comprehensive repertoire of cell surface antigens that can be targeted to stimulate macrophage-mediated destruction of B-cell lymphoma either alone, in combination with CD47 blockade, or in combination with anti-CD20. We developed a high-throughput functional screening platform to measure the ability of primary macrophages to attack B-cell lymphoma cells. We successfully applied this system to screen monoclonal antibody libraries targeting hundreds of distinct cell surface antigens across both mouse and human systems. We identified several new and unappreciated targets for opsonization, and used this information to generate a compendium of 156 novel bispecific antibodies. We discovered dozens of highly active bispecifics that could dramatically stimulate macrophage-mediated cytotoxicity of B-cell lymphoma. Among these, a bispecific comprising a SIRPa decoy domain and a CD38 binding arm (WTa2d1xCD38) exhibited maximal efficacy while minimizing risks of hematologic toxicity. In vivo, this bispecific stimulated robust anti-tumor responses in multiple mouse models of B-cell lymphoma, including an extremely aggressive model of primary CNS lymphoma. Overall, we have developed a multitude of novel therapeutic candidates and combination strategies that can be developed further to employ macrophages as effector cells to benefit patients with B-cell lymphoma. Furthermore, our approach can be rapidly applied to other cancers to create innovative bispecifics that leverage anti-tumor responses by macrophages or other innate immune cells.

Poster Board **#28**

Hsiwen Yeh, PhD

AACR Anna D. Barker Basic Cancer Research Fellowship

Mitochondrial GSH Import by SLC25A39 is Essential for Metastatic Colonization of Breast Cancer Cells

Cancer cells undergo significant metabolic adaptations crucial for supporting their growth and survival during metastasis to distant organs. Understanding alterations in metabolite abundance during this process and their potential therapeutic implications remains a critical gap in current research. Here, employing a mitochondrial metabolomics approach, we investigated distinct metabolic profiles in mitochondria of primary versus metastatic breast cancer cells. Our analysis revealed a notable upregulation of mitochondrial glutathione (GSH) specifically during metastasis, attributed to increased expression of SLC25A39, a mitochondrial GSH transporter. Functionally, depletion of SLC25A39 hindered metastatic colonization of breast cancer cells in lung models, including patient-derived xenografts, while leaving primary tumor growth unaffected. Importantly, we established that mitochondrial GSH import plays a pivotal role in the initial colonization phase of metastasis independent of its conventional antioxidant function. Furthermore, through a CRISPR activation screen, we uncovered that activation of the integrated stress response (ISR) pathway can rescue the anti-metastatic effects of SLC25A39 loss, suggesting a mechanistic interplay between these pathways. Collectively, our findings highlight mitochondrial GSH as a critical and limiting metabolite essential for facilitating breast cancer metastasis.

Poster Board **#29**

Yao Yu, PhD

AACR Sarcoma Research Fellowship

Pharmacologic Degradation of WDR5 Suppresses Oncogenic Activities of SS18-SSX and Provides a Therapeutic of Synovial Sarcoma

Disease-causing aberrations of rare and childhood cancers recurrently target the chromatin pathway genes leading to epigenetic dysregulation. For example, almost 100% of patients with synovial sarcoma (SS) carry an abnormal gene fusion termed SS18-SSX, which produces a disease-specific onco-fusion protein that is incorporated into the SWI/SNF chromatin-remodeling complex and profoundly alters its functionalities. Thus, targeting epigenetic dependencies in these cancer holds great promise for improving current treatment of the affected patients. Leveraging on the cancer cell dependency data, medicinal chemistry tool compounds and genomic profiling approaches, we here show WDR5, a chromatin factor involved in the deposition of histone H3 lysine 4 (H3K4) methylation, to be an unexplored vulnerability of SS. Mechanistically, WDR5 and SS18-SSX associate with one another and colocalize significantly at the target oncogenes where WDR5 is essential for optimal H3K4 methylation and for the chromatin binding of the SS18-SSX-containing chromatin modelers. Using the WDR5-targeting Proteolysis Targeting Chimera (PROTAC) compound, we further show that pharmacologic degradation of WDR5 in SS cells not only suppressed the SS18-SSX-related oncogenic gene-expression programs but additionally led to p53 activation and tumor cell senescence through downregulation of ribosomal proteins (RPs) and activation of nucleolar stress response. Importantly, the WDR5-targeted PROTAC significantly suppressed malignant growth of SS in vitro and in vivo. Taken together, we report WDR5 as a SS dependency and demonstrate the WDR5 PROTAC small-molecule to be a promising strategy for the treatment of SS.

Poster Board **#30**

Mingzeng Zhang, MD, PhD
AACR-Incyte Immuno-oncology Research Fellowship

Quantitative Immune Profiling of Follicular Lymphoma for Precision Therapy

Follicular lymphoma (FL) is a common non-Hodgkin lymphoma in need of novel therapies and biomarkers, especially for first-line treatment. Bispecific T cell-engaging antibodies targeting CD3 and CD20 (CD3/CD20 BsAbs) are emerging therapies showing promise in relapsed and refractory cases. We hypothesize quantitative immune profiling will uncover predictive biomarkers for clinical response and toxicity after first-line treatment with CD3/CD20 BsAbs, utilizing patient cohorts from two early-phase clinical trials.

We applied quantitative tissue imaging via multiplex immunofluorescence panels customized for FL and to define the immune topology of diagnostic FL tissue specimens and interrogate this topology for correlates of clinical outcomes. Simultaneously, we are tracking circulating immune cell subsets from PBMCs and plasma cytokines to define peripheral immune signatures. Preliminary data of PBMC samples from twelve trial patients with FL via mass cytometry showed higher percentages of CD161+ gamma delta (γδ) T cells in patients with G2-4 Cytokine Release Syndrome (CRS) than in those with G0-1 CRS, the most common immune-related adverse event. Additionally, the expression of Ki67 in CD57+ γδ T cells was higher in patients with G2-4 CRS. These results will contribute to identifying peripheral immune signatures that correlate with FL tissue topology and clinical outcomes in pursuit of more actionable, dynamic immune biomarkers derived from peripheral blood.

Preliminary results suggest variations in immune profiles, necessitating further investigation with larger sample sizes to confirm trends and identify specific biomarkers predictive of clinical outcomes. Future research will expand sample sizes and explore immune mechanisms to enhance FL treatment strategies and outcomes.

Poster Board **#31**

Xiaotian Zhang Ph.D.

AACR-MPM Oncology Charitable Foundation Transformative Cancer Research Grant

Mutant NPM1 Hijacks Active Transcriptional Machinery to Maintain Pathogenic Gene Programs in AML through Altered Condensate Formation

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Nucleophosmin (NPM1) is a nucleolar protein with a wide range of functions including ribosome biogenesis and ribosome RNA maturation. In acute myeloid leukemia (AML), the terminal exon of NPM1 is mutated in 30% of AMLs, changing the nucleolar localization signal (NoLS) into a nuclear export signal and a location shift of the mutant protein to the cytoplasm (NPM1c). AMLs carrying this mutation have aberrant expression of the HOXA/B cluster, MEIS1 genes, whose overexpression leads to leukemogenic transformation.

We previously show that NPM1c binds to a subset of active gene promoters in NPM1c leukemia cell lines and primary leukemia blasts at the HOXA/B cluster, MEIS1 genes. We showed the binding of NPM1c on chromatin amplified active transcription of key target genes by maintaining high local-concentration of transcriptional complexes. Yet, NPM1wt forms liquid-liquid mediated phase separation (LLPS) while NPM1c also keep the same intrinsic disordered region (IDR) essential for LLPS. Therefore, we start to study the mechanism of condensate formation of NPM1wt vs NPM1c. We used the purified protein for NPM1wt and NPM1c, and found both proteins is able to form condensate upon purification with low salt. Yet, NPM1c lost the NPM1wt condensate formation ability induced by ribosomal RNA. We further added back NoLS to NPM1c and rescued the ribosomal RNA induced NPM1c condensate to NPM1wt level. Importantly, we could see NPM1c and NPM1wt form much weak interactions in comparison with NPM1c-NPM1c and NPM1wt-wt interaction, showing NPM1c forms novel distinct condensate other than NPM1wt.

Our data suggests NPM1c lost the key RNA binding domain for the formation of LLPS and obtain the neomorphic function to hijack and amplify the gene expression.

Poster Board **#32**

Binbin Zheng-Lin, MD, MSc
AACR-AstraZeneca Clinical Immuno-Oncology Research Training Fellowship (CORE)

Low RNA Expression of Wild-Type (wt) Homologous Recombination (HR) Genes Predicts Substantially Longer Overall Survival (OS) in Advanced Pancreatic Adenocarcinoma (PDAC) Treated with Platinum Therapy

Advanced PDAC with HR deficiency (HRD) benefits from DNA-damaging agents. Nevertheless, their use is restricted to only 5–9% of cases with germline *BRCA1/2* or *PALB2* mutations. Additional mechanisms may impair unmutated HR genes, inducing an undetected HRD phenotype.

METHODS: Whole exome and transcriptome sequencing of 14,061 advanced PDAC cases were performed by Caris Molecular Science. RNA expressions for each wtHR gene were normalized and divided into quartiles. Overall survival (OS) was stratified by platinum exposure (cisplatin, oxaliplatin, carboplatin) and RNA expression quartiles. Events were extracted from insurance claims.

RESULTS: Patients with mutated *BRCA1* had similar survival to those in the bottom quartile of *wtBRCA1* expression (median OS 12.57 vs. 14.58 months; HR 1.01, 95% CI 0.797-1.28, p=0.931), indicating similar functional HRD. With platinum treatment, those in the bottom quartile of *wtBRCA1* expression had longer survival compared to the top quartile (median OS 17.93 vs. 10.40 months; HR 1.58, 95% CI 1.42-1.75, p<0.00001). The bottom quartile cohort had lower median OS without platinum treatment (12.57 months, 95% CI 11.74-13.22). Similar results were seen in other wtHR genes, including *BRCA2, RAD51*, and *FANCA*, with significant median OS differences of approximately 5 months with platinum treatment.

CONCLUSION: A significant percentage of advanced PDAC patients with unmutated HR genes may benefit from DNA-damaging agents. Our findings support using mFOLFIRINOX over gemcitabine/nab-paclitaxel in patients and may provide improved inclusion criteria for trials testing PARP inhibitors like olaparib. Comprehensive analysis with all HR genes and external validation using past trial data are ongoing.

Poster Board **#33**

Jin Zhou, PhD

AACR-Exelixis Renal Cell Carcinoma Research Fellowship

RBM39-DGAT1 Axis Serves as an Oncogenic Driver in Clear Cell Renal Cell Carcinoma

Accounting for 85% of renal cancers, clear cell renal cell carcinoma (ccRCC) is a lethal disease that is classically resistant to cytotoxic chemotherapy. JMJD6 has been identified to play critical roles in ccRCC tumorigenesis. DGAT1 is an enzyme critical for triglyceride synthesis which is a direct target gene of JMJD6. Mechanistically, JMJD6 interacts with RBM39, co-occupies *DGAT1* gene promoter to induce *DGAT1* expression. Depletion of *JMJD6* or *DGAT1* inhibites ccRCC tumorigenesis; however, the efficacy of DGAT1 inhibitor is limited in preclinical ccRCC models. RBM39 is an emerging cancer target, and its protein degrader, indisulam, has shown good inhibitory effects on solid cancers in clinical trials. However, the role of RBM39 in ccRCC tumorigenesis has not been characterized before. Our findings show that both indisulam treatment and *RBM39* knockdown induce cell growth defects in multiple ccRCC cell lines. Additionally, *RBM39* knockdown decreases tumor growth in animal models. RNAseq data of *RBM39* knockdown reveal that cell metabolism is involved in the defective effects of RBM39 on ccRCC cell growth. Further study will be conducted to verify the exact mechanism by which cell metabolism mediates the role of RBM39 and the effect of indisulam in vivo. We will also explore whether indisulam-induced decreased *DGAT1* expression could potentially compensate for the limited efficacy of DGAT1 inhibitors. By investigating if lower doses can be applied in combination treatment to reduce toxicity in mice, we aim to develop a better therapeutic strategy for kidney cancer.