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Poster Board **#1**

Kim Blenman, PhD, MS

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

Characterization of Pre-Existing Autoantibodies in Breast Cancer

It is hypothesized that pre-existing autoantibodies have a role in immune-related adverse events induced by the drug treatments that we give patients with cancers, such as breast cancer. If we could identify these autoantibodies, it could help the medical and scientific community to better understand why these immune related adverse events are happening and identify potential drug targets to help reduce the effects of the adverse event or prevent it all together. The purpose of this study was to find pre-existing autoantibodies in patients with breast cancer treated with anti-PD-L1 immunotherapy and who have experienced a drug-induced thyroid disease (i.e., hypothyroidism) as an immune-related adverse event. From >21,000 autoantibody candidates, we found 2 autoantibodies (NFKB2; EMCN) that may potentially cause drug-induced thyroid disease and 2 autoantibodies (MLIP; LMOD1) that may be protective against drug-induced thyroid disease. We have also identified the target sites on proteins that these specific autoantibodies bind. In future studies these targets will be validated in larger numbers of patients with breast cancer and other cancers and the role of these targets in the drug-induced thyroid disease will be evaluated in human cell lines and animal models. This study has contributed to cancer research by providing potentially new drug targets and screening tools for drug-induced immune related adverse events. These contributions could help cancer patients in the future by improving their experience with the drug therapies that are given for their cancers.

Poster Board **#2**

Maria Teresita Branham, PhD

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

ID4 Loss Reprograms Triple-Negative Breast Cancer Toward a Differentiated Phenotype and Reveals a Therapeutic Vulnerability

Background: Triple-negative breast cancer (TNBC) remains one of the most aggressive subtypes, lacking targeted therapies. The transcriptional regulator ID4 is frequently overexpressed in basal-like TNBC and associated with poor prognosis. Preliminary results suggest that targeting ID4 may reprogram TNBC cells toward a less aggressive, more differentiated state. These findings provide the foundation for our recently awarded BCRF-AACR project aimed at investigating the molecular mechanisms and therapeutic implications of ID4 loss in TNBC.

Objective: To evaluate whether ID4 loss reprograms TNBC toward a differentiated, less aggressive phenotype and uncovers actionable therapeutic targets.

Methods: ID4 was silenced in MDA-MB-231 cells using CRISPR-Cas9. Phenotypic assays and transcriptomic analysis of TCGA basal-like TNBC tumors stratified by ID4 expression were conducted. AGX51-induced ID4 degradation was tested in vitro and in vivo.

Results: ID4 knockout markedly reduced cell proliferation, colony formation, and in vivo tumor growth. Transcriptomic profiling of ID4-low basal-like tumors revealed enrichment for luminal differentiation (Hallmark Estrogen Response Early/Late) and immune activation (Interferon Gamma/Alpha Response) pathways. ID4 loss increased ER and GATA3 expression in vitro. AGX51-mediated degradation of ID4 mirrored these effects, suppressed tumor growth in vivo without toxicity, and reduced proliferation. Preliminary data suggest AGX51 may also impair TNBC stem-like cell function.

Conclusions: These findings position ID4 as a key driver of TNBC plasticity and suggest that its loss may reprogram TNBC toward a more differentiated phenotype. Future studies will define the mechanisms of ID4-driven reprogramming, evaluate its therapeutic potential, and assess endocrine therapy sensitization as part of our BCRF-AACR–supported project.

Poster Board **#3**

Alejandro J. Cagnoni, PhD
AACR Maximizing Opportunity for New Advancements in Research in Cancer (MONARCA) Grants for Latin America

Targeting Glycocheckpoint Galectin-1 to Overcome Immunotherapy Resistance in Colorectal Cancer

Colorectal cancer (CRC) represents the third most common malignancy and the second leading cause of cancer related deaths worldwide. Although immune checkpoint blockade therapies have achieved long-term responses in several malignancies, in CRC, their clinical benefit is still limited. Thus, identification of novel biomarkers and additional therapeutic modalities for CRC are urgently required.
Galectin-1 (Gal-1), an evolutionary-conserved glycan-binding protein, has emerged as a key player in immune evasion programs. Gal-1 is upregulated in CRC tumor tissues, inducing tolerogenic programs and favoring tumor evasion. Moreover, Gal-1 has been proposed as a biomarker of poor prognosis in different tumor types and as a predictor of the response to immunotherapy.
In this project we propose a dual approach towards determining the role of Gal-1 on CRC, both as a biomarker of response to immunotherapy and as an immunotherapeutic target. First, we will evaluate the capacity of Gal-1 as a biomarker of resistance to anti-PD-1 therapy. For that aim, we will perform a longitudinal study to assess the expression of circulating Gal-1 on plasma samples from a local cohort of Argentine CRC patients, before and after immunotherapeutic treatment. Furthermore, we aim at establishing the effect of Gal-1 blockade with a newly developed anti-Gal-1 neutralizing monoclonal antibody on CRC animal experimental models, i.e. a chemically induced model and an orthotopic model of metastatic CRC. In this context, considering the acute need for novel therapeutic strategies to hamper CRC progression and overcome resistance to anticancer therapies, galectin glycocheckpoints emerge as novel biomarkers and therapeutic targets with great potential of translation into the clinical practice.

Poster Board **#4**

Denisse A. Castro Uriol, MS, MD

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

Understanding the Molecular Basis and Transformation Risk in HTLV-1-Associated Adult T Cell Leukemia/Lymphoma (ATLL)

Background. Adult T-cell leukemia/lymphoma (ATLL) is an aggressive hematologic), with no established standard of care and poor outcomes. Hypothesis. We hypothesize that Latin American ATLL cases differ biologically from those in other regions. This study has three aims: (1) to investigate clinical, viral, and molecular factors linked to higher risk of malignant transformation in HTLV-1 carriers; (2) to identify genomic drivers of ATLL in Peruvian patients with HTLV-1 infection and a family history of ATLL; and (3) to develop and validate a predictive model to estimate ATLL risk in HTLV-1 carriers. Methods. A multicenter prospective cohort was established in Peru in collaboration with five academic institutions. Aim 1 involves enrolling 300 asymptomatic HTLV-1 carriers (aged ≥18), collecting clinical data and biological samples, and monitoring HTLV-1 proviral load (PVL) and clonality every six months. Aim 2 includes whole genome sequencing (WGS) on 24 individuals (HTLV-1 positive and negative) from four families affected by ATLL, with segregation analysis to identify pathogenic variants. Aim 3 will generate a predictive risk model using data from Aims 1 and 2 and validate it in 200 additional HTLV-1 carriers from Apurímac, Peru. Preliminary results. Launched in February 2025, the study is ongoing. To date, 13 ATL patients and 26 family members (18 HTLV-1 positive, 8 negative) have been enrolled. DNA and serum samples have been collected and are awaiting PVL and clonality analysis. Conclusions. This underscores the importance of family screening. PVL and clonality are promising biomarkers for ATLL risk assessment and treatment monitoring.

Poster Board **#5**

Nika Danial, PhD

AACR-MPM Oncology Charitable Foundation Transformative Cancer Research Grant

Identification of Lipid-Targeted Molecular Regulators of H3K27M

Histone mutant diffuse midline gliomas (H3K27M DMGs) are lethal tumors driven by progenitor-like cells that subvert normal differentiation. These gliomas retain some developmental plasticity, where H3K27M glial progenitors can partially differentiate to glial-like cells and a concomitant loss of tumorigenic capacity. We have recently found that n3-polyunsaturated fatty acids (n3-PUFAs), a class of semi-essential lipids present in serum and diet, are necessary and sufficient for differentiation of H3K27M glial progenitors. Importantly, dietary enrichment of n3-PUFAs in the brain triggers this developmental shift in H3K27M DMG orthotopic models, reduces tumor burden, and increases survival. As n3-PUFAs are known to act through binding of protein targets, we hypothesize that these lipids directly bind specific proteins to alter downstream pathways permissive to differentiation. To identify potential pro-differentiation mediators in H3K27M DMG, we have profiled n3-PUFA protein interactors using cellular thermal shift assay (CETSA) and capture with bioorthogonal lipid probes. Preliminary results revealed candidate n3-PUFA interactors that will be functionally validated in H3K27M DMG cell models. Understanding lipid-dependent mechanisms controlling lineage differentiation in H3K27M DMGs will provide important mechanistic advancements in understanding how cellular hierarchies are established in H3K27M DMGs. In the fullness of time, this work may lead to the development of glioma-inhibitory strategies with therapeutic potential.

Poster Board **#6**

Mercedes B. Fuertes, PhD

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

Monoclonal Antibody-Based Immunotherapy Against MICA in Triple Negative Breast Cancer

Triple-negative breast cancer (TNBC), which lacks HER2 and hormone receptors, accounts for 10–15% of breast cancers and is associated with aggressive growth, poor differentiation, and limited treatment options.

MHC class I-chain related gene A (MICA) is a stress-induced protein expressed on tumor cells but absent in normal tissues, making it an attractive therapeutic target. We developed an anti-MICA monoclonal antibody (mAb) that induces antibody-dependent cellular cytotoxicity (ADCC) by NK cells, promotes antibody-dependent cellular phagocytosis, and removes immunosuppressive soluble MICA via macrophages. This mAb has demonstrated efficacy in preclinical lymphoma and renal carcinoma models. As MICA is expressed in TNBC and upregulated by chemotherapy, we hypothesize that MICA-targeted immunotherapy will improve TNBC outcomes.

Preliminary data show MICA expression in multiple human TNBC cell lines and robust ADCC induction by our humanized mAb. In an aggressive murine TNBC model, the combination of our anti-MICA with anti-PD-1 induced complete and durable responses.

This project will evaluate the therapeutic efficacy and underlying mechanisms of our anti-MICA mAb and an antibody-drug conjugate (ADC) derived from it in syngeneic and xenogeneic TNBC models, in combination with chemotherapy or immune checkpoint inhibitors. To support clinical translation, we will analyze TNBC patient biopsies to quantify MICA expression and perform ex vivo assays to assess the cytotoxic potential of these agents, ultimately estimating the proportion of patients who may benefit from MICA-targeted therapies.

By advancing MICA-targeted therapies, this work aims to develop a precision approach for TNBC, with potential applicability to other breast cancer subtypes.

Poster Board **#7**

Francesca S. Gazzaniga, PhD

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

Targeting Microbiome-Immune Interactions in Triple Negative Breast Cancer

Triple Negative Breast Cancer (TNBC) is a subtype of breast cancer that is treated with chemotherapy and an antibody targeting the immune checkpoint inhibitor, Programmed Cell Death Protein 1 (PD-1). However, the prognosis remains poor for the 40% of patients who do not respond. The gut microbiota has been implicated in the anti-tumor response to immunotherapy, yet how the microbiome impacts response to treatment in TNBC remains unknown. We identified Repulsive Guidance Molecule b (RGMb) and Programmed Cell Death Ligand 2 (PD-L2) as putative cancer immunotherapy biomarkers and targets that are modulated by the gut microbiota. We demonstrated that healthy microbiomes suppress RGMb/PD-L2 on immune cells, and blockade of RGMb/PD-L2 interactions increases the efficacy of PD-1 blockade in a preclinical mouse model of breast cancer. Whether RGMb/PD-L2 expression correlates with response in patients is unknown. Our central hypothesis is that high RGMb expression on tumor infiltrating T cells and high PD-L2 expression by either immune or cancer cells are associated with worse response rates. To test this hypothesis, we constructed tumor microarrays of biopsies from TNBC patients prior to treatment and stained them with a panel of thirty-two immune and tumor markers. Spatial analysis revealed interactions between RGMb+ CD8 T cells and PD-L2 expressing cells were significantly higher in tumors that recurred versus tumors that had no recurrence. These results indicate that RGMb/PD-L2 co-localization could be a biomarker for recurrence in TNBC. Furthermore, these results suggest that RGMb/PD-L2 disrupting antibodies could serve as novel treatments to increase TNBC responses.

Poster Board **#8**

Chloe M. Hery, MS, PhD
AACR-Merck Cancer Disparities Research Fellowship

The Sleep After Breast Cancer (Sleep ABC) Study: Examining Sleep Changes and Biopsychosocial Factors in Breast Cancer Patients

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Background: Marginalized groups and those with a cancer diagnosis have higher stress and poorer sleep quality. Sleep interventions targeting Social Determinants of Health (SDoH) could reduce breast cancer (BC) related disparities, as SDoH are also associated with increased risk of BC and poorer survival.
Objective: The overall objective of this research is to use a multi-level design with three levels of influence (individual, interpersonal, and community/neighborhood level) to examine longitudinal changes in sleep duration and sleep quality from BC diagnosis through treatment by underserved communities (rural, urban, Appalachian), while exploring biopsychosocial factors (biological specimens, psychological stress, social support) and the built environment.
Specific Aims: 1) To characterize longitudinal trends in sleep duration and sleep quality. 2) To identify risk factors (sociodemographic, clinical, social support, built environment) associated with sleep duration and quality over time. 3) Assess how sleep duration and quality affect premature biological aging, stress, and inflammation markers in BC patients during and after treatment.
Methodology and Study Design: We will enroll 100 newly diagnosed, stage 1-3 BC patients. Participants will be assessed over 4 timepoints and will complete a survey, non-invasive biospecimen collection (saliva, buccal, hair), and wear a sleep watch.
Significance: This project will address cancer health disparities using an interdisciplinary, multifaceted approach combining biological specimens, self-reported sleep quality, and wearable devices to elucidate sleep health disparities that exist among BC patients. This research will help direct future interventions by providing biological and behavioral evidence on factors contributing to poor BC outcomes to lessen cancer health disparities.

Poster Board **#9**

Putzer J. Hung, MD, PhD

AACR-John and Elizabeth Leonard Family Foundation Basic Cancer Research Fellowship

Regulation of Ribosomal RNA Synthesis in Acute Myeloid Leukemia

A distinguishing feature of acute myeloid leukemia (AML) cells is their prominent nucleoli, which demarcates foci of active ribosomal RNA (rRNA) synthesis. rRNAs are specialized non-coding RNAs that form the catalytic components of ribosomes, and their transcription from repetitive ribosomal DNA elements is an essential step in ribosome biogenesis. We hypothesize that rapidly dividing AML cells need to maintain high rates of rRNA synthesis to support their survival and that this cancer dependency pathway can be exploited to cripple leukemic growth. Using a “FISH-Flow” method developed in our lab, we generated a quantitative map of rRNA synthesis across the hematopoietic tree and show that rRNA levels are aberrantly elevated in primary human AML cells compared to normal stem/progenitor cells. We also demonstrate that rRNA synthesis is upregulated by oncogenes such as HoxA9 (which is overexpressed in 70% of AMLs) and that inhibiting rRNA synthesis induces differentiation and chemosensitization of AML cells. We are now moving to validate these findings in vivo. Our aim is to provide novel insights into an unexplored cancer vulnerability that could inform the advancement of safer and more durable therapies for patients with AML.

Poster Board **#10**

Farhia Kabeer, PhD
AACR-AstraZeneca Endometrial Cancer Research Fellowship

Therapeutic Targeting of Deficient Mismatch Repair Endometrial Cancers Beyond Immune Checkpoints

Deficient mismatch repair (dMMR) endometrial cancer (EC) represents a distinct molecular subtype with unique therapeutic opportunities. While immune checkpoint blockade (ICB) has improved outcomes for some patients, only ~40% respond, and many develop resistance, leaving limited treatment options. This project seeks to expand understanding of dMMR EC in detail, uncover mechanisms of ICB resistance, and identify novel therapeutic strategies, including the potential of antibody-drug conjugates (ADCs) and combination immunotherapies.

Aim 1 focuses on evaluating ADC targets in dMMR EC. Despite the global development of nearly 200 ADCs, the relevance of their targets in dMMR EC remains poorly characterized. We will leverage a biobank of ~800 molecularly profiled dMMR EC samples and assess protein expression (e.g., B7-H4, Nectin-4, TROP2, HER2) and immune landscape using multiplex IHC. This will guide prioritization of ADC targets. PDX models from high-expressing tumors, including treatment-naïve cases, will be developed to test ADC-based therapies.

Aim 2 investigates resistance to ICB using humanized PDX models derived from ICB-resistant tumors, paired with matched treatment-naïve samples when available. Building on experience from prior OCC-funded ovarian cancer work, we will establish six new humanized dMMR EC PDX models. These will enable preclinical testing of ADCs and immune checkpoint inhibitor combinations in an immune-competent context.

To date, we have already recruited ~70 dMMR EC patients into our ongoing clinical trial. Together, these efforts will define actionable vulnerabilities and support novel treatment approaches for patients with dMMR EC beyond current ICB options.

Poster Board **#11**

Fernanda G. Kugeratski, PhD

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

Defining the Role of LRRC17^{+} CAFs in the Breast Tumor Microenvironment

Cancer-associated fibroblasts (CAFs) are an abundant cell population of the breast tumor microenvironment (TME). Several CAF phenotypes exist in tumors, being the inflammatory type (iCAF) characterized by the high expression of interleukin 6 (IL-6). Hypoxia promotes the iCAF phenotype and is linked to poor prognosis of cancer patients. We analyzed the changes in the proteome and secretome of mammary CAFs upon activation from normal fibroblasts and upon exposure to hypoxia and identified Leucine Rich Repeat Containing 17 (LRRC17) as the most up-regulated protein in both conditions. Histological analyses show that LRRC17 is uniquely expressed in CAFs of human and murine breast tumors, highlighting its specific association with the tumor stroma across species. We uncovered that LRRC17 is an upstream regulator of IL-6 in CAFs. Additionally, LRRC17+ CAFs reprogram other cells of the breast cancer TME towards an inflammatory state and promote sprouting angiogenesis in vitro. We are currently characterizing the function of LRRC17 in vivo using a full body knockout and two conditional knockout mouse models for LRRC17. Our focus is to determine whether LRRC17+ CAFs affect tumor growth, survival, metastasis, immunosuppression, and angiogenesis in breast tumors. Furthermore, using ethnically and molecularly diverse cohorts of breast cancer patients, we will define spatial ecosystems associated with LRRC17+ CAFs in breast cancer. The targeting of LRRC17 in the breast cancer TME has the potential to alleviate stroma-driven angiogenesis and inflammation and may open new avenues to improve clinical outcomes of breast cancer patients.

Poster Board **#12**

Shawn H.R. Lee, MD, PhD

AACR-St. Baldrick's Foundation Pediatric Cancer Research Grant

Imaging Based Pharmacotyping of Childhood Hematological Malignancies

Background: Relapsed or refractory acute lymphoblastic (ALL) and myeloid leukemias (AML) remain the leading cause of cancer-related mortality in children, with five-year survival for high-risk subsets stagnating below 50%. Functional profiling that complements genomics is urgently needed to improve outcomes for these children. In this project, we aim to establish a scalable, high-throughput imaging-based pharmacotyping platform that quantifies ex-vivo drug sensitivity in paediatric leukemias, across a range of cell types (PDX, banked, fresh). Here, primary or patient-derived xenograft (PDX) blasts are co-cultured for 96 h on bone-marrow mesenchymal stromal cells. A 384-well format allows simultaneous exposure to a 40-agent panel across eight logarithmic concentrations. High-content confocal imaging with machine-learning segmentation enumerates viable blasts and derives LC_{50} and area-under-curve metrics. Orthogonal characterisation with targeted DNA/RNA sequencing and BH3 profiling will map genetic and apoptotic dependencies. Specialist manpower training completed at St. Jude Children's Research Hospital, and key infrastructure installed, including VIAFLO-384 liquid handling. Pilot validation on ten cryopreserved T-ALL specimens is underway; preliminary runs show stromal-supported viability >80% at 96 h and assay coefficient of variation <15 %. After optimisation, we will prospectively analyse de-novo, relapsed, and refractory ALL/AML samples (fresh, banked, PDX) to derive disease- and stage-specific pharmacotypes. Correlating ex-vivo sensitivity signatures with clinical outcome will generate hypotheses for risk stratification and rational drug repurposing. This proof-of-concept study will embed a first-in-region functional precision oncology platform, enabling rapid, low-input drug testing that may ultimately guide personalised therapy and biomarker-driven trials in childhood leukaemia.

Poster Board **#14**
Siva Kumar Natarajan, PhD
AACR-Sontag Foundation Brain Cancer Research Fellowship

ZFTA-RELA Ependymomas Produce Macrophage-Associated Itaconate as an Oncometabolite to Epigenetically Sustain Pathogenic Fusion Expression

ZFTA-RELA ependymomas are malignant brain tumors that are frequently lethal. They are defined by fusions formed between the putative chromatin remodeler ZFTA and the NFκB-mediator-RELA. Through a comprehensive metabolic screen, we identified that ZFTA-RELA cells produced itaconate, a TCA-cycle related metabolite. Itaconate is key macrophage-associated immunomodulator metabolite. However, itaconate production by tumor cells and its tumor-intrinsic role are not well-established. Itaconate is synthesized by the enzyme Aconitate Decarboxylase-1 (ACOD1) and ZFTA-RELA upregulated ACOD1 in an NFκB-dependent manner. Additionally, itaconate production enabled an integrated metabolic/epigenetic feed-forward system that maintained pathogenic ZFTA-RELA fusion expression through epigenetic activation. To supply the metabolic fuel needed to generate itaconate, ZFTA-RELA tumors epigenetically activated PI3K/mTOR signaling to enhance glutaminolysis, which provided the carbons necessary for itaconate synthesis. Consequently, antagonizing glutamine metabolism lowered pathogenic ZFTA-RELA levels and was potently therapeutic in multiple in vivo models. Finally, combining glutamine antagonism with PI3K/mTOR inhibition abrogated spinal metastasis. Our data demonstrates that ZFTA-RELA ependymomas subvert a macrophage-like itaconate metabolic pathway to epigenetically maintain expression of the ZFTA-RELA fusion driver, implicating itaconate as an oncometabolite. Taken together, our results position itaconate upregulation as a previously unappreciated driver of ZFTA-RELA ependymomas. This study, therefore, has implications for future drug development for children with this devastating brain tumor and will further our understanding of oncometabolites as a novel class of therapeutic dependencies in cancers.

Poster Board **#15**

Utthara Nayar, PhD

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

Mechanisms Underlying Allele Bias of a Novel Estrogen Receptor Mutation

Late-stage estrogen receptor (ER)+ metastatic breast cancer (MBC) has very poor prognosis due to ubiquitous endocrine resistance. The most well known mechanism of endocrine resistance is hotspot activating ER mutations (ERmuts) that lead to ligand independence. Hotspot ERmuts are effectively inhibited by the newest class of endocrine therapy, oral selective ER degraders (SERDs), and are clinical biomarkers for SERD responsive tumors.

We found a previously uncharacterized novel non-hotspot ER variant of unknown significance (VUS) from clinical sequencing of tumors with acquired endocrine resistance. It was the most frequent ER VUS in public clinicogenomic databases but paradoxically associated with extremely low ER activity signature by clinical RNAseq. This suggested it is a non-canonical ERmut that decouples ER hyperactivation from endocrine resistance.

We found the VUS confers strong resistance to established endocrine therapies, remaining sensitive to CDK4/6 inhibitors and oral SERDs. It was functionally distinct in terms of transactivation, as it was hyperactive compared to wild-type ER absent ligand, but ligand-responsive, unlike the canonical hotspot ERmut Y537S. Structure modeling suggests altered VUS binding to ligand, while chromatin fractionation showed it was preferentially hyperphosphorylated in the nuclear fraction. RNA-seq revealed that it led to a distinct transcriptome representing an intermediate state between parental and Y537S-mutant cell lines. Further studies will enable us to identify the structural basis of VUS dysregulation and identify potential targetable nodes for these tumors. Our results would help develop this VUS as a clinical biomarker and inform the design of clinical trials to overcome endocrine resistance.

Poster Board **#16**

Verra Ngwa, PhD

AACR-Johnson & Johnson Lung Cancer Initiative Stimulating Therapeutic Advances Through Research Training (START) Grant

Investigating the Role of Metabolic Genes in Lung Squamous Cell Carcinoma Adoptive T Cell Therapy

Lung squamous cell carcinoma (LUSC) represents 30% of non-small cell lung cancer (NSCLC) cases and has a high mortality rate with limited targeted therapies. Unlike lung adenocarcinoma (LUAD), which has seen advancements in targeted therapies, LUSC has not benefited from similar breakthroughs despite having similar genetic abnormalities. While immune checkpoint inhibitor therapies have shown promise in some LUSC patients, a significant portion does not respond effectively, leaving limited treatment options. The metabolic landscape of tumors plays a crucial role in shaping the efficacy of immunotherapies, especially adoptive T cell therapies. However, identifying actionable metabolic vulnerabilities involved in T cell therapy is poorly understood. Here, we performed a high-throughput CRISPR-Cas9 screen targeting metabolic genes in an orthotopic LUSC mouse model to identify key metabolic enzymes that would sensitize the tumors to adoptive CD8+ T cell therapy. By comparing sgRNA enrichment and depletion between tumors treated with adoptive T cells and those receiving PBS, we identified Gene P, involved in medium-chain fatty acid biosynthesis, as a potential suppressor of T cell-mediated killing. This suggests that loss of Gene P could enhance tumor sensitivity to T cell therapy. We are currently repeating the screen and plan to validate Gene P's role in follow-up functional experiments.

Poster Board **#18**

Sara G.M. Piccirillo, PhD

AACR-Novocure Tumor Treating Fields Research Grant

The Impact of Tumor Treating Fields on Cancer Stem-Like Cells Isolated From the Sub-Ventricular Zone of Glioblastoma Patients

Glioblastoma (GBM) is the most aggressive brain tumor in adults that almost inevitably recurs despite radical treatments. Recurrence is driven by residual disease, which is extremely difficult to identify and target. We previously identified and characterized specific anatomic/functional areas of residual disease in GBM patients, including the sub-ventricular zone (SVZ), the most well-characterized neurogenic area in the mammalian brain. Specifically, we showed that the SVZ is a reservoir of cancer stem-like cells (CSCs) seeding recurrence. Thus, the SVZ holds the key to identifying novel therapeutic targets for GBM patients.

Our 2021 AACR-Novocure-funded project on the impact of Tumor Treating Fields (TTFields) on CSCs derived from the SVZ revealed that the antiproliferative effects of TTFields are maintained among patients, and that CSC growth is significantly reduced when TTFields are used at a frequency of 200 kHz. Moreover, functional phenotyping analysis of the innate immune cytokine secretome revealed that CSCs treated with TTFields secrete less VEGF and more soluble CD137 (sCD137) compared with untreated cells. CD137 is a member of the TNF family contributing to the activation of cytotoxic responses in T cells, while sCD137 exhibits immunoinhibitory functions. Clinical trials involving agonistic anti-CD137 antibodies (Abs), which also counteract sCD137-mediated immunoinhibition, are currently underway in patients with advanced tumors. Combined with TTFields, these Abs offer a novel therapeutic opportunity for the treatment of GBM.

Collectively, our results point to the effectiveness of TTFields in GBM and identify a novel therapeutic target in GBM residual disease.

Poster Board **#19**

Sangeetha M. Reddy, MD

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

Dual Targeting Myeloid Cells and Tregs to Enhance CD8 T Cell Immunity

Breast cancers often exhibit defects in antigen presentation that impair T cell–mediated immunity. To overcome this, we tested a triplet regimen combining Flt3 ligand (Flt3L), a CD40 agonist (CD40a), and standard-of-care chemotherapy in murine E0771, 4T1, and AT3 breast cancer models. This triplet therapy significantly improved tumor control compared to standard-of-care chemotherapy alone or any doublet combination. ScRNA-seq and flow cytometry revealed Flt3L expands dendritic cell (DC) subsets, while CD40a activates DCs and macrophages with robust upregulation of the CD8 T cell–recruiting chemokine CXCL9 across DC subsets and inflammatory macrophages and a trend towards increased Il-12b. Consistent with this, treatment increased infiltration of CD8 T cells with stem-like and effector memory phenotypes and reduced exhaustion. TCRseq showed a significant increase in intra-tumoral clonal expansion without a significance increase in new clones, suggesting a local antigen-specific T cell response. Supporting this, FTY720-mediated blockade of lymphocyte egress from lymph nodes did not impair treatment efficacy, indicating that pre-existing intra-tumoral T cells - not recruitment from lymph nodes – were primarily responsible for tumor control. We additionally found that efficacy was dependent on cDC1 cells, both CD4 and CD8 T cells, and IL-12b. Despite this robust immune activation, regulatory T cells (Tregs) remained a resistance mechanism that prevented complete tumor eradication. These findings underscore the ability of this regimen to activate high-quality local T cell responses and highlight the need to overcome Treg-mediated suppression. A clinical trial testing triplet combination in patients with metastatic breast cancers is currently open and enrolling (NCT05029999).

Poster Board **#20**

Yoojeong Seo, PhD

The Bosarge Family Foundation-Waun Ki Hong Scholar Award for Regenerative Cancer Medicine

Manipulating Cell Plasticity to Alleviate Radiation-Induced Pulmonary Fibrosis

Background. Radiation-induced pulmonary fibrosis (RIPF) is a progressive and often irreversible complication of thoracic radiation therapy, marked by alveolar scarring, architectural destruction, and respiratory failure. RIPF remains a significant clinical barrier, lacking effective therapeutic options. Lung regeneration following injury depends on alveolar type II (AT2) epithelial cells, which function as progenitors to alveolar type I (AT1) cells essential for gas exchange. Impaired AT2-to-AT1 transitions—referred to as disrupted epithelial cell plasticity—result in fibrotic remodeling rather than functional repair.

Hypothesis. Pharmacologic restoration of alveolar epithelial cell plasticity can suppress fibrosis and promote regenerative healing in RIPF.

Previous study. We identified PCLAF as a key regulator of AT2 plasticity and regeneration. Loss of PCLAF impairs AT2-to-AT1 transitions, leading to fibrosis. Using a transcriptomics-based approach, we identified phenelzine, an FDA-approved antidepressant, as a pharmacologic activator of the PCLAF-regulated regenerative program. Bleomycin-induced lung injury models showed that phenelzine enhanced AT2 plasticity, reduced fibrosis, and restored AT1 cell populations.

Study Design. We will assess phenelzine's effects on RIPF in mouse models by evaluating fibrosis and regeneration through single-cell RNA sequencing, lung function, histology, and cell plasticity analyses, with a focus on AT2 dynamics and lineage transitions.

Significance and Innovation. Successful completion of this study will provide critical insights into the cellular mechanisms driving RIPF and propose phenelzine as a potential therapeutic and preventative regimen for RIPF. By leveraging single-cell transcriptomics and repurposing an FDA-approved drug, this research offers a rapid and translationally impactful approach to addressing RIPF and advancing therapies for fibrotic diseases.

Poster Board **#21**

Zhe Ying, PhD

Triple Negative Breast Cancer Research Foundation-AACR NextGen Grant for Transformative Cancer Research

Branching Out: How Do Basal-Like Breast Cancer Driver Mutations Initiate Hormone Independence?

Basal-like breast cancer (BLBC) is a molecular subtype of breast cancer that shares transcriptional features with the basal lineage of the mammary gland. Most BLBCs lack expression of ER, PR, and HER2, the three major druggable targets in breast cancer, and represent the largest group within triple-negative breast cancers (TNBC). Unlike other subtypes where molecular targeted therapies have improved survival, BLBC remains difficult to treat due to a lack of well-defined, actionable driver lesions. To address this gap, it is critical to: 1) identify functional BLBC driver lesions, 2) uncover their mechanisms, and 3) pinpoint actionable signaling hubs. Using our in-utero lentivirus injection-based in vivo screening system, we identified Ntrk1, amplified in 28% of human BLBCs, as the most potent driver among 229 BLBC-enriched lesions. Our ongoing work shows that Ntrk1 activates epithelial-autonomous expression of growth factors (GFs) that mimic those secreted by terminal end bud (TEB) niche cells during puberty, driving hormone-independent growth, a hallmark of TNBC. We now aim to define how Ntrk1 controls TEB GF expression and to test whether blocking Ntrk1 and/or TEB GF signaling can serve as effective therapeutic strategies for Ntrk1-driven BLBC.

Poster Board **#22**

Zachary Yochum, MD, PhD
AACR-Exelixis Renal Cell Carcinoma Research Fellowship

Determining the Role of Endogenous Retroviruses in Adaptive Immune Responses in Renal Cell Carcinoma

Although immune checkpoint inhibitors (ICIs) have improved outcomes in advanced solid tumors, including renal cell carcinoma (RCC), most patients succumb to their disease. Unlike ICI-responsive tumors with high mutational/neoantigen burden, RCC has a low neoantigen load, implying alternative antigens drive immune responses. Identifying these antigens is essential to understanding ICI responsiveness and developing novel immunotherapies.

Endogenous retroviruses (ERVs), transposable elements integrated into the human genome, are promising antigen sources in RCC. Though rarely expressed in healthy tissue, ERVs are frequently reactivated in RCC and recent studies demonstrated that ERV-derived HLA class I antigens can drive T cell responses. Systematically mapping ERV-antigens and cognate TCRs could uncover a significant antigen source for T cells in RCC.

Our group recently implemented ENTER-seq, a high-throughput platform using pseudotyped lentivirus to display antigen-HLA complexes and identify antigen-specific T cells and their TCRs. We also developed a library of candidate ERV-derived peptides for display with the ENTER-seq system. We hypothesize ERVs are antigenic targets for tumor-specific T cells in RCC and that CD8+ T cells targeting ERV-peptides are enriched in ICI responders.

We will initially define the role of ERVs in the native anti-tumor immune response by performing ENTER-seq with HLA-matched ERV-peptide libraries on both tumor-infiltrating and peripheral CD8+ T cells from treatment-naive RCC patients and in vitro validation of candidate ERV-antigen-TCR interactions. We will also examine ERV-specific responses in ICI-treated patients using pre- and post-treatment blood samples. Completion of this study will establish ERVs as key antigens and support the development of ERV-targeted immunotherapies.

Poster Board **#23**

Youssef Youssef, MD

AACR-AstraZeneca Endometrial Cancer Research Fellowship

CD200^{+} Endometrial Cancer Shapes Dysfunctional NK Cell Phenotype via CD200R1 to Evade Immunity

Endometrial cancer (EC) is the most common gynecologic cancer in the USA and expected to surpass ovarian cancer in mortality. Advanced-stage EC has poor outcomes with high relapses (>35%) and low chemotherapy response (50%). Immune checkpoint blockades (ICB) are often ineffective in EC, indicating a need for better understanding the tumor microenvironment (TME). Cytotoxic NK (cNK) cells are often impaired in tumors due to skewed differentiation towards a suppressive tissue-resident (trNK) phenotype. In single-cell RNA sequencing of treatment-naïve EC samples (n=10), we identified a trNK population enriched for the inhibitory receptor CD200R1, corresponding with elevated CD200 ligand expression on tumor cells. Our work shows that CD200R1 expression on NK cells is associated with less cytotoxic phenotype and mediates maturation arrest. Notably, CD200 is known to promote NK cell tolerance in pregnancy and endometriosis. Immunohistochemistry revealed that trNK cells were more frequent within EC glands compared to stroma. Hypothesis: CD200+ ECs promote dysfunctional trNK with impaired differentiation into effector cNK cells, enabling immune evasion and reducing ICB efficacy. In 17 EC samples analyzed by flow cytometry, CD200R1 expression was significantly higher in trNK compared to benign endometrium (32% vs 5%; p=0.006), correlating with reduced expression of cytotoxic/maturity markers (granzymes, perforin, CD94, CD16, EOMES). Co-culture experiments with EC lines overexpressing CD200 impaired NK maturation, increasing ILC-like cells and reducing CD94^{+}CD16^{+} cNKs. These findings support a model in which CD200+ ECs promote dysfunctional NK differentiation via the CD200/CD200R1 axis. Ongoing studies are evaluating if blockade of this pathway enhances ICB responses (NCT05199272).