Melanoma Research Alliance

2026 Annual Scientific Retreat

Poster Session Reception

February 26th 5:20-6:20pm

Poster Abstracts

February 25th – 27th 2026, | Washington DC

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Poster Abstracts

Poster 1:

GNAQ-induced Melanomagenesis in a Zebrafish Model of Uveal Melanoma; Colin Kenny (University of Iowa)

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Abstract: Melanocytes reside in diverse microenvironments that influence their susceptibility to oncogenic transformation, however, studying rare melanoma subsets has been hindered by the lack of suitable pre-clinical animal models. We developed a primary, immune-competent zebrafish model to study uveal melanoma (UM), utilizing choroidal melanocyte-targeted injection and electroporation of plasmids containing human GNAQQ209L and CRISPR/Cas9 cassettes for tumor suppressor gene deletion. Single-cell transcriptional profiling of primary melanocytes and melanoma from the eye and skin revealed distinct transcriptional signatures with EMT pathways more prominent in eye tumors, highlighting the importance of anatomical context. Additionally, we identified a population of tfec- and pax3a-expressing melanocyte progenitor cells in mitfa-deficient embryos and adult zebrafish eyes, which were highly susceptible to GNAQ-driven transformation. While previous studies have linked mitfa deficiency to accelerated UM onset, our findings suggest that an expanded progenitor population in mitfa-deficient animals drives this susceptibility. Our study establishes a critical role for Mitfa-independent melanocyte progenitors in UM pathogenesis.

Funding and disclosures: This project is funded by the Melanoma Research Alliance Young Investigator Award. No other financial interests or relationships to disclose.

Poster 2:

Rewiring exhausted T cell-derived chemokines to improve anti-tumor immunity; Kelly Kersten (Sanford Burnham Prebys Medical Discovery Institute)

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Abstract: Immune checkpoint blockade (ICB) has shown great promise in melanoma patients, but a majority fails to respond. CD8+ T cells are critical mediators of anti-tumor immunity and the main target for ICB. However, the onset of terminal functional T cell exhaustion poses a major challenge. Thus, we need a better understanding of the complex mechanisms that regulate functional T cell exhaustion to improve the efficacy of immunotherapy for melanoma patients.

Solid tumors are heavily infiltrated with tumor-associated macrophages (TAMs) and their abundance correlates with T cell exhaustion and poor prognosis. In our recent work we discovered a spatiotemporal co-dependency between exhausted T cells (TEX) and TAMs in cancer. We showed that TEX actively recruit TAMs that 'capture' T cells in long-lived synaptic interactions that contribute to functional T cell exhaustion. Thus, a mechanism of immune evasion fueled by reciprocal interactions between TEX and TAMs in the TME could potentially explain why some cancers fail to respond to immunotherapy.

In this proposal we will study the molecular mechanisms by which TAM – T cell interactions dictate immunotherapy efficacy in mouse models of melanoma. TEX in mouse and human melanoma highly express myeloid-related chemokines CCL3/4/5 that are known for their role in myeloid and T cell recruitment through binding to their shared receptor CCR5. We hypothesize that through CCL3/4/5, TEX specifically recruit immunosuppressive TAMs to the TME to shut down anti-tumor immune responses causing resistance to ICB. We will use a multidisciplinary approach of sophisticated in vivo and in vitro models to study the role of CCL3/4/5 in the onset and progression of CD8+ T cell exhaustion, as well as the extrinsic effects of T cell-derived CCL3/4/5 on the melanoma TME, specifically CCR5+ macrophages, and its impact on ICB responsiveness of melanoma. This work will aid the design of novel immunotherapy approaches for melanoma patients.

Funding and disclosures: This study is supported by the Melanoma Research Alliance Young Investigators Award. No other financial interests or relationships to disclose.

Poster 3:

Immunotherapeutic cytokine/antibody fusion protein to treat acral melanoma; Jamie B. Spangler (Johns Hopkins University)

Jamie B. Spangler[1]; Jakub Tomala[1]; Marie Portuallo[1]; William Rosenthal[1]; Steffanus Hallis[1]; Vito W. Rebecca[1]

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Abstract: One of the most transformative breakthroughs in melanoma therapy has been the emergence of immunotherapies, treatments that activate the patient's own immune system to fight disease. These life-saving therapies have been shown to effect complete and durable cures in patients whose cancer is refractory to all other interventions. However, only a minority of patients respond to these therapies, and certain melanoma subtypes, such as acral melanoma, show greater resistance to immunotherapies. There is thus an urgent and unmet need to design novel immunotherapeutic strategies to increase response rates and improve patient outcomes.

Our research aims to establish the potential for our team's newly engineered immunotherapeutic to treat acral melanoma, a rare but deadly subtype of melanoma that manifests on the hands, feet, or underneath the nails. Our therapeutic is based on interleukin-2 (IL-2), a naturally occurring protein that strongly activates effector cells of the immune system and stimulates anti-cancer immune responses. IL-2 has been used clinically to treat metastatic melanoma for 25 years, but its performance has been limited by toxicity, rapid clearance from the bloodstream, and lack of tumor targeting. The Spangler Lab has previously engineered an IL-2/antibody fusion protein that overcomes the limitations of IL-2 as a drug by reducing its toxicity, extending its persistence in the bloodstream, and targeting its activities to the tumor. Here, we tested our newly designed fusion proteins in exclusive mouse models of acral melanoma developed by our collaborative team. Synthesizing complementary skillsets in protein engineering, tumor biology, and drug development, we have established the promise of our IL-2/antibody fusion protein in animal models of acral melanoma and elucidated genetic and phenotypic features of disease associated with therapeutic response. Overall, this interdisciplinary research is fundamentally advancing our understanding of acral melanoma, and empowering the development of a novel immunotherapeutic to cure this devastating disease.

Funding and disclosures: This study is supported by the Melanoma Research Alliance's Pilot Award. Johns Hopkins University has filed patents related to the fusion proteins described herein, with JBS and JT listed as co-inventors.

Poster 4:

Proteogenomoic and translatomic analysis of acral melanoma; Sarah Slavoff, (Yale University)

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Abstract: Acral melanoma is a rare skin cancer that develops on sun-shielded skin of the palms and soles, and is often diagnosed at later, more advanced stages, resulting in poor treatment outcomes. Acral melanoma bears a low mutational burden, and is more commonly associated with copy number variations and chromosomal rearrangements than the well-characterized driver mutations that cause UV-exposed melanoma. This unique genetic fingerprint also renders targeted therapy and immunotherapy less effective against acral melanoma. Foundational studies have identified unique genetic alterations in acral melanoma, including but not limited to amplification of KIT and CRKL, but the molecular landscape of acral melanoma remains incompletely understood relative to UV-exposed melanoma. It is essential to identify novel biomarkers and driver mutations in order to improve diagnosis and treatment of acral melanoma.

In recent years, interest in the "dark proteome" of cancer has seen rapid growth. We define the dark proteome as genomically encoded peptides, "microproteins" of fewer than 100 amino acids, and protein isoforms and proteoforms (e.g., N-terminal extensions and splice variants incorporating novel exons) that were previously excluded by genome annotation consortia. The dark proteome is now well known to be aberrantly and specifically expressed in multiple tumors, driving cancer pathogenesis and also achieving overrepresentation in the HLA I immunopeptidome. We therefore hypothesized that dark proteins could contribute to the unique proteome of acral melanoma, representing never-before-seen biomarkers of this rare skin cancer, and conducted a mulitomic analysis of acral melanoma patient derived cells and healthy melanocyte controls.

We reanalyzed existing RNA-seq data from dozens of acral melanoma patient samples, healthy donor melanocytes and non-cancerous nevi, and identified pronounced downregulation of a dark protein encoded in the C1ORF122 locus. We provide molecular and mechanistic characterization of this unannotated proteoform that supports a role for its loss in acral melanoma progression. In addition, we have carried out new proteomic and translatomic (high-resolution ribosome profiling) analyses of the dark proteomes of patient-derived acral melanoma cells and healthy melanocytes, identifying hundreds of unannotated microproteins at the highest level of stringency, dozens of which are specifically detected in acral melanoma cells, pending orthogonal validation. We present these initial catalogs to the research community in order to inform future translation applications in acral melanoma diagnosis and therapeutic development.

Funding and disclosures:
This study is funded by the Melanoma Research Alliance Pilot Award and the Mark Foundation for Cancer Research.

Poster 5:

Targeting lysosomal catabolism to address acral melanoma metastasis; Vito Rebecca (Johns Hopkins University)

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Abstract: AM is the most lethal subtype of cutaneous melanoma and is highly metastatic to the lungs and liver, yet in vivo mouse models of metastatic AM have not been described leaving the AM metastasis driver landscape understudied. To overcome this hurdle, we recently engineered a syngeneic orthotopic mouse model of metastatic AM whereby tumor cells implanted into the acral (volar) skin of the foot versus the non-acral (non-volar) skin of the flank exhibit a phenotype switch marked by a lower proliferative capacity, yet an elevated metastatic capacity. Interestingly, our preliminary bulk RNAseq analysis of foot versus flank tumors revealed that implantation in the foot microenvironment (ME) elevates expression of the melanocyte lineage factor Sox10 and the lysosomal enzyme cathepsin K (catK). Lysosomal catK possesses potent type I collagenolytic activity capable of degrading bone and its expression is associated with elevated metastatic capacity in advanced cancers including breast and gastric. Further, lysosomal catK promotes metastasis by enabling lysosomal catabolism of extracellular-derived collagen matrix proteins via macropinocytosis; however, a link to acral melanoma metastasis has not been previously reported. Our data find targeting cathepsin k pharmacologically suppresses the metastatic capacity of human AM cells orthotopically implanted in plantar skin, demonstrating a first example of a targetable vulnerability to address acral melanoma metastasis.

Funding and disclosures: This study is supported by the Melanoma Research Alliance Young Investigators Award. No other financial interests or relationships to disclose.

Poster 6:

Efficacy and safety of RP1 plus nivolumab in patients with advanced anti–PD-1–failed acral melanoma; Jacqueline Smith (Replimune, Inc.)

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Abstract:
Background: Acral melanoma is a rare and aggressive type of melanoma (2%–3% of all cases) that often has poor outcomes. Acral melanoma responds poorly to available therapies, such as immune checkpoint inhibitors, particularly after progression on first-line treatment. RP1 (vusolimogene oderparepvec) is an oncolytic immunotherapy expressing human granulocyte-macrophage colony-stimulating factor and a fusogenic glycoprotein (GALV-GP-R–). RP1 + nivolumab (nivo) demonstrated an ORR of 32.9% by blinded independent central review (BICR) using RECIST 1.1 in patients (pts) with anti–PD-1–failed advanced

melanoma from the IGNYTE trial (NCT03767348). Here we report an ad hoc analysis of RP1 + nivo efficacy and safety in pts with acral melanoma.

Methods: The IGNYTE phase 2 registrational cohort enrolled pts with stage IIIB–IV cutaneous melanoma and confirmed progression on anti–PD-1 ± anti–CTLA-4 for ≥8 weeks as the last prior treatment (N = 140). RP1 was administered intratumorally at 1 × 10^6 plaque-forming units (PFU)/mL initially, then at 1 × 10^7 PFU/mL Q2W (≤7 doses) with intravenous nivo.

Results: Of 140 pts with anti–PD-1–failed cutaneous melanoma, 18 (12.9%) had acral melanoma. Of these 18 pts, 50.0% (9/18) had stage IVM1b–d disease, 94.4% (17/18) had BRAF wild-type tumors, and 72.2% (13/18) had PD-L1–negative (<1%) tumors. Most pts (61.1% [11/18]) had both anti–PD-1 and anti–CTLA-4 prior treatment, and 72.2% (13/18) had primary resistance to anti–PD-1. Following treatment with RP1 + nivo, the confirmed ORR was 44.4% (8/18) by BICR using RECIST 1.1, including 16.7% (3/18) complete response and 27.8% (5/18) partial response. Median (95% CI) duration of response was 11.9 (3.6–NR) months (ongoing). Most treatment-related adverse events (TRAEs) were grade 1/2; the most common TRAEs (any grade) were chills, pyrexia, fatigue, injection-site pain, and nausea. Grade ≥3 TRAEs were reported in 2 (11.1%) pts.

Conclusions: RP1 + nivo demonstrated deep and durable efficacy and was well tolerated in pts with advanced anti–PD-1–failed acral melanoma. RP1 + nivo represents a promising treatment approach for this rare, aggressive melanoma subtype.

Funding and disclosures: This study was funded by Replimune, Inc. CR received consulting fees from Bristol Myers Squibb, Egle Therapeutics, IO Biotech, Maat Pharma, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Philogen, Pierre Fabre, Regeneron, Roche, Sanofi, Sun Pharma, and Ultimovacs; received honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, and Sanofi; received travel support from Pierre Fabre; and served on advisory boards for Bristol Myers Squibb, Egle Therapeutics, Maat Pharma, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Philogen, Pierre Fabre, Regeneron, Roche, Sanofi, Sun Pharma, and Ultimovacs. Co-Author disclosures relevant to this study: JJS, GMB, BC, TLB, KKT, and CGM received research funding from Replimune, Inc. EMC, JN, MMM, CL, and AS have nothing relevant to disclose. DS received honoraria from Replimune, Inc. and served as a consultant/advisor for Replimune, Inc. GKI served as a consultant/advisor for Replimune, Inc. and received research funding from Replimune, Inc. TMWD and MKW served as a consultant/advisor for Replimune, Inc. JZ, MV, and JWH are employees and shareholders of Replimune, Inc.

Poster 7:

Vascular Regulation of Tumor Immune Exclusion and Progression in melanoma; Minah Kim (Columbia University)

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Abstract: An immunosuppressive tumor microenvironment (TME) constrains therapeutic efficacy and worsens prognosis. Beyond T-cell abundance and functionality, their spatial proximity to malignant cells is a critical determinant of tumor control. However, the vascular mechanisms that govern intratumoral T-cell positioning remain poorly defined. Through RNA sequencing of endothelial cells isolated from tumor cores versus peripheries in a mouse melanoma model, we identified intercellular adhesion molecule 1 (ICAM-1) as a candidate regulator of T-cell localization. As tumors progressed, T cells shifted from a balanced core–margin distribution to pronounced core exclusion, coinciding with elevated lymphocyte function-associated antigen-1 (LFA-1) expression on T cells —a pattern less evident in other immune subsets. This redistribution was accompanied by peripheral enrichment of endothelial ICAM-1 and loss of vascular integrity. Functionally, ICAM-1 blockade restored intratumoral T-cell infiltration, enhanced effectoractivity, and significantly delayed tumor growth. Together, these findings identify endothelial ICAM-1 as a vascular determinant of T-cell positioning and highlight the ICAM-1/LFA-1 axis as a modifiable checkpoint to improve T-cell access to the tumor core and augment antitumor immunity.

Funding and disclosures:
This work is funded by the Melanoma Research Alliance Young Investigator Award and the NIH/NCI (R21 CA293766-01).

Poster 8:

Epigenetic Potentiation of IL-7 Signaling Reinvigorates Melanoma TILs; Goran Micevic (Yale School of Medicine)

Maya G. Deshmukh[1], Danielle Sohai[1], Simon Milette[1], Koonam Park[1], Kamal Obbad[1], Krasimir Spasov[1], Samuel Katz[1], Karen Anderson[1], Marcus Bosenberg[1], Goran Micevic[1]

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Abstract: Adoptive cell transfer (ACT) of tumor-infiltrating lymphocytes (TILs) shows promise for patients with checkpoint inhibitor–resistant melanoma, yet clinical benefit remains limited to roughly 20% of patients due to low antitumor activity, poor in vivo persistence, and insufficient memory/stemness features. Memory $CD8^+$ T cells possess superior longevity and antitumor potential and may overcome these limitations, but their representation within TIL populations is typically low and further reduced by conventional ex vivo expansion protocols.

Interleukin-7 (IL-7) signaling is a key regulator of memory T cell differentiation. Enhancing IL-7 signaling during TIL expansion could promote memory features, augment tumor clearance, and improve clinical outcomes. We recently demonstrated that IL-7 signaling can be potentiated by epigenetic agents to enhance antitumor efficacy in a murine melanoma model. Here, we sought to determine whether epigenetic modulation could potentiate IL-7 signaling and memory differentiation in human TILs.
TILs were expanded from five patients with metastatic melanoma refractory to immune checkpoint blockade (anti–PD-1 ± anti–CTLA-4) using either conventional protocols ("conventional TILs") or in the presence of epigenetic inhibitors ("epiTILs"). Single-cell RNA sequencing of the initial TIL isolates, expanded conventional TILs, and epiTILs revealed that initial TILs exhibited transcriptional exhaustion signatures (HAVCR2, LAG3, ENTPD1, CTLA4). Conventional TILs upregulated effector genes (GZMB, PRF1, TBX21, IFNG, TNF) but maintained exhaustion features, whereas epiTILs upregulated both effector and memory/stemness-associated genes (TCF7, LEF1, IL7R, CCR7, KLF2) while downregulating exhaustion modules. Principal component analysis confirmed a global transcriptional shift from exhausted toward memory-like states following epigenetic treatment.

Epigenetically, this reprogramming correlated with modest changes in overall chromatin accessibility but marked alterations in DNA and histone methylation. ATAC-seq demonstrated regained accessibility in distal and promoter regions of IL7R and TCF7, consistent with enhanced IL-7 responsiveness. Functionally, epiTILs produced 17-fold higher $TNF\alpha^+$ and $IFN\gamma^+$ $CD8^+$ T cell frequencies upon antigen re-stimulation and exhibited a two-fold increase in tumor cell killing in co-culture assays ($p = 0.001$). These outcomes were accompanied by elevated IL-7R expression and increased STAT5 phosphorylation, confirming functional activation of IL-7 signaling.

Collectively, our findings demonstrate that epigenetic therapy reprograms patient-derived TILs toward a memory/stem-like state, restores cytotoxic function, and reduces exhaustion. This approach represents a promising strategy to enhance the efficacy of TIL-based ACT for patients with advanced melanoma.

Funding and disclosures: This work was funded by the Melanoma Research Alliance Young Investigator Award. No other financial interests or relationships to disclose.

Poster 9:

WRN deficiency drives acral and mucosal melanoma formation via genomic rearrangements at AT-repeats; Meng Wang

(Georgia Cancer Center, Augusta University & Department of Dermatology, University of California, San Francisco)

Meng Wang[1,2]; Makoto Goto [3], Sine Phelan [4], Sean Dinneen [4], Noel Cruz Pacheco [2], Hui Pan [2], Anastasia Samarkina [2], Iwei Yeh [2,5], Boris Bastian [2,5]

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Abstract: Germline biallelic inactivation of WRN causes Werner syndrome (WS), a rare autosomal recessive disorder characterized by premature aging and associated with a markedly increased risk of acral and mucosal melanomas, as well as several other rare cancer types. Although the elevated cancer risk in WS patients is generally attributed to increased genomic instability resulting from WRN deficiency, the underlying molecular mechanisms remain poorly defined, and it is unclear why WS patients are particularly susceptible to specific cancers such as acral and mucosal melanomas. To address these, we analyzed whole-genome sequencing (WGS) data of acral and mucosal melanomas arising from WS patients and found that all tumors harbor a recurrent 15.7-Mb deletion on chromosome 5p, with both breakpoints located at TA repeats, that juxtaposes TERT with sequences at ~16.98 Mb. Analysis of public WGS data confirmed that this deletion is present exclusively in WRN-null, but absent from WRN-proficient acral and mucosal melanomas. Long-read sequencing and multi-omics profiling of a WRN-null cell line demonstrated that this deletion activates TERT via enhancer hijacking. In addition, we showed that WRN loss gives rise to a characteristic rearrangement signature marked by breakpoints at TA repeats, affecting not only TERT but also other key cancer genes, including CDKN2A/B and NF1. Together, our findings establish a mechanistic link between WRN deficiency and TERT activation and identify WRN loss as the source of a distinctive TA-repeat–associated genomic rearrangement signature in cancers.

Funding and disclosures: This work was funded by the Melanoma Research Alliance Young Investigator Award and 1R35CA220481.

Poster 10:

AstroID resource: a scalable, relational database structure for longitudinal biomarker discovery;

Janis M. Taube, MD. (Johns Hopkins University SOM)

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General audience description: We previously found that a collection of immune cells within the tumor are required for protection from cancer and responses to current FDA-approved immunotherapies in patients. In this work we identify new mechanisms that control these protective immune populations in the tumor. Our studies provide novel insights and new mechanisms to target to modulate the immune cells in the tumor, potentially boosting immune protection from cancer and responses to immunotherapies in patients.

Abstract: Background: The biological sciences are producing increasingly larger datasets for biomarker discovery. While common data models have been developed for medical terms as they relate to patient health outcomes, a data model that supports longitudinal tracking of biospecimens and relating them against an individual patient experience is a large, unmet need.

Method: A structure and associated taxonomy were achieved through a six-tier build in Research Electronic Data CAPture (REDCap), which organizes the complexity of the therapeutic decisions, biospecimens, and outcomes that characterize a longitudinal patient experience. Modules were developed to support export of REDCap data into a Structured Query Language (SQL) format for merging with extended biomarker data, also housed in SQL.

Results: The resultant AstroID resource is a relational structure for clinical and biospecimen data that meets several desired goals: searchable, flexible, generic, Health Insurance Portability and Accountability Act-compliant, auditable, and easy-to-use. The essential elements forming the core of the six-tiered build are provided, so others can readily adopt this schema, as well as an example of an extended, customized build to support biomarker discovery for patients with melanoma. Two examples where this data structure was used to support biomarker discovery and development are described, and example queries of the database are also presented. To the extent possible, the data dictionary was aligned with large data models, such as those for the National Institutes of Health's Human Tumor Atlas Network. The structure can readily scale to accommodate thousands of patients, multimodality data, and spatial characterization of billions of cells. Radiologic imagery can also be included along with pathology imagery to support spatial studies, including artificial intelligence-driven analyses.

Conclusions: This effort provides a database model for investigators conducting research on large volumes of biospecimens with clinical annotation. We have now deployed this structure in our laboratories and have over 1B cells spatially mapped, each effectively tagged with the clinical information from longitudinal patient experiences. While the description uses the example of cancer biomarkers, this data structure could be used to characterize longitudinal biospecimens from any disease process. In the near future,

automatic synchronization between the electronic medical record and one or more AstroID databases is anticipated.

Funding and disclosures: This work was funded by the Melanoma Research Alliance, The Mark Foundation for Cancer Research, the Marilyn and Michael Glosserman Fund for Basal Cell Carcinoma and Melanoma Research, and the Bloomberg-Kimmel Institute for Cancer Immunotherapy. This study was also supported by NCI R01CA142779 and NIH T32CA009071.

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Poster 11:

Nanoparticle Reprogramming of Antigen Presentation for Acral Melanoma; Joel Sunshine (Johns Hopkins School of Medicine)

Grace Shoemaker[1]; Kevin Zhang[1]; Ethan Idnani[1]; Marie Portuallo[2]; Vito Rebecca[1,2]; Joel Sunshine[1]

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Abstract: Although high-throughput clinical and molecular data are still emerging, patients with acral melanoma (AM) continue to exhibit substantially lower overall survival following immune checkpoint inhibitor (ICI) therapy compared to those with cutaneous melanoma. This poor responsiveness stems, at least in part, from diminished surface expression of tumor-associated antigens, which normally arise from the high mutational burden characteristic of melanoma and serve as key triggers for immune recognition. Given the aggressive nature of AM and its limited response to current immunotherapies, we seek to reinvigorate anti-tumor immunity by reprogramming acral tumor cells toward a cDC1-like phenotype.

Effective T cell activation requires three coordinated signals: peptide–MHC recognition (signal 1), co-stimulatory engagement (signal 2), and cytokine signaling (signal 3). By delivering all three signals as plasmid DNA (pDNA) using nanoparticle-based delivery, we hypothesize that a robust and systemic anti-tumor immune response can be initiated. To enable this strategy, we first optimized a poly(beta-amino ester) nanoparticle (PBAE-NP) delivery platform using GFP and firefly luciferase (fLuc) reporter constructs in vitro and in vivo. In vitro, we synthesized and evaluated over 75 distinct PBAE formulations across six melanoma cell lines (B16-F10, YUMM1.7, YUMM4.1, 38885-01FP, WM4324, and WM4235). While optimal polymer performance varied by cell line, we identified formulations which achieved greater than 60% GFP expression across all models tested.

For in vivo validation, 5×10^5 YUMM4.1 cells were implanted into the mouse footpad, and the top six PBAE formulations identified in vitro were evaluated. All six achieved strong transgene expression, with bioluminescent flux ranging from 100- to 500-fold above untreated controls as measured by IVIS imaging. Building on this platform, we designed and tested 13 plasmid constructs encoding antigen-processing and presentation factors in YUMM4.1 cells. A leading PBAE formulation delivering CIITA resulted in a ~300-fold upregulation of MHC-II relative to untreated cells, an effect that could not be recapitulated by IFN-γ stimulation alone. Notably, this upregulation occurred without concomitant induction of PD-L1. We are currently initiating a pilot therapeutic study, assessing whether co-delivery of signal 1, 2, and 3 plasmids can engender a more pro-inflammatory tumor microenvironment and treat local and metastatic spread in vivo.

Funding and disclosures: This work was funded by the Melanoma Research Alliance Young Investigator Award, Johns Hopkins Center for Translational Immunoengineering (P41EB028239), and Dermatology Foundation (Dermatopathology Career Development Award).

Poster 12:

Real-World, Evidence-Based, Retrospective Study of Patients Infused with Commercially Released Lifileucel for Unresectable or Metastatic Melanoma; Barbara Ma (Weill Cornell Medicine)

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Abstract:
Background: Lifileucel is a tumor-derived autologous T-cell therapy approved by the US FDA for the treatment of patients with advanced (unresectable or metastatic) melanoma previously treated with an immune checkpoint inhibitor and, if BRAF V600-mutated, a BRAF ± MEK inhibitor. The benefit of commercial lifileucel has not yet been investigated in a real-world clinical setting. We report the first multicenter experience of lifileucel in patients with advanced melanoma.

Methods: This was a retrospective study of adults with advanced melanoma treated per the US prescribing information label across 4 US centers. The primary objectives were to evaluate the real-world effectiveness and safety of lifileucel based on responses assessed by the treating physician and adverse event (AE) data collected via voluntary spontaneous reporting. A preconditioning lymphodepletion (LD) regimen (cyclophosphamide 60 mg/kg daily over 2 days, fludarabine 25 mg/m2 daily over 5 days) was administered and further dose adjustment was performed per institutional practices followed by lifileucel infusion and up to 6 doses of interleukin-2 (IL-2; 600,000 IU/kg).

Results: Forty-one eligible patients who had ≥1 completed response assessment were included in this study. Baseline patient characteristics included median age, 59 years (range, 28–79); male, 54%; BRAF V600 mutation–positive, 44%. Melanoma subtypes were cutaneous (71%), mucosal (17%), acral (10%), or unknown primary origin (2%); liver and brain metastases were present in 32% and 29% of patients, respectively. Patients had received a median of 3 (range, 1–7) systemic anticancer therapies (including neoadjuvant/adjuvant therapy) prior to treatment with lifileucel. Following lifileucel infusion, patients received a median of 5 (range, 1–6) doses of high-dose IL-2. The

physician-assessed objective response rate (ORR) for the 41 eligible patients was 44% (n=18). Sixteen patients (39%) had a confirmed partial response. Two patients (5%) had a confirmed complete response. The median follow-up was 6 months (1-15 months). Physician-assessed ORR by lines of prior systemic therapy in the metastatic setting was 52% in patients who received ≤2 prior lines of therapy (n=23) and 33% in patients who received ≥3 prior lines of therapy (n=18). ORR by IL-2 dose was 58% for ≤3 doses (n=12) and 38% for ≥4 doses (n=29). A report of serious AEs that subsequently resolved in 1 patient was received.

Conclusions/Summary: This study confirms the benefit of lifileucel in patients with advanced melanoma in the real-world clinical setting; the efficacy was especially pronounced in those patients with fewer prior treatments.

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Poster 13:

Therapeutic Targeting of Hdm2/HdmX E3 Ligase in Melanona; Julio A. Camarero, PhD (University of Southern California)

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Abstract: The main goal of this project is to test the efficacy of a novel class of orally active compounds, cyclotides, that target the Hdm2/HdmX E3 ligase in melanoma. To our knowledge, our lead compound MCo-52-2 is the first inhibitor of Hdm2/HdmX that specifically targets its E3 ligase activity and exhibits strong anticancer properties both in vitro and in vivo. This compound represents a new class of inhibitor that stabilizes p53 not by antagonizing the p53-binding domains of Hdm2/HdmX, as other compounds do, but by inactivating the E3 ligase activity of the Hdm2/HdmX complex. In addition, inactivation of the Hdm2/HdmX E3 ligase activity stabilizes many other tumor suppressor proteins that are key to carcinogenesis and metastasis. This specific mechanism of action underlies the strong biological activity of cyclotide MCo-52-2 against several human cancer cell lines, acting in a p53-independent manner. This project has enabled the development of preclinical syngeneic melanoma models using our E3 ligase inhibitor.

Funding and disclosures: The study was funded by the Melanoma Research Alliance Established Investigator Award and R35-NIH/NIGMS.

Poster 14:

Pembrolizumab Versus Placebo as Adjuvant Therapy for High-Risk Stage II Melanoma: 4.5-Year Follow-up of KEYNOTE-716; Megan Insco (Dana-Farber Cancer Institute)

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Abstract:
Endogenous retroviral (ERV) RNA is highly expressed in cancer, although the molecular causes and consequences remain unclear. Across multiple cancer types, we identified recurrent truncating mutations in ZC3H18 (Z18), a nuclear RNA surveillance component. We show that Z18 truncating (Z18trunc) mutations are oncogenic and that Z18 plays an evolutionarily conserved role in nuclear surveillance of oncogenic ERV RNA. In zebrafish, Z18trunc accelerated melanoma onset and selectively increased ERV RNA. Z18 mutant human cancer cell lines and patient tumors also upregulated ERV RNA. In engineered human melanoma cells, Z18trunc enhanced ERV RNA accumulation more than loss of one Z18 allele, indicating dominant negative activity, and directly stabilized and relocalized ERV RNA to the cytoplasm. Expression of Z18-regulated zebrafish or human ERV RNA was sufficient to accelerate melanoma in zebrafish and was required for Z18trunc-mediated zebrafish melannoma and human melanoma cell growth. These findings reveal a mechanism underlying elevated ERV transcripts in cancer and support aberrant RNA accumulation as a broad driver of oncogenesis.
Funding and disclosures: This work was funded by the Melanoma Research Alliance Team Science Award, National Cancer Institute K08 CA248727, Ladieu Family Melanoma Research Fund, King Family Fund for Melanoma Research, and the Damon Runyon Clinical Investigator Award.

Poster 15:

Dissecting the Role of Folate Receptor beta-driven One-Carbon Metabolism in Tumor-Associated Macrophages; Brian C. Miller, MD PhD (University of North Carolina at Chapel Hill)

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Abstract: Immunosuppressive tumor-associated macrophages (TAMs) are associated with worse survival and resistance to immune checkpoint inhibitors (ICI) in patients with melanoma. Depleting pro-tumor TAMs in preclinical models improves the efficacy of ICI, but effective therapies that translate these results to patients are lacking. To discover mechanisms that enable pro-tumor TAM function, we analyzed the transcriptional profiles of pro-tumor TAMs in ICI-resistant melanoma patients. One of the most highly upregulated genes was FOLR2, which encodes for folate receptor beta. FRβ is a high affinity folate transporter uniquely expressed by myeloid cells and is upregulated on pro-tumor TAMs. Folate is a requisite coenzyme for one-carbon (1C) metabolism, a pathway that is critical for the maintenance of cellular redox balance, nucleotide synthesis, and methylation reactions. The mechanisms by which FRβ promotes pro-tumor TAM functions are unknown.

To interrogate the importance of FRβ for TAM biology, we created two new mouse models on the C57BL/6J background – Folr2 complete and conditional knock-out mice. Remarkably, deleting this single macrophage receptor polarized TAMs to an anti-tumor state, activated effector T cells, and reduced melanoma tumor growth by 60%. These phenotypes were reversed by supplementing the mouse diet with excess folate. We found that folate is depleted in the tumor microenvironment (TME), suggesting it is a limiting yet vital nutrient for pro-tumor TAM biology. To confirm these in vivo findings, we evaluated the functional properties of wild-type and Folr2-/- bone-marrow derived macrophages (BMDMs) cultured in physiological folate concentration media. Genetic ablation of FRβ results in increased pro-inflammatory cytokine production and decreased T-cell suppression capacity of BMDMs. Interestingly, Folr2-/- BMDMs also generate increased ROS. Metabolomics revealed that these cells have lower reduced glutathione pools, indicating dysregulated redox homeostasis. Inhibiting ROS via antioxidant supplementation effectively reverses the pro-inflammatory functions of Folr2-/- BMDMs. Together, these data suggest that

FRβ-mediated 1C metabolism is critical for sustaining immunosuppressive functions of TAMs through mitigation of oxidative stress. Our studies underscore the importance of 1C metabolism as a pivotal regulator of TAM biology and establish FRβ as a novel metabolic checkpoint necessary for pro-tumor TAMs.

Funding and disclosures: This work was funded by the Melanoma Research Alliance Young Investigator Award, V Scholar Award, and Burroughs Welcome CAMS, K08.

Poster 16:

Defining Patient Selection and Disease Context for TEAD Inhibition in Cutaneous Melanoma;

John M. Lamar (Department of Molecular and Cellular Physiology, Albany Medical College)

John M. Lamar[1], Janine S. A,[1]. Warren, Emily Norton[1], Ryan Kanai[1], Lindy Davis[1], Paul J. Feustel[1]; Tacy T. Tang[2], and Jessica Scarchilli[1]

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Abstract: The transcriptional co-activators YAP and TAZ drive TEAD-dependent gene programs and play central roles in melanoma and other cancers. TEAD inhibitors that disrupt YAP/TAZ–TEAD signaling have shown strong promise in preclinical models and early-phase clinical trials. However, two critical questions remain: how can we identify patients likely to benefit from TEAD inhibitors, and at what stages of melanoma progression will TEAD inhibition be most effective? To address patient selection, we combined RNA-seq and bioinformatic analyses of metastatic cutaneous melanoma cells and patient datasets to develop a YAP/TAZ transcriptional signature. This gene signature strongly correlated with YAP/TAZ activity in human melanomas and predicted melanoma cell line dependence on YAP/TAZ or TEAD, suggesting its potential utility as a biomarker to identify patients most likely to benefit from TEAD inhibitors. To define optimal disease contexts for intervention, we used genetic and pharmacological approaches to inhibit YAP/TAZ–TEAD signaling in human cutaneous melanoma cells and assessed effects on tumor growth, dissemination, and metastatic outgrowth in mouse xenograft models. While YAP/TAZ knockdown did not prevent tumor formation, it significantly slowed primary tumor growth and reduced dissemination to distant tissues. Notably, both genetic and pharmacological TEAD inhibition in disseminated tumor cells that had already seeded the lung markedly impaired metastatic outgrowth. These findings provide strong preclinical evidence that TEAD inhibition may be an effective adjuvant strategy to prevent metastasis in stage III melanoma. The poster will also present preliminary results from our MRA-funded work on acral melanoma, including initial testing of TEAD inhibitors and early progress toward a drug-repurposing pipeline to identify more effective therapeutic options.

Funding and disclosures: 1. Melanoma Research Alliance Award (# 1435113)
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2. Albany Medical College. Tacy T. Tang reports former employment with Vivace Therapeutics and has equity interest in Vivace Therapeutics. All other authors declare no conflict of interest.

Poster 17:

Augmenting Natural Killer Cell Responses to Melanoma; a Phase I clinical trial of Memory-Like Natural Killer Cells in combination with Nivolumab and Relatilimab; George Ansstas (Washington University School of Medicine)

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Abstract: Melanoma is an immunogenic cancer that responds well to immunotherapies and targeted therapies, but nearly half of metastatic melanoma patients will progress or relapse with limited subsequent treatment options.
Natural killer (NK) cells are innate lymphocytes with broad anti-tumor activity and improved safety profile over T cells, and can recognize MHC Class I negative tumor cells, a common mechanism of immunotherapy resistance through T cell evasion.
Human NK cells can be induced to exhibit innate memory-like (ML) properties following a brief combined stimulation with IL-12, IL-15, and IL-18, with enhanced recognition, functionality, longevity, and proliferative potential. Early phase clinical studies of ML NK cells in patients with AML show this treatment to be safe, effective, and feasible.
Robust preclinical data has demonstrated that ML NK cells generated from either healthy donors or patients with melanoma have effector activity against melanoma tumor cells both in vitro and in vivo. We were able to translate this laboratory evidence to a Phase I clinical trial for patients with metastatic melanoma. This trial tests the safety and preliminary efficacy of ML NK cells in combination with immune checkpoint blockade against PD1 and LAG-3. We hypothesize that ML NK cells are safe, efficacious, and will persist and expand. This is a single center, two arm Phase 1 study comparing ML NK cells from either an autologous or allogenic donor source.
The study has opened and is accruing at Washington University in Saint Louis and has treated 3 individuals with acceptable safety. Preliminary efficacy ranges from partial response to disease progression. Continued accrual is ongoing.

Funding and disclosures: This work was funded by the Melanoma Research Alliance RTFCCR Award.

Poster 18:

Quality of Life in Rare Melanomas: A Report from the Melanoma Research Alliance's RARE Registry; Jennifer E. Ward (Vanderbilt University Medical Center)

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Abstract:
Purpose: Rare melanoma subtypes, including acral lentiginous melanoma (ALM) and mucosal melanoma (MM), are associated with poor clinical outcomes and remain underrepresented in research related to patient experience. This study aimed to characterize patient-reported quality-of-life (QoL) among individuals with rare melanomas enrolled in the Melanoma Research Alliance's (MRA) RARE Registry and to compare physical and mental health functioning relative to normative population expectations.

Methods: A cross-sectional analysis was conducted among 230 registry participants who completed the Short Form-12 (SF-12) survey, including 64 with ALM, 107 with MM, and 59 with non-acral cutaneous melanoma (CM). Physical (PCS) and Mental (MCS) Component Summary scores were calculated using United States (U.S.) norm-based scoring (mean=50, SD=10). Chi-square goodness-of-fit tests compared observed distributions of T-score categories (≤1 SD below mean, within ±1 SD, ≥1 SD above mean) to expected normative proportions (16%, 68%, 16%). One-way ANOVA was used to compare descriptive variables across subtypes. Findings should be interpreted in the context of a voluntary, web-based registry sample.

Results: Mean PCS scores were below the U.S. population norm among participants with ALM (45.0±13.3) and MM (45.6±10.5), whereas CM participants demonstrated mean PCS within the normative range (50.9±9.3). Mean MCS scores were below 50 across all subtypes (ALM: 43.9±11.9; MM: 47.4±11.0; CM: 45.3±11.5). PCS and MCS scores were not correlated within subtypes (r range=0.000–0.095; all $p>0.45$). Distributional analyses revealed significant deviations from normative expectations for both PCS and MCS in

ALM and MM (all $p<0.005$), characterized primarily by overrepresentation of scores ≥1 SD below the mean. In CM, MCS, but not PCS, distributions differed significantly from norms ($p<0.001$).

Conclusions: Patients with rare melanomas (ALM and MM) demonstrate clinically meaningful deviations in QoL relative to population norms, with patterns across physical and mental domains that differ from CM. These findings highlight the importance of the unique experience of the rare melanoma community and the need for further study to better understand this population.

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J.E. Ward, serves a dual role in the RARE registry, serving on the initial development committee as a patient-advocate and participant prior to transitioning to a research-support role.

Poster 19:

Melanoma Research Alliance (MRA) RARE Registry: Inspired by Patient Advocates Working Closely with MRA; Jessica Scales (Melanoma Research Alliance)

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Abstract:

Background: Melanoma is an aggressive cancer arising from melanocytes found in both sun-exposed and sun-shielded parts of the body. Rare melanomas represent patients diagnosed with melanoma subtypes that are not typically associated with sun exposure, including acral (palms, soles and nail beds), mucosal (mucosal linings of tissue), and uveal (eye) melanomas. Together these rare subtypes represent about 10% of all diagnosed melanoma cases: uveal melanoma is the most frequent at 5%, followed by acral and mucosal melanomas at 3% and 1%, respectively. Patients with rare melanomas continue to face delayed diagnoses, poorer prognoses, and limited effectiveness of currently approved therapies compared to the more common cutaneous melanoma counterpart.

Process: In October 2022, the Melanoma Research Alliance (MRA) sponsored the first direct-to-patient registry called RARE, specifically for acral melanoma (AM) and mucosal melanoma (MM), including cutaneous melanoma (CM) as a comparator arm. The RARE Registry was inspired by and continues to be monitored by an Oversight Committee of rare melanoma patients, caregivers, and medical advisors. A major objective of the RARE Registry is to advance knowledge about AM and MM from a patient's perspective and disease journey by having participants complete eight surveys centered on demographics, disease and treatment history, inherited genetics and biomarker testing, health and lifestyle, and quality of life. Participants can also share medical records on the registry platform, either manually or through an electronic health records integration tool, to provide additional clinical information (pathology, tumor genomics, surgery, etc.) and for validating patient reported data.

Conclusions: Since its establishment and as of July 2025, 597 participants have enrolled in RARE, with 213 reporting a history with MM, 165 with AM, and 219 with CM. Survey responses are being analyzed in real-time for each of the three melanoma cohorts independently and in combination, with aggregated de-identified data accessible to participants via their online dashboard and de-identified integrated datasets of patient reported and clinical data soon to be available for researchers worldwide. Strategies have been implemented to more than double enrollment numbers over the past year. In addition, key recommendations by the strong RARE Oversight Committee have been adopted to maintain and enhance participant engagement.

Implications: The RARE Registry is actively enrolling patients and data insights will be regularly reported. Initial findings suggest that this patient-driven platform is valuable for collecting meaningful patient data for rare melanoma subtypes like AM and MM, and provides an opportunity to partner rare melanoma patients with researchers to address critical knowledge gaps in the diagnosis and treatment of AM and MM. Ongoing work involves the establishment of a biorepository to collect archived and prospective samples from RARE participants for future integrative studies and the launch of a research portal for

clinicians and researchers to access the de-identified patient-reported data, clinically abstracted data, as well as molecular data from the biorepository.

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