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Meeting Report From the 2025 Cure Ocular Melanoma (CURE OM) Global Science Meeting, Amsterdam, the Netherlands, October 2025

Andrew E. Aplin[1] | Katherina Alsina[2] | Allison S. Betof[3] | Joseph Birkett[4] | Marcus O. Butler[5] | George Cole Jr.[6] | Rizwan Haq[7] | Florian A. Karreth[8] | Vinit B. Mahajan[9,10] | Rahul Marpadga[11] | Prithvi Mruthyunjaya[10] | Paul Nathan[12,13,14] | Jonas A. Nilsson[15] | Gary Palmer[6] | Joseph J. Sacco[16,17] | Takami Sato[18] | Sarah Stanhope[19] | Pang-ning Teng[20] | Kyleigh LiPira[20]

[1]Department of Pharmacology, Physiology, and Cancer Biology, Thomas Jefferson University and Sidney Kimmel Comprehensive Cancer Center, Philadelphia, Pennsylvania, USA | [2]Castle Biosciences, Friendswood, Texas, USA | [3]Stanford University School of Medicine, Stanford, California, USA | [4]Aura Biosciences, Boston, Massachusetts, USA | [5]Princess Margaret Cancer Centre, Department of Medicine and Immunology, University of Toronto, Toronto, Ontario, Canada | [6]IDEAYA Biosciences, Inc., South San Francisco, California, USA | [7]Dana-Farber Cancer Institute, Boston, Massachusetts, USA | [8]H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida, USA | [9]Molecular Surgery Laboratory, Department of Ophthalmology, Stanford University, Palo Alto, California, USA | [10]Alan Adler Center for Ophthalmic Oncology, Stanford University, Palo Alto, California, USA | [11]Replimune, Woburn, Massachusetts, USA | [12]Mount Vernon Cancer Centre, Rickmansworth, UK | [13]University College London, London, UK | [14]University College London Hospital, London, UK | [15]University of Gothenburg, Gothenburg, Sweden | [16]University of Liverpool, Liverpool, UK | [17]The Clatterbridge Cancer Centre, Liverpool, UK | [18]Department of Medical Oncology, Thomas Jefferson University and Sidney Kimmel Comprehensive Cancer Center, Philadelphia, Pennsylvania, USA | [19]Immunocore Ltd., Abingdon, UK | [20]Melanoma Research Foundation, Washington, District of Columbia, USA

Correspondence: Andrew E. Aplin (andrew.aplin@jefferson.edu)

Received: 13 April 2026 | **Revised:** 12 May 2026 | **Accepted:** 26 May 2026

ABSTRACT

The 2025 Cure Ocular Melanoma (CURE OM) Global Science Meeting took place in Amsterdam, The Netherlands on October 25th, 2025. Several promising drug candidates are in development; however, there is still an urgent need for better prevention, detection, and treatment of uveal melanoma. The purpose of this meeting was to promote international collaboration and idea exchange between scientists, industry, and patient advocates.

1 | Introduction

In conjunction with the 22nd International Congress of the Society for Melanoma Research, the 2025 Cure Ocular Melanoma (CURE OM) Global Science Meeting was held at the RAI Convention Center in Amsterdam, The Netherlands on October 25th, 2025. The Melanoma Research Foundation's (MRF) created the CURE OM initiative in 2011 to increase awareness, education, and research funding for ocular melanoma. Uveal melanoma is the most common form of ocular melanoma. Successful treatments exist for primary tumors; however, about half of uveal melanoma cases metastasize to other parts of the body. Once the disease has spread, the chance of survival is low (Kujala et al. 2003; Nathan et al. 2021). Several promising drug candidates are being developed to treat metastatic melanoma, but there is still an urgent need for better prevention, detection, and treatment.

The purpose of this meeting was to encourage international collaboration and idea exchange between scientists, industry, and patient advocates. Dr. Andrew E. Aplin (Thomas Jefferson University) organized the meeting and guided discussions for the day. The event was attended by 55 participants from 7 countries. Six industry sponsors took part in the meeting and shared their latest advancements. Three patient advocacy organizations also attended the meeting. This report reviews the topics

Research Highlights

- Uveal melanoma is the most common eye cancer in adults and the liver is the predominant organ of metastatic outgrowth.
- Standard chemotherapies rarely induce clinical responses in uveal melanoma patients with macrometastasis; however, tebentafusp and liver perfused melphalan provide benefit.
- There is substantial ongoing research and clinical trial activity in ocular melanoma.

discussed at the meeting. The meeting agenda can be found in the supplement.

2 | Session 1: Powering the Immune Arsenal: ICIs, Vaccines, Viruses & Cellular Approaches

Dr. Katherina Alsina (Castle Biosciences) chaired the first session of the day, which focused on immunotherapy and vaccine approaches.

Dr. Rahul Marpadga (Replimune) provided a history of the evolution of oncolytic viruses, as a treatment approach for cancer. These viruses are genetically engineered to enhance oncolytic activity to induce lysis of local cancer cells and immune responses to potentially generate systemic anti-tumor effects (Khushalani et al. 2023; Lin et al. 2023; Thomas et al. 2019). There are many genetically modified viruses under investigation for the treatment of cancer. One notable example of an FDA approved treatment is talimogene laherparepvec (T-VEC), a modified herpes simplex virus type 1 (HSV-1) used to treat melanoma. T-VEC is modified from wild type HSV-1 in several major ways. The first is deletion of genes that cause it to be a pathogen. The second is the insertion of a gene that produces granulocyte-macrophage colony-stimulating factor (GM-CSF) that activates the immune system, specifically dendritic cells, to attack cancer cells (Nassief et al. 2024).

A new development in HSV-1 based oncolytic immunotherapy from Replimune is RPx, a platform developed using a potent strain of HSV-1 isolate that kills a broad range of cancer cell lines and is also engineered to express a fusogenic gibbon-ape leukemia virus glycoprotein (GALV-GP) to enhance cell fusion and augment immunogenic cell death with the goal of leading to increased local and systemic anti-tumor activity. The first iteration of RPx is RP1, which also encodes GM-CSF to activate and mature dendritic cells. RP1 is currently being developed in advanced melanoma patients who progressed on an anti-PD-1 containing regimen. The second iteration of RPx is RP2, which further expresses an anti-CTLA-4 antibody-like molecule to improve T cell activation and provide local secretion of anti-CTLA-4 antibody without the associated systemic toxicities. RP2 is intended to target tumors that are less immune sensitive. There are 7 ongoing clinical trials for RP1 and RP2 with over 700 patients treated. RP2 is being tested in uveal melanoma patients in contrast to RP1, which is being tested in cutaneous melanoma patients.

Next, Dr. Allison Betof (Stanford University) shared the urgent need for novel treatments for uveal melanoma and highlighted some promising treatments in development. Unlike most melanomas, uveal melanomas often respond poorly to immune checkpoint inhibitors (ICI). The genetic code of uveal melanoma is closer to normal tissue than the average skin melanoma. This means that immune cells have a harder time distinguishing uveal melanoma from normal tissue. Additionally, a mix of low T-cell levels and high immune suppressive factors makes it challenging for immunotherapies to properly work. Combination therapies and/or non-ICI strategies may increase patient response to treatment and ultimately improve their long-term survival.

Dr. Betof shared the results of a Phase 1 clinical trial (NCT04336241). This study tested the safety, best dosage, and side effects of the combination therapy of RP2 and the ICI, Nivolumab. Patients were randomized to either RP2 only or RP2 plus Nivolumab. Out of 17 uveal melanoma cases treated, 5 (29.4%) patients' tumors shrank significantly, and 5 (29.4%) patients' tumors stayed stable in size (Sacco et al. 2024). The median duration of response for both groups was 11.5 months. The study also examined whether this approach would be effective for patients who are not eligible for Tebentafusp. Tebentafusp is the first drug to significantly improve survival for patients with metastatic uveal melanoma (Nathan et al. 2021); however, many tumors do not express the HLA subtype that allows Tebentafusp to target the melanoma cells. Patients without the necessary HLA (HLA-A*02:01) have an urgent need for effective treatments. Strikingly, patients with and without the necessary HLA for Tebentafusp responded equally to the RP2 therapies. This positions RP2 plus Nivolumab as a potential treatment for patients who either cannot take or do not respond to Tebentafusp (Sacco et al. 2024). The Phase 2 trial is in open enrollment (Sacco, Moser, et al. 2025).

Dr. Betof also highlighted the pilot trial of Lifileucel (NCT05507095) for metastatic uveal melanoma, which completed accrual and has a manuscript in preparation. The results from a Phase 1 clinical trial of Anzu-cel (IMA203) are also promising. This treatment takes a patient's own T cells, engineers them to target PRAME, a protein expressed in 90% of uveal melanoma patients. 10 of 15 (67%) of patients had significant tumor shrinkage. The median progression-free survival for this group was 8.5 months (range of 1.4–32.9 months), with an overall survival rate of 71% at 12 months (Patel et al. 2025). The Phase 2 expansion to the Phase 1b (NCT03686124) cohort is recruiting in Germany and the United States.

Dr. Joe Sacco (University of Liverpool) discussed how recent advancements have improved outcomes of immunotherapy treatment for uveal melanoma. The development of Tebentafusp led to many insights into uveal melanoma, and several of these discoveries have challenged the notion that uveal melanoma is a universally "cold" tumor. The results from the IMCgp100-202 clinical trial (NCT03070392) revealed that most patients had T-cells moving into the tumor. However, the balance of immune suppressive and activating factors in the microenvironment is more impactful to success than the actual number of T-cells (Sacco, Kirk, et al. 2025). Patients whose disease has spread, but not to the liver, benefit from a combination of Ipilimumab plus Nivolumab (Liang et al. 2023; Rodriguez et al. 2020). The CHOPIN trial suggests

that percutaneous hepatic perfusion (PHP) changes the tumor microenvironment to drive better responses to Ipilimumab and Nivolumab (Tong et al. 2023). Dr. Sacco then looked to the future, exploring how translational research can guide the investigation of new agents. He argued that increased biopsies on treatment and at progression of disease are vital to understanding the mechanisms of resistance in uveal melanoma. Measuring circulating tumor DNA (ctDNA) is also a promising mechanism for predicting patient survival. These fragments of dead tumor cells found in the bloodstream can be used to check effectiveness of new therapies (Ramelyte et al. 2024).

The development of novel models continues to be important for drug discovery. Dr. Sacco's team at University of Liverpool is developing a novel chick embryo model (chorioallantoic membrane, CAM) to grow uveal melanoma and liver cells together. The next step for this research is to develop a model augmented with a patient's own tumor and immune cells to characterize cell interactions and pilot drug testing. A novel humanized patient-derived xenograft (PDX) model from Drs. Takami Sato and Mizue Terai (Thomas Jefferson University, Philadelphia) is also in development. Finally, Dr. Sacco emphasized the importance of collaboration for research, highlighting the international ocular melanoma natural history study (OMNi).

3 | Session 2: Fueling Discovery: Tools Driving OM Research Forward

Dr. Corine Bertolotto (INSERM, Nice) led the second session of the day, which focused on new tools to help researchers study ocular melanomas.

Dr. Florian Karreth (Moffitt Cancer Center, Tampa) highlighted his team's efforts to create novel uveal melanoma mouse models. There are multiple limitations to current uveal melanoma mouse models, as they do not replicate the disease well. Dr. Karreth's team developed a mouse model that resembles the genetics and progression of uveal melanoma in humans. The model has the potential to spread on its own. Unfortunately, the animals must be euthanized due to their eye tumors before the spreading cells have a chance to develop into proper metastatic tumors. This can be addressed by injecting cancer cells into the bloodstream or spleen of healthy mice, which then form metastasis in the liver or other organs. In these transplant models, metastasis resembles the patterns found in humans, representing a valuable tool to study uveal melanoma metastasis (Xu et al. 2026).

Dr. Jonas Nilsson (University of Gothenburg) shared the latest insights from his lab. Dr. Nilsson's group uses PDX models, which are designed to grow patient tissue and are still the gold standard for exploring disease genetics and drug targets. Because of the difference between mouse and human immune systems, PDX models have limitations for studying immunotherapies. To combat this, his team injected tumors and T-cells from the same patient into a new type of mice, hIL2-NOG, where the T cells could survive and exert anti-tumoral activities. This model is useful for studying T cell therapies for melanoma and other solid tumors and for testing cell therapy products such as tumor-infiltrating lymphocytes. A clinical trial (HAITILS), in which the quality of the TILS from a novel manufacturing procedure was verified in PDX models, has just been completed at the Sahlgrenska Hospital in Gothenburg (Jespersen et al. 2017; Nilsson et al. 2022). Using genetic studies, his team found that melanomas have increased HER2, a protein that promotes cancer growth. This suggests that existing cancer therapies that target HER2 might be effective. They found that HER2 CAR-T cell therapies are effective at eradicating uveal melanoma (Forsberg et al. 2019). While this is promising, the field may be moving away from cellular therapies due to the time-intensive nature of the treatment and novel technologies enabling HER2 CAR-T cell generation inside a patient.

Dr. Nilsson's team shifted their focus to studying antibody-drug conjugates (ADCs). ADCs are chemotherapy treatments that only target the tumor (Tsao et al. 2025). Two ADCs, Kadcyla and Enhertu, treat cancers with high HER2 levels, such as breast cancer. They found that Enhertu, but not Kadcyla, is effective at treating uveal melanoma in PDX models and that the mechanism of action is likely different than what has previously been thought.

Drs. Prithvi Mruthyunjaya and Vinit Mahajan (Stanford University) discussed liquid biopsy proteomics and its potential for use in uveal melanoma. Biopsies are necessary to assess risk and to assess prognosis. Liquid biopsies are easier to perform and less invasive than tissue biopsies. They don't sample tissue directly from the tumor. This means that typical genetic information is not collected and tumors are not visualized under the microscope.

The team at Stanford developed TEMPO, a technology that characterizes thousands of proteins found in liquid biopsies (Wolf et al. 2023). This tool can identify protein signatures that are unique to uveal melanoma. The research team found 3 different protein expression profiles that correlate with disease prognosis. Specific combinations of proteins can also classify tumors as low risk (class 1) or high risk (class 2). The team's new tool "TEMPO-chat" measures how tumor cells talk to each other at the protein level. They found that each of the 3 uveal melanoma profiles communicates differently with the immune system. These insights could help predict what treatments will work for a patient.

4 | Session 3: Innovation Lightening Talks from Industry

The industry panel chaired by Dr. Rebecca Lee highlighted 5 current and upcoming products that have the potential to improve disease management, survival, and quality of life for patients with uveal melanoma.

Castle Biosciences (Dr. Katherina Alsina, Director—Uveal Melanoma) discussed their prognostic testing for uveal melanoma. The testing includes DecisionDx-UM, DecisionDx-PRAME, and DecisionDx-UMSeq, which can be performed from a single primary tumor biopsy sample to assess metastatic risk based on gene expression profiling (GEP), PRAME status, and multiple DNA markers. Based on results reported from the prospective, multi-center COOG2 study (Harbour et al. 2024), Castle Biosciences has updated their clinical reporting as of March 2025 to include results incorporating GEP class with PRAME

status. Class 1 tumors without PRAME expression (Class 1/PRAME-) have the lowest risk of metastasis and most favorable prognosis (96% metastasis-free survival (MFS) at 5 years); Class 1 tumors with PRAME expression (Class 1/PRAME+) have an intermediate risk (81% 5-year MFS); Class 2 tumors are all generally considered high risk; however, Class 2/PRAME- tumors have better outcomes and longer metastasis-free survival (58% 5-year MFS) compared to Class 2/PRAME+ tumors (45% 5-year MFS). Findings from the COOG2 study show that GEP classification remains the most powerful predictor of metastasis-free survival, with *PRAME* status offering important supplementary risk information. Integrating both markers may improve the selection of high-risk patients for clinical trial enrollment.

IDEAYA Biosciences (Dr. Gary Palmer, SVP of Medical Affairs) highlighted their ongoing development of Darovasertib. Darovasertib is an oral medication targeted to inhibit overactive protein kinase C signaling caused by the genes encoding either G protein subunit alpha Q (GNAQ) or G protein subunit alpha 11 (GNA11), which are frequently mutated in uveal melanoma (Cao et al. 2023). IDEAYA Biosciences has 4 clinical trials testing Darovasertib in both primary and metastatic uveal melanoma settings.

Aura Biosciences (Joseph Birkett, Executive Director of Medical Affairs –EU/ROW) discussed their investigational drug belzupacap sartalocan (AU-011; Bel-sar). This medication works in two distinct ways. Bel-sar selectively binds to tumor cells and causes them to die via a process known as necrosis after activation with infrared light. Then, molecules released from dying cells alert the immune system to kill more tumor cells (Kines et al. 2021). Phase 2 clinical trial (NCT04417530) results are promising, showing Bel-sar's potential to become the first approved vision-preserving therapy in primary uveal melanoma if the Phase 3 results are positive. The Phase 3 clinical trial (NCT06007690), which is currently enrolling, is a randomized, masked, controlled trial to evaluate the efficacy and safety of belzupacap sartalocan (AU-011) treatment compared to sham control in subjects with primary indeterminate lesions or small choroidal melanoma (CoMpass).

Delcath Systems (Johnny John, SVP Clinical Operations and Medical Affairs) presented the results of the Phase 2 combined percutaneous hepatic perfusion (PHP) with Ipilimumab plus Nivolumab in metastatic uveal melanoma (CHOPIN) trial (NCT04283890). Seventy-six patients were randomly selected to either receive 2 treatments of PHP or 4 treatments of Ipililumab plus Nivolumab and 2 treatments of PHP. Progression free survival at 1 year was 54.7% in the combination therapy versus 15.8% for PHP-only and the objective response rate was 76.3% in the combination therapy versus 39.5% for PHP only. Both groups had a similar survival rate 1 year after treatment (82.8% for the combination therapy and 82.2% for PHP-only). However, 2 years post treatment, the combination treatment had a better survival rate (49.6%) than the PHP-only group (22.1%) (Kapiteijn et al. 2025).

iOnctura (Lars van der Veen Co-Founder, CSO) highlighted their small molecule PI3Kδ inhibitor, roginolisib. PI3Kδ is a protein that is essential to the communication between tumor cells and the tumor environment. Roginolisib works by blocking the inactive form of PI3Kδ, which allows for high selectivity. In a Phase 1 clinical trial (NCT06879717), Roginolisib doubled the overall survival rate for metastatic uveal melanoma patients when compared to historic controls. No serious treatment-related adverse events were noted. Phase 2 trials (NCT06717126) are ongoing with 86 patients already enrolled.

4.1 | Lunch and Learn

During lunch, topics were placed at tables to facilitate discussions. Topics included the VISION Registry, patient advocates, preclinical models, and grant funding. Translational models were a popular topic for discussion, as well as networking and collaboration.

5 | Session 4: T Cell Engagers & the RECIST Disconnect: What Tebentafusp Teaches Us

The fourth session of the day focused on the T cell engager Tebentafusp. Dr. Martine Jager (Leiden University) chaired this session.

Dr. Sarah Stanhope (Immunocore) reviewed the Phase 3 clinical trial of Tebentafusp in metastatic uveal melanoma (NCT03070392). Tebentafusp engages the immune system by creating a bridge between T-cells and tumor cells, allowing any T-cell, rather than a small subset of T cells, to detect the tumor. Tebentafusp significantly improved patient survival when compared to controls (Hassel et al. 2023). After reviewing the top responders of both treatment groups, Tebentafusp still outperformed the control regarding longevity. Overall, Tebentafusp was well tolerated, but there were expected side effects, including fever and chills. Most side effects occurred within the first 4 weeks of treatment, including dose escalation. Reactions became less frequent and severe with multiple doses.

The reduction in ctDNA levels seen after treatment was also promising. At week 9 of treatment, 88% of patients saw reductions in ctDNA and 37% had no detectable ctDNA. Survival increased significantly for patients with no ctDNA. The researchers believe that the ctDNA data may be a better predictor of success than tracking tumor size alone. There are a few theories to explain this. An increased immune response causes inflammation of the tumor. This may look like tumor growth even if Tebentafusp had some positive benefits. This inflammation can slow tumor growth, leading to lower ctDNA levels. Some tumors die through necrosis, which may mimic stable disease.

Professor Paul Nathan (Mount Vernon Cancer Centre & University College London) discussed additional therapies to improve the prognosis for high-risk uveal melanomas. These adjuvant therapies begin after primary treatment, such as enucleation and radiation, to reduce the chance of the disease from coming back in other parts of the body. The ATOM clinical trial (NCT06246149) will test whether Tebentafusp will prevent or delay recurrence after treatment of high-risk uveal melanoma. This study will focus on the relapse free survival of patients (a reflection of whether the disease does or doesn't relapse), and any treatment related adverse events. Patients who are AJCC stage III or AJCC stage II with the presence of

high-risk genetic changes in the cancer are potentially eligible. They also need to be positive for the HLA*A2.01 immune marker to be eligible since Tebentafusp requires HLA*A2.01 expression to work. Two hundred ninety patients will be randomly selected for either 24 weekly injections of Tebentafusp or no added intervention. There will be approximately 24 study sites—15 in Europe and 9 in North America. The US sites opened in April 2026.

Dr. Takami Sato (Thomas Jefferson University) discussed how a tumor and its immune microenvironment changes with Tebentafusp treatment. Biopsies taken from metastatic uveal melanoma tumors pre- and post-Tebentafusp treatment were analyzed and compared. The research team identified a group of genes associated with a T-cell's ability to replicate and mature into cancer-killing effector T-cells (Sacco, Kirk, et al. 2025). This set, called a T cell fitness signature, was associated with better responses to Tebentafusp. After treatment, T-cells accumulated in metastatic tumors. Tebentafusp also affected a set of immune cells, such as macrophages, that help to kill cancer cells. After treatment, M2-to-M1 macrophage reprogramming occurred with anti-tumoral activity. Overall, the findings highlight the importance of T-cell recruitment in the response to Tebentafusp.

6 | Session 5: Targeted Therapy: Assessing Darovasertib-Crizotinib for Optimal Outcomes

The final session of the day focused on the combination therapy of Darovasertib and Crizotinib. This session was facilitated by Dr. Jonas Nilsson (University of Gothenburg).

Dr. George Cole (Ideaya Biosciences) provided an update on Darovasertib clinical trials. Darovasertib is an oral, potent, and selective inhibitor of the classical (α, β) and novel (δ, ε, η, θ) isoforms of protein kinase C (PKC). Crizotinib is an oral small-molecule, multi-tyrosine kinase inhibitor of mesenchymal-epithelial transition (MET)/hepatocyte growth factor receptor (HGFR), anaplastic lymphoma kinase (ALK), receptor tyrosine kinase, and Recepteur d'Origine Nantais (RON) kinases. Mutations in either GNAQ or GNA11 are initiating events and genetic drivers of uveal melanomas and signal through PKC.

There are a few ongoing and planned trials to test Darovasertib across multiple stages of uveal melanoma. Dr. Cole presented the findings from the first 68 patients from a Phase 2 expansion trial (NCT03947385). This study is testing Darovasertib and Crizotinib for treatment of metastatic uveal melanoma. This combination therapy appears to have manageable levels of adverse effects. The confirmed ORR ($n = 63$) was 30% with a DCR of 89%. Median PFS was 6.8 months with ~50% of patients being treated for > 6 months. When compared to other trials, Darovasertib + Crizotinib demonstrated progress regarding tolerability, long-term patient survival, and disease response. The results of this trial formed the basis for the Phase 3 trial of frontline Darovasertib + Crizotininb in patients with metastatic uveal melanoma (NCT05987332).

Dr. Marcus Butler (Princess Margaret Cancer Centre) presented the results from the neoadjuvant Optim-UM-09 trial (NCT05907954). Typically, primary uveal melanoma is treated with radiation or removal of the affected eye. Both treatments can lead to permanent vision loss. This trial sought to determine whether Darovasertib treatment could lead to decreased tumor size and radiation dose and, in turn, preserve vision for more patients. Patients were treated for up to 12 months with Darovasertib followed by primary local treatment. Patients who responded favorably to Darovasertib were given an additional 6 months of Darovasertib after primary treatment. The results are promising. Using Darovasertib before surgery or radiation shrank the tumors in 82%–84% of patients. Seventy percent of patients receiving radiation needed less radiation in areas important for vision. Fifty-seven percent of patients originally destined for eye removal no longer required surgery. Sixty percent of patients saw improvements in their vision. Darovasertib was well tolerated overall, with a low rate of serious adverse events. A Phase 3 neoadjuvant clinical trial (OptimUM-10, NCT07015190) will study how well Darovasertib performs in a larger population and compare long-term results to current standard of care therapy.

Dr. Rizwan Haq (Dana Farber Cancer Center) discussed ways to target the signaling protein Gα as a potential treatment of uveal melanoma. As noted above, most uveal melanomas have mutations affecting Gα. The research team found that mutations in the GNAQ or GNA11 genes led to changes in where Gα was located within the cell. His team identified the protein needed to transport Gα and demonstrated that blocking this protein decreased the growth and metastasis of uveal melanoma in mice.

6.1 | Next Steps

The 2025 CURE OM meeting brought together key investigators, industry sponsors, and patient advocates. Together, they discussed the many approaches researchers are taking to improve survival and quality of life for more patients. The approval of Tebentafusp highlighted the urgent need for new treatments that work for all uveal melanoma patients. Several clinical trials are ongoing to assess new drugs and combination therapies. More work is needed to assess the safety and efficacy of these treatments before they can come to market. Treatments that preserve vision could be the next step in improving the lives of patients who survive. New tools such as ctDNA and liquid biopsies have the potential to make predicting disease risk more accurate and less invasive. Global collaboration between industry, scientists, and advocates is necessary to continue moving the research field forward.

Author Contributions

Allison S. Betof: writing – review and editing. **Vinit B. Mahajan:** writing – review and editing. **Prithvi Mruthyunjaya:** writing – review and editing. **Andrew E. Aplin:** conceptualization, writing – review and editing, writing – original draft. **George Cole Jr.:** writing – review and editing. **Rizwan Haq:** writing – review and editing. **Katherina Alsina:** writing – review and editing. **Paul Nathan:** writing – review and editing. **Rahul Marpadga:** writing – review and editing. **Jonas A. Nilsson:** writing – review and editing. **Marcus O. Butler:** writing – review and editing. **Pang-ning Teng:** conceptualization, funding acquisition, writing – review and editing. **Florian A. Karreth:** writing

– review and editing. **Joseph J. Sacco:** writing – review and editing. **Takami Sato:** writing – review and editing. **Sarah Stanhope:** writing – review and editing. **Gary Palmer:** writing – review and editing. **Kyleigh LiPira:** conceptualization, funding acquisition, writing – review and editing. **Joseph Birkett:** writing – review and editing.

Conflicts of Interest

Katherina Alsina is an employee of Castle Biosciences, Joseph Birkett is an employee of Aura Biosciences, George Cole Jr. and Gary Palmer are employees of IDEAYA Biosciences, Rahul Marpadga is an employee of Replimune, and Sarah Stanhope is an employee of Immunocore Ltd.

Data Availability Statement

The authors have nothing to report.

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