Melanoma Research Alliance

2026 Annual Scientific Retreat

Speaker Abstracts

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PD-1 positions CD8+ memory T cells in skin irAE sites via TGFb dependent engraftment: Niroshana Anandasabapathy

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Abstract: TRM cells are implicated in autoimmunity, successful response to immune checkpoint blockade in the tumor microenvironment, and tissue toxicities that occur after immune checkpoint blockade . Here, we identified that signaling through the immune checkpoint programmed death

receptor 1 (PD-1) strongly impacts the early specification of CD8+ TRM cells in the skin. PD-1 is expressed broadly across mouse and human skin TRM cells, and supports early TRM skin colonization, skin-specific programming and silencing of other differentiation programs. PD-1 also promotes TGFβ responsivity and skin engraftment, positioning TRM along sites where immune related adverse events commonly occur. Here we present recently published and new data that highlight the importance of this regulatory axis for anti-tumoral immunity and aPD1 toxicity pathogenesis.

Funding: N.A. and Y.L. were supported by a Melanoma Research Alliance-Brigham and Women's Hospital combined grant (to N.A.). Additional support was provided by the National Institute of Arthritis and Musculoskeletal and Skin Disease (R01 AR080436 and AR083208; to N.A.) and Weill Cornell Medicine.

Disclosures: N.A. is on the scientific advisory board of Network Bio, Shennon Pharma, and Panther Life Sciences. She has consulted for Verrica, Genmab, 23&me, and Johnson&Johnson in the prior 5 years. None of these are of relevance to the work presented.

Overcoming upfront resistance to neoadjuvant CTLA-4 plus PD-1 blockade: Christian Blank

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Abstract: Neoadjuvant checkpoint inhibition using ipilimumab plus nivolumab has become one of the treatment options for macroscopic stage III melanoma. It has been shown to induce the highest pathological response rates and is until now the only combination tested in a phase 3 trials versus adjuvant PD-1 blockade. To further improve response rates and reduce toxicity, personalisation of neoadjuvant immunotherapy is needed. Based our translational work I will discuss our novel concept of systemic immune activatability and propose novel combination therapies to achieve both reduced toxicities and improved outcome for melanoma patients.

Funding: Melanoma Research Alliance, Bristol Myers Squibb

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Fuel for function: Elucidating the metabolic constraints on CD8+ tumor-infiltrating lymphocyte function in melanoma: Tim Bullock

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Abstract: The ability of cytotoxic CD8+ T cells to recognize and respond to melanoma is established, as has the functional limitation imposed by immune checkpoints in the tumor microenvironment. Immune checkpoint inhibition has revolutionized the therapy for metastatic melanoma patients, yet too many patients receive no initial benefit or non-durable benefit. Thus, understanding what additional constraints exist on T cell function is paramount. The metabolic state of T cells provides crucial support for their functional activities, and we and others have demonstrated defects in the metabolic activity of tumor infiltrating lymphocytes. Using single cell readouts of T cell metabolic activity, we have determined that T cell effector functions more closely align with their metabolic activity than transcription factors that have been implied to regulate functional states. Further, while immune checkpoint inhibition increases the number of tumor-infiltrating CD8+ T cells, it does not elevate their metabolic or functional activity, suggesting that these are independent limitations. We have identified a key lesion in the glycolytic pathway that limits CD8+T cell metabolic activity, a deactivating post-translational modification of enolase. Further, an association with a candidate regulatory enzyme has been identified and inhibitors show promise at supporting T cell function, and these inhibitors also are cytotoxic to an array of human melanoma cell lines. We propose this metabolic defect could explain why some patients receive limited benefit from immune checkpoint inhibition therapy and alleviating it will augment T cell function and possibly increase the proportion of patients who receive durable benefit from immune checkpoint blockade. Further, armoring T cell cellular therapies against this defect also may preserve their function as they enter tumor deposits.

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The X and Y of sex disparities in cancer: the role of sex chromosomes and gonadal hormones in melanoma progression: Nora Engel

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Abstract: There is a striking and unexplained male predominance across many cancer types. Melanoma is a quintessential example of this disparity, exhibiting stark differences between males and females in incidence, progression, and response to therapy. These imbalances have not been explained and suggest that there are sex-specific protective and susceptibility factors that could be targeted for better outcomes. Yet standard-of-care therapies are delivered with no consideration for the biological sex of the patient. Our goal is to elucidate the mechanisms underlying these sex differences in melanoma and lay the groundwork for future development of sex-aware therapeutic strategies.

The two main factors that contribute to sex differences are the sex chromosome composition and sex hormones, collectively shaping a sex-specific transcriptomic and epigenetic landscape in normal somatic cells as well as in cancers. Our hypothesis is that sex differences in melanoma result from these two factors via mechanisms that are intrinsic to the tumor cells and mechanisms related to the host, in particular the immune response.

Sex chromosome and sex hormone effects are coupled and covary with each other. To disentangle them, we used the Four Core Genotypes mouse model. In this model, sex chromosome composition is independent of the gonadal sex, allowing us to identify independent and joint effects of each. We challenged the FCG mice with male and female melanoma cell lines and compared melanoma growth as well as the transcriptomes and epigenomes of the resulting tumors. We identified sex differences intrinsic to the melanoma cells in addition to host effects dependent on the sex chromosome composition and gonad type.

To distinguish sex differences in gene expression typical of normal melanocytes and those specific to melanoma cells, we isolated male and female mouse melanocytes and found hundreds of sex-biased genes. Comparison with Braf V600E Pten-/- Cdkn2a-/- XX and XY cells yielded a subset of melanoma-specific sex-biased genes, suggesting that male and female melanocytes may exhibit differences even at the initiation stage. Overall, our studies establish a compelling framework to identify the sources of sex biases in cancer that have traditionally been disregarded.

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The role of aging in immune mediated reactivation from metastatic melanoma dormancy: Mitchell Fane

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Abstract: Age is the strongest prognostic risk factor for melanoma-related death, and metastasis remains the primary driver of mortality. Yet despite this clear link, the mechanistic basis for why melanoma progression and metastatic outgrowth disproportionately worsen in older adults (>65 years) remains poorly understood. A key gap lies in the field's reliance on young (~8-week-old, equivalent to 20 human years) mouse models, which fail to capture the age-related dynamics such as immune dysfunction that shape metastatic behavior. Moreover, most studies have focused exclusively on lung metastasis, despite melanoma commonly metastasizing to sites such as the liver, which are more resistant to immune checkpoint inhibitors.

To address these limitations, we developed novel syngeneic models of melanoma metastasis and colonization in young (8 weeks), middle-aged (12-16 months), and geriatric (22-26 months) mice, targeting metastases specifically to the lung or liver. Strikingly, both lung and liver metastases were increased in middle-aged mice, whereas young and geriatric mice showed limited outgrowth, recapitulating human data where melanoma incidence is low in young adults (<50 years), peaks between ages 65-79, and decreases thereafter (79+).

These aging mouse models allow us, for the first time, to systematically assess immune surveillance pathways associated with age-induced melanoma reactivation (middle-aged) and dormancy (young and geriatric). Of the various immune subsets profiled, we found that γδ T-cells are decreased in the lungs and livers of middle-aged mice with metastatic disease but are elevated in young and (surprisingly) geriatric mice. Depletion of γδ T-cells in both young and geriatric mice reawakened dormant melanoma cells and promoted aggressive metastasis.

We next assessed cytokine-specific changes in the pre-metastatic lung and liver that might explain this altered γδ T-cell phenotype. We found the cytokine ARG1 was markedly increased by $CD11b^+$ myeloid cells in the middle-aged lung and liver only. r-ARG1 treatment in young mice was sufficient to induce metastatic reactivation, reduce γδ T-cell abundance, promote γδ T-cell exhaustion, and also reduced human Vγ9Vδ2 T-cell killing of human melanoma cells ex-vivo.

Finally, in vivo treatment with the ARG1 inhibitor CB-1158 reduced metastatic outgrowth in both the lung and liver of middle-aged mice, with no effect in young or geriatric hosts. Treatment was associated with increased γδ T-cell abundance, enhanced activation, and reduced exhaustion within the metastatic TME of middle-aged mice.

These findings uncover a previously unrecognized age-specific ARG1-γδ T-cell immunoregulatory axis that drives melanoma reactivation and metastatic progression selectively in middle-aged hosts. This work underscores the critical need for age-appropriate modeling and identifies ARG1 and γδ T-cells as a promising therapeutic target in elderly melanoma patients.

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Mitochondrial guidance for T cell exhaustion: Ping-Chih Ho

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Abstract: Accumulation of depolarized mitochondria commits T cell to exhaustion, yet the precise mechanism remains unclear. Here, we uncover that exhausted CD8+ T cells increase proteasome activity due to the accumulation of depolarized mitochondria, which drives the selective degradation of mitochondrial proteins and releases of regulatory heme (RH) levels through hemoprotein breakdown. Elevated RH in turn disrupt BACH2-mediated transcriptional regulation and thereby exacerbating T cell exhaustion and compromising stemness-like properties. Inhibition of RH nuclear import prevents Bach2 degradation and enhances the anti-tumor efficacy of antigen-specific T cells. Notably, we uncovered that the therapeutic efficacy of human CD19 CAR-T cells in B-cell acute lymphoblastic leukemia patients negatively correlates with proteasome gene signature in their CAR-T cells. Manufacturing CAR-T cells in the presence of Bortezomib, an FDA-approved proteasome inhibitor, prevents T cell exhaustion and improves therapeutic efficacy. Our findings identify a proteasome-guided heme signaling axis, governed by mitochondrial integrity, as a regulator of CD8+ T cell exhaustion and propose innovative therapeutic strategies that exploit this previously unrecognized pathway to optimize adoptive cellular immunotherapy.

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Disclosures: P.-C.H. is a co-founder of Pilatus Biosciences.

Targeting interactions between melanoma metabolism and radiation therapy: Aparna Kesarwala

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Abstract: The current standard of care for patients with advanced melanoma that has spread beyond its initial location involves surgical excision and adjuvant therapy, including radiation therapy and/or immunotherapy. While immunotherapy has significantly improved clinical outcomes for many patients, melanoma-specific survival is only 50% at 10 years, indicating that novel combination therapeutic regimens are required for those patients who become refractory to immunotherapy. Altered metabolism in melanoma has been previously correlated with therapeutic response, including immunotherapy resistance, suggesting it is a promising avenue for therapeutic intervention. Thus, there is an urgent need to understand the effects of targeting metabolism on radiation and immunotherapy response so that novel approaches can be developed to augment the efficacy of these therapies for patients with melanoma. We will present data regarding metabolic proteins as targetable biomarkers.

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Novel genetic predictor in personalized treatment selection of anti-PD1 therapies in metastatic melanoma: results from IO-GEM consortium: Tomas Kirchhoff

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Abstract: Despite successes of immune checkpoint inhibition (ICI) in metastatic melanoma (MM), a large fraction of patients does not respond to the current regimens, and for those refractory patients, the current treatment options are limited. While there is an urging clinical need for better biomarkers predicting most optimal regimens, such indicators with applicable clinical relevance are currently sparse, and almost non-existent for refractory melanoma. Given the emerging evidence that mitochondria-driven metabolism of the cytotoxic T cell-based anti-tumor immunity, in > 1,300 MM patients treated by FDA approved frontline ICI, we have discovered, validated and published the observations that mitochondrial haplogroup T (HG-T), predicts resistance to both single-line anti-PD1 (nivo) and anti-CTLA4/anti-PD1 combination (ipi/nivo; COMBO) therapies, reducing the overall response rate of both to < 18%. These findings have been validated in both Checkmate-067 MM trial as well as a large international consortium IO-GEM. We have further shown that HG-T associates with a peripheral blood phenotype with significantly reduced

effector/exhausted T cells, pointing to the mt—haplogroup (MT-HG)-controlled mechanism of mtROS detoxification, significantly impacting T-cell differentiation to effector states. While this work provides clear evidence that HG-T is a nivo-based anti-PD1 resistance biomarker, in our newly unpublished findings we have demonstrated that HG-T patients respond, with superior rates (ORR>60%), to single line pembrolizumab (pembro) that has been used interchangeably with nivo. As both antibodies show comparable clinical efficacy in our entire patient population (as expected from established clinical estimates), we have noted that outcomes differ by HG-T status. HG-T patients treated with pembro (n=666) had significantly better outcomes than those treated with nivo (n=445), with 61% vs. 25% ORR. Intriguingly, pembro-treated HG-T patients exhibited ~1 year longer median PFS and OS compared to NIVO-treated HG-T patients. PEMBRO also showed superior initial efficacy compared to COMBO (n=382), with CB of 61% vs. 32% (OR = 3.47, p = 0.014), and a similar ~1 year improvement in median PFS, while OS was comparable regardless of whether HG-T patients were treated with PEMBRO or COMBO. We have extended these observations to the biological setting exploring the immunological implications of HG-T-mediated nivo resistance. By developing novel metabolic T-cell fusions (cybrids), we have demonstrated that HG-T cybrids show reduction in ATP respiration and reduced T-cell activation compared to other MT-HGs. While cytotoxic T cell differentiation investigations are underway along with the metabolic analyses of MT-HGs, these data collectively suggest a novel biological paradigm of MT-HG-controlled effects on anti PD1 therapies, implying selective use of anti PD1 antibodies for achieving better treatment outcomes. We strongly suggest that the proposed findings will have imminent clinical implications in other melanoma treatment regimens beyond metastatic setting (e.g. neoadjuvant therapies) but will also provide important clinical potential for T-cell based therapies and biomarker-based predictions in emerging personalized vaccine -based treatments. At the same time, it is reasonable to expect that the improvement of outcomes driven by the strategies of MT-HG stratification may be widely applicable in immune checkpoint-based therapies of other cancer types.

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Noninvasive prediction of severe toxicity from immune checkpoint blockade: Aaron Newman

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Abstract: Immune checkpoint inhibitors (ICIs) have revolutionized melanoma treatment, significantly improving outcomes. Nevertheless, too many melanoma patients undergoing ICI treatment experience severe and often debilitating immune-related adverse events (irAEs), which remain difficult to predict prior to treatment initiation. In a retrospective melanoma cohort treated with ICIs, we previously found that elevated levels of activated circulating CD4 effector memory T (TEM) cells and higher T cell receptor diversity in pretreatment peripheral blood were strongly associated with the development of severe irAEs, irrespective of the affected organ system (Lozano et al., Nature Medicine, 2022). Here, we present data from an extended prospective validation cohort from 57 patients across two academic medical centers.

Of 57 patients, 34 received combination anti-PD1/anti-CTLA4 ICIs, 6 received combination anti-PD1/anti-LAG3 ICIs, and 17 received anti-PD1 ICI. After treatment initiation, 19 patients experienced severe irAEs (grade 3+) at a median of 12.1 weeks (range 3-54), including 5 with life-threatening (grade 4) irAEs. irAEs were graded on a 5-point scale using the Common Terminology Criteria for Adverse Events v5.

Peripheral blood mononuclear cells (PBMCs) were prepared from pretreatment (Cycle 1 Day 1) blood samples obtained from all patients. We performed mass cytometry (CyTOF) on all PBMCs using a 38-marker panel to deeply profile immune subsets. CyTOF revealed significantly elevated circulating activated CD4 TEM cells in patients who developed severe irAEs ($P<0.00001$; AUC=0.86), including those treated with combination ICIs ($P<0.00001$; AUC=0.89). Moreover, activated CD4 TEM levels exhibited progressive elevation across increasing irAE grades (P=2.8e-5, Jonckheere-Terpstra test).

We also performed bulk RNA-seq on pretreatment PBMC samples from 24 patients. The data were analyzed using (i) CIBERSORTx to estimate CD4 memory T cell abundance and (ii) MiXCR for clonotype assembly followed by quantification of T cell receptor (TCR) diversity using Shannon entropy. Applying the previously trained composite model (Lozano et al.), we determined a composite model score for each patient by combining of CD4 memory T cell abundance and TCR diversity. The composite model score was strongly associated with severe irAE development (P=0.0009, AUC=0.88), and in a median split, identified patients with shorter time to severe irAE development (3 months vs. not reached; P=0.006; HR=10.5). Notably, composite model features and the overall score had no significant association with immunotherapy benefit.

Single-cell RNA-seq profiling and flow cytometry were also performed for pretreatment PBMC samples from a subset of patients (n=10). Peripheral immune subsets including CD4 TEM showed high concordance between paired scRNA-seq, flow cytometry, and CyTOF samples, and CD4 TEM cell levels were again significantly higher in patients who developed severe irAE, whether profiled by scRNA-seq or flow cytometry ($P<0.05$).

In summary, we prospectively validated the strong association of both circulating activated CD4 TEM levels and a composite model score measured by RNA-seq with severe irAE development, independent of affected organ system, ICI therapy type, response status, or institution. These findings hold promise for future pretreatment risk stratification of ICI therapy.

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Targeting fatty acid and glucose metabolism in melanoma: Rachel Perry

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Abstract: Metabolic reprogramming is a defining feature of melanoma pathogenesis, progression, and therapeutic responsiveness, manifesting in alterations of both fatty acid and glucose metabolic pathways that support tumor growth, immune evasion, and host systemic physiology. Despite advances in immunotherapy and targeted agents, treatment resistance and debilitating complications such as cancer-related fatigue (CRF) remain significant barriers to durable clinical benefit. In this talk, I will synthesize mechanistic insights from two complementary bodies of work that leverage metabolic targeting to improve melanoma outcomes.

First, our studies demonstrate that modulation of fatty acid partitioning profoundly influences the tumor immune microenvironment and the efficacy of immunotherapy. Using murine melanoma models, we show that the thiazolidinedione (TZD) class drug rosiglitazone – a peroxisome proliferator-activated receptor γ (PPARγ) agonist clinically used to enhance systemic insulin sensitivity – enhances anti-PD-1 immunotherapy responses. TZD treatment reduced circulating insulin, increased fatty acid availability within the tumor microenvironment, and directly and indirectly lowered PD-1 expression on tumor-infiltrating $CD8^+$ T cells, resulting in improved control of tumor growth when combined with checkpoint blockade. Clinical correlative analyses reveal that subcutaneous adipose tissue and tumor PPARγ expression correlate with greater immunotherapy efficacy, highlighting metabolic state as a modulator of antitumor immunity. These results elucidate a metabolic mechanism linking fatty acid handling and immune reinvigoration in melanoma, and propose metabolic adjuvants to sensitize to immunotherapy.

Second, targeting glucose metabolism via dichloroacetate (DCA), a pyruvate dehydrogenase kinase inhibitor, offers a promising strategy to mitigate systemic metabolic consequences of melanoma beyond direct antitumor activity. In preclinical tumor-bearing models, DCA did not significantly alter tumor growth or interfere with standard therapies, but reduced circulating lactate and preserved physical function in late-stage disease. These effects translated to higher muscle membrane potential, delayed proteolysis, and reduced oxidative stress – physiological states relevant to cancer-related fatigue, a major cause of morbidity in melanoma patients. Since DCA has been tested for metabolic indications with a favorable safety profile, these findings open a translational avenue for treating CRF in cancer populations.

Together, this integrated metabolic framework highlights dual axes of vulnerability in melanoma: (1) fatty acid metabolism as a lever to shape immune competence and therapeutic sensitivity, and (2) glucose and lactate metabolism as a determinant of systemic host resilience and quality of life. By combining insights into how tumor and immune cells compete for and adapt to nutrient cues, we propose strategies that extend beyond tumor cytotoxicity to encompass metabolic support of antitumor immunity and host function. Such multifaceted metabolic interventions may complement existing therapies, providing synergistic benefits in melanoma management.

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Microglial reprogramming enhances antitumor immunity and immunotherapy response in melanoma brain metastases: Berta Lopez Sánchez-Laorden

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5. Translational Cancer Research Group, Area 3 Cancer, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain

Abstract: Melanoma is one of the tumor types with the highest risk of brain metastasis. However, the biology of melanoma brain metastasis and the role of the brain immune microenvironment in treatment responses are not yet fully understood. Using preclinical models and single-cell transcriptomics, we have identified a mechanism that enhances antitumor immunity in melanoma brain metastasis. We show that activation of the Rela/Nuclear Factor kB (NF-kB) pathway in microglia promotes melanoma brain metastasis. Targeting this pathway elicits microglia reprogramming toward a proinflammatory phenotype, which enhances antitumor immunity and reduces brain metastatic burden. Furthermore, we found that proinflammatory microglial markers in melanoma brain metastasis are associated with improved responses to immune checkpoint inhibitors in patients and targeting Rela/NF-kB pathway in mice improves responses to these therapies in the brain, suggesting a strategy to enhance antitumor immunity and responses to immune checkpoint inhibitors in patients with melanoma brain metastasis.

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A novel genetically engineered allograft model (GEAM) of Kit-activated melanomas: Hensin Tsao

Hensin Tsao[1,2]

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2. Harvard Medical School

Abstract: Acral lentiginous melanoma (ALM) is a biologically distinct melanoma subtype characterized by poor outcomes, limited therapeutic options, and a unique mutational landscape independent of ultraviolet exposure. KIT mutations are enriched in acral and mucosal melanomas, yet clinical responses to c-KIT inhibitors remain modest and heterogeneous. In this work, we describe a mechanistically informed framework for studying KIT-mutant acral melanoma and leveraging this biology for therapeutic innovation. Using the recurrent KIT(K642E) mutation (Kit(K641E) in mice), we developed a genetically defined murine melanoma "avatar" that faithfully recapitulates key features of human KIT-mutant disease, including enhanced proliferative capacity, chromosomal instability, partial sensitivity to c-KIT inhibition, and tumorigenicity in immunocompetent hosts. While pharmacologic c-KIT blockade suppresses tumor growth, durable responses remain limited, underscoring the need for combinatorial strategies. To address this, we engineered a hybrid biomimetic nanovaccine that fuses dendritic cell membranes with KIT-mutant melanoma membranes, enabling simultaneous antigen presentation and a panoply of tumor antigens. This platform demonstrates efficient lymph node and tumor homing, robust dendritic cell maturation, $CD8^+$ T-cell activation, favorable macrophage polarization, and significant therapeutic and prophylactic antitumor efficacy in vivo, with minimal toxicity. Collectively, these findings establish a tractable preclinical model for KIT-mutant acral melanoma and introduce a versatile immunotherapeutic strategy with potential to overcome the intrinsic resistance of this aggressive melanoma subtype.

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Tumor evolution and heterogeneity in uveal melanoma: insights from a post-mortem study: Samra Turajilc

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Abstract: Uveal melanoma is a rare but aggressive melanoma subtype with a distinct molecular landscape and dismal prognosis once metastatic. Until tebentafusp's approval, no treatment improved survival in metastatic uveal melanoma (mUM). Despite advances in primary disease characterization, the molecular evolution of mUM remains poorly understood.

Through the PEACE (Posthumous Evaluation of Advanced Cancer Environment) study, we performed comprehensive post-mortem tumour sampling in 12 mUM patients, amounting to 478 samples from up to 15 metastatic sites per patient. Nine patients received immune checkpoint inhibitors and five received tebentafusp.

We integrated targeted panel sequencing, RNA-seq, detailed histopathology, and radiological assessment to characterize late-stage mUM evolution. We observed copy number heterogeneity to drive the evolution of late-stage mUM, with chromosome 8q gain near-ubiquitous and whole genome doubling being a frequent event. Tumours harbouring BAP1 vs SF3B1 driver mutations exhibited distinct evolutionary trajectories. To characterize the immune microenvironment in tebentafusp-exposed tumours, we performed IHC and high-plex spatial profiling. While genomic disruption of antigen presentation machinery, including HLA genes, was rare, tebentafusp-exposed tumours showed reduced gp100 and HLA-A expression.

This study represents the largest and most comprehensive post-mortem mUM dataset to date, revealing the diverse evolutionary landscape and heterogeneity underlying treatment resistance in lethal metastatic uveal melanoma.

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Stromal lipids and melanoma metastasis: Amaya Virós

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Abstract: Tumour cells respond dynamically to cues from the tumour microenvironment (TME), yet the specific stromal signals that govern metastatic burden and organ tropism remain poorly defined. We demonstrate that lipid species derived from young subcutaneous adipocytes, particularly phosphatidylcholines, are avidly taken up by melanoma cells. This lipid uptake enhances PI3K–AKT signalling, fatty acid oxidation, mitochondrial respiration (OXPHOS), and oxidative stress, collectively leading to a reduction in metastatic burden. Melanoma cells with high OXPHOS preferentially colonise the lung and brain, and pharmacological attenuation of oxidative stress in young animals redirects metastatic dissemination from the lung toward the liver.

In contrast, the aged TME is characterised by reduced overall lipid availability but an enrichment in ceramides. Uptake of these ceramides by melanoma cells is associated with increased metastatic potential. Ceramides from the aged microenvironment activate an S1P–STAT3–IL-6 signalling cascade that biases metastatic spread toward the liver. Moreover, in the aged skin, the relative scarcity of lipids that can be taken up by melanoma cells imposes lower OXPHOS in the melanoma cell, which further facilitates metastasis. Perturbation of these pathways—through inhibition of OXPHOS in the young TME or blockade of IL-6 receptor signalling in the aged TME—attenuates the age-dependent patterns of metastasis driven by lipid composition.

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LAG-3 receptor-ligand biology and targeted next-generation immunotherapies: Jun Wang

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Abstract: Immune-checkpoint blockade, led by PD-1/PD-L1–targeted therapies, has transformed cancer treatment yet benefits only a subset of patients. Although LAG-3 targeting has recently been approved for cancer, its mechanism of action remains incompletely understood. We decoded the flexible dimerization features of LAG-3 through its D2 immunoglobulin domain, which critically shape T-cell suppression. These insights inform alternative strategies for LAG-3–directed immunotherapy for cancer. We further revealed a central role of TCR proximity in LAG-3–mediated suppression and developed the first checkpoint-based bispecific T-cell silencer (LAG-3/TCR BiTS) to selectively attenuate LAG-3+ autoreactive T cells. These findings informed novel approaches for treating autoimmunity or immune-related adverse effects during cancer immunotherapy.

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Sustaining antitumor response of CD8+ T cells by distinct metabolic orchestration: Bin Zhang

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Abstract: The CD8+ T cells within tumor microenvironment are the most essential component in tumor immunity. Activation of CD8+ T cells is coupled to various metabolic reprogrammings. Glutathione (GSH) as the key role in oxidative metabolism to buffer increased reactive oxygen species (ROS) in activated T cells, is important for T cells effector functions in the context of inflammation. The function and mechanism by GSH metabolism in regulating anti-tumor immunity of CD8+ T cells remain unknown. Here, we show that GSH is dependent on glutathione peroxidase 4 (Gpx4) to maintain CD8+ T cell activity, and A2AR signaling pathway interacts with the GSH-Gpx4 axis to reprogram the metabolism and survival of functional CD8+ T cells. Interestingly, A2AR signaling blockade increases effector function of antitumor CD8+ T cells, but facilitates the assumption of intracellular GSH, leading to rapid ferroptosis. Notably, combination treatment with a potent ferroptosis inhibitor liproxstatin-1 (Lip-1) and A2AR antagonists elicits a synergistic antitumor efficacy and enhanced mitochondrial functionality of antitumor CD8+ T cells in multiple mouse tumor models. Finally, we generate a gene expression signature for GSH metabolism in tumor-infiltrating CD8+ T cells positively correlating with favorable clinical outcomes. Our work demonstrate a critical role of GSH metabolism in modulating antitumor CD8+ T cell survival and functionality, pointing to new strategies of targeting these cells for cancer immunotherapy.

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