Reaching for the Stars

FEATURES FROM THE 2023 MRA SCIENTIFIC RETREAT
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SAVE THE DATE
2024 MRA Scientific Retreat & Patient Forum
February 21-23, 2024 | Washington, DC
An annual highlight for the Melanoma Research Alliance (MRA) is promoting collaboration and discussion among key stakeholders in the melanoma community at our Annual Scientific Retreat. The 2023 Scientific Retreat was held March 8 – 10, in Washington D.C. and marked the 15th anniversary of this important gathering. The Retreat, an invitation-only think-tank style conference, brings together over 300 academic investigators, pharmaceutical and biotech representatives, government officials, donors, and patient advocates for scientific presentations, conversations, and learning.

At the Retreat, participants heard about the latest discoveries in melanoma prevention, diagnosis, and treatment, many of which are being made by MRA-funded investigators. Participants also had the opportunity to network with and hear from patients, survivors, and loved ones who have all been personally impacted by melanoma.

This year’s scientific presentations and panel discussions focused on a variety of topics, spanning the development of novel treatment strategies, the use of artificial intelligence and other imaging techniques in melanoma care, optimal management of brain metastases and leptomeningeal disease, moving a drug candidate or device from the lab into the clinic, and research into rare melanoma subtypes. Together these presentations offered an exciting, and in-depth picture of the current state of melanoma research and highlighted areas of unmet patient need.

In addition to the scientific sessions, the program also included a breakfast for MRA Young Investigator Awardees focused on mentorship in scientific research, a poster session where MRA-funded researchers had the opportunity to present their work, and nineteen topic-focused networking roundtables to choose from. We know that the introductions, discussions, and partnerships forged at the Retreat have a lasting impact on the field at large and will further accelerate progress in melanoma prevention, detection, diagnosis, treatment, and beyond.

Sincerely,

Marc Hurlbert, PhD
CHIEF EXECUTIVE OFFICER

Joan Levy, PhD
CHIEF SCIENCE OFFICER

Tanisha Jackson, PhD
SCIENTIFIC PROGRAM DIRECTOR

Rachel Fischer, PhD
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“Research is the difference between life and death for patients.”

JAMIE GOLDFARB
Each year, MRA convenes global thought leaders from across the melanoma research community to exchange ideas, report on scientific successes and challenges, and network and forge new collaborations.

To start the Retreat, Jamie Goldfarb and Ken Billett, both melanoma survivors, shared how their lives have been shaped by recent advances in melanoma research.

Jamie was diagnosed with Stage 4 melanoma after the birth of her son in 2009. Her doctor told her that he’d do everything he could to give her six months with her newborn. Instead, Jamie chose to enroll in a clinical trial offered at the National Cancer Institute.

“Because of that clinical trial, I have been completely disease free for the last ten years,” she told attendees. “Research is literally the difference between life and death for patients.”

“I’m here today because of you and the scientists and researchers who came before you,” said Ken Billett. His journey with melanoma began in the 1990s and since then, he has had 10 distinct melanomas removed. In 2013, melanoma was found in both of his lungs. Ken began treatment with targeted therapies that exploited the c-Kit mutation found in his tumors. This controlled his melanoma for the next six years. In 2020, Ken began immunotherapy to treat the growing melanoma metastases throughout his body. By February 2023, Ken’s melanoma is stable.

“I’m fortunate,” says Ken. “That’s why it’s important to speak up about my experiences. I’m here for a reason.”

With these words, Dr. Georgina Long, of the Melanoma Institute Australia, took to the stage to deliver the opening keynote lecture.
“The drugs we use now are providing long term control of melanoma in more than 50% of people,” said Dr. Georgina Long of the Melanoma Institute Australia, who delivered the opening keynote address of MRA’s 2023 Scientific Retreat. “To continue our progress, the bar needs to be raised quickly toward a cure,” said Dr. Long. The problem, said Dr. Long, is not really knowing specific mechanisms of resistance yet. “The bottom line is that we see many associations with resistance. Some are conflicting. But at this point, there is nothing to target specifically,” she said. Fortunately, researchers are continuing to look at every aspect of melanoma biology—the tumor, its microenvironment, the patient’s blood and microbiome analyzed by state-of-the-art genomics, proteomics, and immune phenotyping platforms—to tackle resistance and move us ever closer to a cure for melanoma.

MRA’s Scientific Program Director, Dr. Tanisha Jackson, moderated a session featuring new research focused on novel treatment targets, strategies to overcome immunotherapy resistance, and reach Dr. Long’s goal of “zero deaths from melanoma.”
Using PDX Models to Study Melanoma Tumors and Uncoupling MEK and ERK to Treat

Dr. Gatien Moriceau of the University of California, Los Angeles, is exploring new therapeutic strategies for melanoma by creating models from portions of a patient’s tumor that are implanted into immunodeficient mice, called Patient-Derived Xenografts (PDX) models. “These models allow us to conserve the molecular and histological characteristics of the patient’s tumor,” said Dr. Moriceau. Researchers can then use these models to study the genomic characteristics of tumors, understand how they develop resistance to therapies, and test potential new drugs before advancing them into clinical trials.

Dr. Moriceau’s team designed their PDX models to develop acquired resistance to therapies that inhibit MAPK (mitogen-activated protein kinase), an enzyme involved in cell division and tumor growth. They found that the resistant tumors had highly recurrent changes in several genes: NRAS, RAF1/CRAF, BRAF, and MAP2K1/2. The researchers then used whole genome sequencing to analyze and understand these variants. Their observations supported the idea that genomic instability is a possible cause of resistance, and validated chromothripsis, a mutational process of chromosomal rearrangements, as a potential strategy to prevent the development of resistance. The study also reinforced the invaluable use of PDX models in oncology research. “With PDX models, we can integrate very precise profiling data to exploit novel therapeutic vulnerabilities. We can use this biobank of PDX models to validate biological concepts and to improve precision oncology.”

Exploring the Immune Inhibitory Landscape in Melanoma: VISTA

Dr. Matthew Vesely of the Yale School of Medicine explored the potential use of checkpoint immunotherapies—other than currently approved drugs that target PD-1, CTLA-4, or LAG-3. Specifically, he focused on an immune checkpoint gene called VISTA (V-domain Ig-containing suppressor of T-cell activation), also known as PD-1H (programmed death-1 homolog). VISTA regulates the activity of T cells, an important part of the immune system, but little is known about VISTA in melanoma. “VISTA is a pretty complicated system,” said Dr. Vesely. “It is expressed on activated T cells and almost all other immune cells, except B cells, as far as we know.”

Dr. Vesely set out to determine how much VISTA expression occurred in melanoma, identify critical cells that expressed VISTA, and see how VISTA expression relates to PD-L1 expression and patient survival. Using an immunofluorescence technique on a melanoma tissue array (which included biopsy samples from 209
primary cutaneous melanoma cases), he found that about 55% of the melanomas tested expressed VISTA. In the microenvironment, VISTA was expressed at high levels on tumor-infiltrating CD11b+ myeloid cells, another important immune system cell, which was associated with greater melanoma recurrence and poorer survival compared to tumors with low CD11b+ VISTA expression. In contrast, PD-L1 was most highly expressed on CD68 macrophages and this had no link to recurrence or survival in this cohort. Finally, in Dr. Vesely’s cohort, there was little correlation between VISTA and PD-L1 expression, suggesting that individual tumors have distinct immunosuppressive tumor microenvironments that are regulated by different immune checkpoints such as PD-L1 and VISTA.

Dr. Vesely said that the next steps are to more specifically identify cell subsets expressing VISTA in the melanoma tumor microenvironment. Furthermore, with additional samples from patients treated with immunotherapies, Dr. Vesely would like to determine whether VISTA expression impacts immunotherapy response.

**Loss of CD226 in T Cells Drives Melanoma Immunotherapy**

Dr. Tobias Bald and his team at the University Hospital Bonn wanted to better understand the underlying cellular mechanisms for immunotherapy resistance and how to overcome them. They focused their attention on CD226, a molecule on the surface of immune cells that can activate cells and promote an immune response against tumors in preclinical models. Their aim was to see whether CD226 plays a role in immunotherapy resistance and in the function of tumor-infiltrating lymphocytes (TILs), which recognize and kill cancer cells.

Their research in mouse models showed that many CD8+ TILs had low CD226 on their surface and were not functioning well in the tumor microenvironment. On the other hand, TILs with high CD226 maintained their function. The researchers then found that CD155, a ligand for CD226, inhibited CD226 expression. Maintaining CD226 expression resulted in better antitumor activity and improved T-cell activity. In studies to examine how CD226 functions in melanoma, they observed that T cells lacking CD226 are less capable of controlling melanoma tumors in mouse models.

In pre-treatment samples donated by melanoma patients, higher expression of CD226+ CD8+ T cells correlated with improved progression-free survival after the patients were treated with checkpoint immunotherapies. Loss of CD226, therefore, is linked to impaired T-cell function and an increased risk of melanoma invasion and treatment resistance. “Our findings argue for the development of therapies aimed at maintaining the expression of CD226 in tumor-infiltrating T cells to improve the survival of melanoma patients,” said Dr. Bald.
Targeting PTPs for CDK6-Induced Immunotherapy Resistance in Melanoma

Understanding how melanoma develops resistance to immunotherapy is a critical goal for developing new strategies to treat the many patients who don’t respond to current immunotherapies, which are now the standard of treatment for advanced melanoma. Dr. Haizhen (Jen) Wang and her team at the Medical University of South Carolina set out to learn more about how resistance develops and more importantly, how it can be beaten. In an analysis of clinical data from patients with melanoma treated with a single-agent immunotherapy, Dr. Wang’s team found that high CDK6, a kinase that regulates tumor growth, was strongly linked to poor progression-free survival. Depleting CDK6, but not CDK4, in the cells of the tumor microenvironment significantly inhibited tumor growth in mouse models that had the same genetic backgrounds. Dr. Wang’s data suggest that CDK6 depletion reshapes the tumor immune microenvironment, and that the antitumor effect depends on depleting CDK6 from specific types of immune cells called CD8⁺ and CD4⁺ T cells.

Furthermore, they found that CDK6 phosphorylates and increases the activity of protein tyrosine phosphatases (PTPs), which are enzymes involved in the regulation of T-cell activity. Dr. Wang said that the data suggest that targeting PTPs may increase T-cell activity to improve the efficacy of T cell-based immunotherapies like tumor-infiltrating lymphocytes (TILs) and chimeric antigen receptor T cells (CAR-Ts) and offer a potential route to overcome resistance to existing checkpoint immunotherapies.

Targeting the JNK-ITCH Signaling Pathway in Melanoma

Dr. Lixin Wan of the H. Lee Moffitt Cancer Center and Research Institute explored the role of an enzyme that functions in both tumor cells and immune cells called ITCH ubiquitin E3 ligase. ITCH’s role in immune cells has been well characterized, so Dr. Wan’s aimed to better understand the importance of ITCH in melanoma growth and progression. Dr. Wan’s team found that ITCH acts on the wild-type BRAF protein (which can allow melanoma to grow aggressively) and that its actions are promoted by an enzyme called JNK and cytokines that promote inflammation. This results in the BRAF protein adopting a shape that continues to spur tumor growth. When ITCH is depleted, BRAF is no longer active and melanoma cell and tumor growth is decreased. In addition, the researchers found that “itchy mice” (mice deficient in ITCH) developed smaller tumors and more TILs in the microenvironment of the tumors. Dr. Wan said that these results together support earlier findings that ITCH plays a dual role in in melanoma and its microenvironment and could function as a switch for melanoma cell plasticity—the ability of a cell to change its characteristics. ✤
Each new discovery by melanoma researchers takes us one step closer to ultimately curing it.

Discovery Research Expands the Possibilities

Each new discovery by melanoma researchers takes us one step closer to better understanding melanoma, the best ways to treat it, and to ultimately cure it. Researchers are continuing to discover potential new therapeutic targets in the laboratory, which can launch them on the journey to finding a drug or device that will ultimately save lives.

Dr. Sohail Tavazoie’s keynote address delivered at MRA’s 2023 Scientific Retreat provided a perfect illustration of just such a journey. It started when he and his team at The Rockefeller University were exploring therapies to prevent metastasis. A graduate student in his lab identified two microRNAs (small non-coding RNA molecules that regulate genes) that were overexpressed in highly metastatic melanoma cells. When the research team followed up on this finding, they saw that the two microRNAs had a common target—the ApoE gene—one that is well-known for its association with Alzheimer’s disease.

Further work revealed that ApoE plays a critical role in metastasis formation thanks to its effects on the immune system and angiogenesis (the formation of new blood vessels that helps support tumor growth and metastasis). Dr. Tavazoie’s team then applied their insights toward developing a treatment to prevent metastasis, and identified an experimental compound, which increased ApoE production and was effective at reducing growth and metastasis of melanoma tumors in mice models.
The next steps were forming a small biotech company, Inspirna, doing toxicology studies, and filing an Investigational New Drug (IND) application to the FDA to test the experimental therapeutic RGX-104 in a Phase 1 clinical trial which is currently open. So far, RGX-104 has been well tolerated and some patients with advanced cancers in the study show stable disease, while others show tumors that are regressing in size.

Dr. Tavazoie’s lab has also uncovered a role for hereditary genetic differences—meaning inherited traits passed down from your biological parents—of the ApoE gene that could predispose someone to developing metastatic melanoma. Dr. Tavazoie stated that studying these inherited genes, what researchers call the germline, is an important area of research, and that germline genetic variation could help explain why certain individuals might develop metastatic disease while others do not.

Following Dr. Tavazoie’s address, Dr. Genevieve Boland of Massachusetts General Hospital led a Session that highlighted some additional new discovery research efforts that may one day impact melanoma treatment.

**Targeting Lipocalin-2 (LCN2)**

Dr. Neta Erez of Tel Aviv University and her team wanted a deeper understanding of the microenvironment of melanoma brain metastases. Specifically, how do the immune cells and molecules around the tumor interact with each other and affect melanoma progression? “Most such studies are done on primary tumors,” said Dr. Erez. “So much less is known about the metastatic microenvironment.” Using a mouse model, she and her team found that brain metastasis was promoted by interactions between immune cells in the brain and astrocytes—important cells in the Central Nervous System (CNS) that can also induce inflammation. The team also learned that the cytokine lipocalin-2 (LCN2), plays a major role in activating astrocytes and thus promoting inflammation in the brain. Although LCN2 has been linked to other diseases of the brain, such as Alzheimer’s disease, and is implicated in several types of cancer, it had not been well-studied in brain metastases. Using a mouse model, the researchers found that LCN2 was an important regulator of melanoma brain metastasis. In the clinical setting, they found high levels of LCN2 in both the blood and tissue samples of brain metastases from patients with Stage 4 melanoma, and a strong link to disease progression and poor survival. “We think that LCN2 is a potential prognostic marker and a possible novel therapeutic target for the prevention or treatment of brain metastasis,” said Dr. Erez.

**Targeting Thymine DNA Glycosylase (TDG)**

Checkpoint immunotherapies can be a highly effective treatment for some patients with metastatic melanoma, but unfortunately, many patients do not respond to the current agents. Dr. Alfonso Bellacosa and his team at the Fox Chase Cancer Center set out to find alternate therapies for such patients. They started by looking at how immune responses are regulated in patients with melanoma and then focused on epigenetic modulators. These are molecules that can modify DNA and ultimately gene expression without changing the underlying DNA sequence itself. One type of epigenetic modification is DNA methylation, which affects gene expression. When DNA has low levels of methylation, referred to as being hypomethylated, expression of different genes can become uncontrolled. About 40% of metastatic melanomas have prominent DNA hypomethylation, which also correlates with a low inflammatory response and resistance to anti-PD1 checkpoint immunotherapies.
Metastatic melanoma tumors that are hypomethylated were associated with increased levels of an enzyme, thymine DNA glycosylase (TDG), which demethylates DNA and is linked to poor survival. These findings led the team to consider TDG as a possible new target for melanoma. They identified inhibitors of TDG and found that these inhibitors may be an innovative way to sensitize metastatic melanoma to existing checkpoint immunotherapies by reversing the hypomethylation associated with resistance to immunotherapies. “This research may lead to ground-breaking new combinations of TDG inhibitors with immune checkpoint blockade to treat immunotherapy refractory melanoma,” said Dr. Bellacosa.

Targeting Undruggable Proteins in Melanoma with “Bicycles”

Dr. Sarah Slavoff of Yale University reported on her team’s work to identify drugs targeting proteins upregulated in acral melanomas. Acral melanomas, a rare melanoma subtype, tend to not respond as well as cutaneous melanomas to currently approved therapies. Because of this, Dr. Slavoff and her colleague, Dr. Ruth Halaban believe that inhibiting or eliminating these newly identified potential drivers could lead to novel therapeutics.

Unfortunately, these driver proteins are considered “undruggable” with classical drug discovery approaches, so the researchers used a different approach and found that a certain class of compounds, called cell-permeable bicyclic peptides, have the potential to rapidly bind to these difficult targets. Structurally, these “bicycle proteins” consist of two circles—much like the two tires of a bicycle. “They can adopt quite complex and interesting three-dimensional configurations that bind to the surface grooves on target proteins with a really exquisite sensitivity and specificity,” said Dr. Slavoff. “We can get peptides into cells.” The bicyclic peptides can also be developed rapidly and modified easily. “This makes them ideal for potentially inhibiting or degrading undruggable driver proteins,” said Dr. Slavoff. “Our work is still in the early stage of developing bicyclic peptides that target melanoma proteins but we’re excited about where we’re taking this in the future.”

Targeting Tumors with a New IL-2/antibody Fusion Protein

Interleukin-2 (IL-2), a cytokine that stimulates immune cells, was the first immunotherapy to receive US Food and Drug Administration approval for treating cancer. IL-2 had great potential for treating melanoma but came with some major downsides. It was short-acting, had severe toxicities, and seemed to get in its own way by acting on both effector cells (immune cells that destroy cancer cells) and regulatory T-cells (immune cells that can limit immune responses). Combining IL-2 with an appropriate antibody could help improve its action, but developing a compound that could work in the clinic has proved challenging.

Dr. Jamie Spangler and her team at The Johns Hopkins University decided to tackle this challenge by studying the immune response at the molecular level and reshaping it. “We turned to protein engineering to create an IL-2 antibody that would be more biased toward effector cells,” she said. Her team developed a “single-agent IL-2/antibody fusion protein” called an immunocytokine that selectively stimulates immune effector cells. When they tested the new immunocytokine in a mouse model of melanoma, the compound had robust activity against the tumor, both on its own and when combined with existing checkpoint immunotherapies. Additional modifications allowed the team to selectively target the cytokine in the tumor microenvironment, which should increase safety by avoiding the systemic toxicity of IL-2. “Overall, our strategy offers insight into the design and development of translationally promising IL-2 therapies to treat melanoma,” said Dr. Spangler. 

Sarah Slavoff, PhD – Yale University
About 90% of patients with melanoma are diagnosed with the cutaneous type, associated with sun exposure. However, there are several other rare melanoma subtypes that do not share the same biological mechanisms or respond to the same therapies as the more familiar cutaneous melanoma. Two of these subtypes—acral melanoma and uveal melanoma—were the focus of a session at MRA’s Scientific Retreat, moderated by Dr. Joan Levy, MRA’s chief science officer. The presenters highlighted recent research findings on the genomic alterations and biological pathways of acral melanoma and some potential new treatment targets for both acral and uveal melanoma.

**New Insights Into Rare Melanomas**

About 90% of patients with melanoma are diagnosed with the cutaneous type, associated with sun exposure. However, there are several other rare melanoma subtypes that do not share the same biological mechanisms or respond to the same therapies as the more familiar cutaneous melanoma. Two of these subtypes—acral melanoma and uveal melanoma—were the focus of a session at MRA’s Scientific Retreat, moderated by Dr. Joan Levy, MRA’s chief science officer. The presenters highlighted recent research findings on the genomic alterations and biological pathways of acral melanoma and some potential new treatment targets for both acral and uveal melanoma.

**Identifying Genomic Alterations and Potential Therapeutic Targets for Acral Melanoma**

Acral melanoma develops on “acral” skin surfaces, namely the palms of the hands, soles of the feet, and under the nails. While acral melanoma can develop among people of all races, in the United States, it disproportionately impacts people of color. It is also the most common form of melanoma in Mexico and other countries in Latin America, Asia, and Africa, where treatment options are also scarce.

“Acral melanoma is usually misdiagnosed and patients arrive at the clinic in later stages,” said Dr. C. Daniela Robles-Espinoza of the National Autonomous
Dr. C. Daniela Robles-Espinoza and her research team are now looking at how genomic alterations and biological pathways associated with acral melanoma in the Latin American population compare to published genomic findings in the European/Caucasian acral melanoma patient population. However, many challenges exist when doing genomics research in Latin America and other low- or middle-income countries. “There’s often a disconnect between the medical and scientific communities,” said Dr. Robles-Espinoza. “Many times, the research priorities are not aligned.” Also, carrying out such research in these countries is very expensive. “Most of our work has been to establish facilities and workflows and train people to do these kinds of analyses,” said Dr. Robles-Espinoza.

Initial results from her team’s work with patients in Mexico are showing genomic profiles similar to those of patients from other countries but with some differences in the specific mutations and the age of the patient at melanoma onset. For example, genomic sequencing showed that less than 40% of tumors have classic driver mutations of BRAF, NRAS, and NF1 genes which are often seen in cutaneous melanomas; instead, the team identified KIT as the most common mutation. They also observed that patients with NRAS mutations were younger at time of diagnosis. RNA analyses are showing that acral melanoma tumors have immunosuppressive qualities that are more pronounced in samples from ulcerated tumors.

The team, in collaboration with Dr. Patricia Possik at INCA in Brazil, is also creating patient-derived xenograft (PDX) models to further their preclinical studies. Most of the tumors were donated by patients in Brazil and Mexico with stage 3 acral melanoma who have not received treatment beyond surgery. The team plans to use these PDX models to study disease development, progression, and to identify potential therapeutic targets and other relevant biomarkers. To date, the team has established 40 PDX models and despite the difficult and painstaking process, they have had a 56% success rate. This work is important because melanoma researchers cannot easily access cell lines or PDX models for many rare melanoma subtypes. Creating these model systems is a labor-intensive and exacting process and as a result these model systems are maintained by only a handful of researchers globally. As a result, the lack of access to these model systems serves a barrier for researchers who want to study rare melanoma subtypes. In addition, once characterized, the models will be shared broadly with the research community. “We hope that, with this work, we can contribute to the efforts to molecularly characterize acral melanoma, and close the knowledge gaps in understudied populations,” said Dr. Robles-Espinoza.

Dr. Rolando Perez-Lorenzo of Columbia University discussed potential new therapeutic targets for acral melanoma, noting that this type of melanoma has responded poorly to available targeted therapies and checkpoint immunotherapies. His team’s work has focused on inhibiting casein kinase II (CK2), an enzyme that plays a role in cellular processes and is often associated with resistance to therapy in melanoma and poor survival outcomes. In a model using human melanoma cells, the CK2 inhibitor, CX-4945, inhibited the signaling of two pathways that play important roles in the progression and survival of cancer: the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase (PI3K) pathway. The experimental CK2 inhibitor enhanced the activity of trametinib, a targeted therapy that stops the growth of melanoma cells by inhibiting the MAPK pathway (approved for use in advanced melanoma). Dr. Perez-Lorenzo said that the results so far suggest that combining CK2 inhibitor with trametinib might improve the response rates in this patient population.
inhibitors with certain therapies that target specific kinase enzymes (e.g., trametinib and imatinib) may improve outcomes in patients with difficult-to-treat acral melanoma. Ongoing work is looking at combination therapy using CK2 inhibition and checkpoint immunotherapies.

Exploring Possible New Targets for Treating Uveal Melanoma

Uveal melanoma is the most common cancer of the eye in adults and is the second most common melanoma subtype after cutaneous melanoma. About 2,500 patients in the United States are diagnosed with uveal melanoma each year. “Nearly half of these patients will die from liver metastases within 5 to 10 years after their diagnosis, even if the primary lesion is successfully treated,” said Dr. J. Silvio Gutkind of the University of California, San Diego.

“To date, there are limited therapeutic options to treat metastatic uveal melanoma, which typically doesn’t respond to available checkpoint immunotherapies,” said Dr. Gutkind.

Although MAPKi (mitogen-activated protein kinase inhibitor) therapy (e.g., selumetinib) has been studied as a treatment for uveal melanoma, recent research has shown that MAPKi alone is not effective in treating this type of cancer. Tebentafusp, a bispecific fusion protein that allows the immune system to attack and kill uveal melanoma by creating a bridge between tumor and immune cells - was approved by the U.S. Food and Drug Administration in 2022 for the treatment of adult patients with unresectable or metastatic uveal melanoma. However, to be eligible for treatment, patients must test positive for a specific type of human leukocyte antigen (HLA), known as HLA-A*02:01. Only 50% of patients are eligible for this treatment and 80% have disease that progresses despite treatment, said Dr. Gutkind.

Using a novel computational biology approach to identify interactions between genes that lead to loss of gene function, Dr. Gutkind’s team discovered that the enzyme FAK (focal adhesion kinase) is involved in a signaling network that controls the growth of uveal melanoma. This means that targeting FAK could potentially be an effective treatment strategy. A Phase 2 clinical trial of defactinib, a FAK inhibitor, combined with an inhibitor of RAF/MEK (another pathway involved in cell proliferation and survival) is currently underway in patients with metastatic uveal melanoma.

Dr. Gutkind said that more research is needed to understand how to best target FAK in order to effectively treat this aggressive form of melanoma. The challenges now are to select the appropriate patient population, determine the best combination with available checkpoint immunotherapies, and overcome adaptive resistance, which occurs when a mutation in the tumor cell allows it to become resistant to treatment. Dr. Gutkind added that his laboratory is already applying the lessons learned from this work to preclinically test the combination of defactinib with the RAF/MEK inhibitor for its effects in treatment-resistant cutaneous melanoma.

In a collaborative effort to address the lack of rare melanoma model systems, MRA has created model catalogs for acral and mucosal melanoma.

These catalogs will serve as a launching pad for researchers who want to study these rare melanoma subtypes—providing easier access to basic information and helping them to avoid the timely process of creating new models from scratch. In addition, this effort fosters collaboration, transparency, and helps synergize efforts and avoid unnecessary duplication of effort.

EXPLORE THE CATALOGS:

CureMelanoma.org/ResearchResources
An early melanoma diagnosis is more likely to have a positive outcome than one diagnosed later. That’s a fact, but patients often delay having skin lesions checked for a variety of reasons, including long wait times to see a dermatologist—if they can even find one close by. In many cases, a primary care doctor is the first clinician to evaluate a skin lesion and make a melanoma diagnosis—a task that even experienced clinicians find challenging. But help is on the way. Research is confirming that artificial intelligence (AI) and machine learning algorithms can detect melanoma with remarkable accuracy and may revolutionize the speed of diagnosis. New imaging technologies are also being studied that can help inform and guide diagnosis and treatment decisions. A session at MRA’s 2023 Scientific Retreat, led by Dr. Maria Wei, of the University of California San Francisco, focused on the potential of both technologies to improve outcomes for patients as well as workloads for physicians.

Artificial Intelligence can Boost Screening Accuracy
Disparities in melanoma care and outcomes exist, and are associated with race, place of residence, provider type, as well as insurance status. New and faster methods of melanoma detection can be especially helpful for groups of patients who have difficulty accessing care, said Dr. Wei. Problems getting to healthcare providers and
insurance status can determine where and when a person seeks care. Rural areas have fewer dermatologists than urban areas, so primary care providers are often the most likely clinicians to first evaluate a skin lesion in rural communities, said Dr. Wei. Providers in rural areas also perform more skin biopsies than those in urban areas and could benefit from additional diagnostic tools, she said.

To address some of the barriers to access, the American Academy of Dermatology now recommends the expanded use of teledermatology. “This is really quite a change from before the [COVID-19] pandemic when teledermatology was not widely used,” said Dr. Wei. “Since the pandemic, teledermatology has not just been accepted, but embraced.” Patients are now having video visits and sending images to their primary care physicians. Dr. Wei and her team are looking at how teledermatology can be combined with AI to detect melanoma at the earliest possible stage in collaboration with Veteran’s Administration (VA) hospitals around the country, who often treat a diverse patient population.

Dr. Albert Chiou of Stanford University agreed that teledermatology has helped patients get expert opinions about lesions, but added that it often can place additional burden on limited healthcare resources. For example, for the first time at his institution, the number of virtual encounters with patients submitting photos in the past year equaled the volume of traditional in-person visits. Dr. Chiou and his team are working to develop an AI-assisted triage tool to help with diagnosis of melanoma.

The team is also working to overcome biases that have emerged with existing AI models that may make these systems less robust in detecting melanoma in realistic clinical scenarios, particularly among skin of color. Overcoming these biases is very important if AI algorithms are to improve—and not exacerbate—existing health disparities among racial and ethnic minorities as it relates to melanoma early detection.

Dr. Chiou’s analysis showed that including diverse data sets, including images of melanoma among diverse skin tones and less common forms of melanoma, can improve the diagnostic performance of these algorithms. His team has also collected data from 811 patients who provided photos of skin lesions. Using these data and elements from a previous AI algorithm, the team developed a new classifier algorithm for melanoma lesions. To further train the classifier, they added more than 20,000 additional images from previous patients. They are currently evaluating the performance of their classifier, which they named the MRA-Stanford-Cleveland Clinic (MRA-SC) dataset, using benchmark datasets to assess its ability to identify malignant tumors and malignant melanocytic lesions. The team will use the algorithm to assess its potential to help triage lesions in the primary care setting.

**New Imaging Technologies May Help with Diagnosing Melanoma and Predicting Responses to Immunotherapy**

Dr. Jesse Wilson of Colorado State University, an engineer, is studying laser-based imaging techniques that do not require a biopsy to help diagnose melanoma. He described his team’s efforts to see whether a software plugin with existing clinical instrumentation could generate images that look like conventional biopsy sections. He also discussed the use of “image2image neural networks,” which are machine learning techniques used to help clinicians visualize and identify melanoma-specific features in dermoscopy photographs. This tool may help researchers understand how artifacts in current datasets confuse neural networks. It may also lead
to the generation of more accurate melanoma datasets that can then be used to develop better computer vision algorithms, in addition to direct clinical applications. “We would like to see if this could be a useful tool for primary care settings for a physician to prioritize referrals to a specialist, and to help inform their decision to biopsy,” said Dr. Wilson. He plans to submit a grant application to the National Institutes of Health in June to continue this work.

Once a physician has accurately diagnosed melanoma, the next challenge is determining whether a recommended treatment will work for the patient. “Immunotherapy is expensive, so it will be helpful to identify patients who will actually respond,” said Dr. Pratip Bhattacharya, of the MD Anderson Cancer Center. Dr. Bhattacharya, a physicist, said that his team is developing an imaging tool to predict responses to immunotherapy by actually viewing metabolic processes as they unfold in live tissue. “We are essentially trying to do real-time imaging of immunotherapy resistance,” he said.

Solving the mystery of resistance began with an idea that the build-up of acid in the space surrounding cells in the tumor microenvironment was one of the key causes of resistance. The team then looked at options for imaging that microenvironment. They found that “hyperpolarized” (HP) magnetic resonance spectroscopy could provide a 10,000-fold better imaging signal than conventional magnetic resonance imaging (MRIs). “The downside is that there is a very small window of time, a couple of minutes, to get real-time metabolic imaging,” said Dr. Bhattacharya. The challenge now is to see whether the team can use what they see to develop a biomarker for immunotherapy resistance. They are also studying a melanoma mouse model to determine whether changing the pH sensitivity in the tumor microenvironment before and after starting immunotherapy, could improve responses to checkpoint immunotherapy in melanomas expected to be treatment resistant.

Dr. Michael Postow of the Memorial Sloan Kettering Cancer Center is also studying immune responses to therapy by exploring PET (positron emission tomography) imaging of CD8⁺ T cells (cytotoxic T lymphocytes), white blood cells that can recognize and destroy cancer cells. The number of CD8⁺ T cells in the tumor microenvironment has been shown to correlate with treatment outcomes. But obtaining biopsies to count CD8⁺ T cells is not easy, and it usually does not reflect the entirety of the tumor, said Dr. Postow. To overcome this challenge, his team is using PET scanning with a radioisotope (called a radioisotope PET tracer) that can detect CD8⁺ T cells. The researchers are also using another imaging technique called autoradiography which is used to measure the presence of radioactivity in different tissues. In these studies, autoradiography on tumor tissue that has been removed from patients after receiving the radioisotope PET tracer is being used to confirm that the tracer is in the tumor microenvironment and is associated with CD8⁺ T cells.

A phase 2 clinical trial is underway to see whether CD8⁺ T cell PET imaging will correlate with major pathologic responses (defined as a tumor that completely disappears or reduces to less than 10% of the original tumor size) after one dose of neoadjuvant therapy (nivolumab + ipilimumab delivered before surgery) in patients with resectable stage 3 and 4 melanoma.

Dr. Postow presented very early results from five of the seven patients accrued in the study so far. One dose of the neoadjuvant therapy appeared to result in some type of pathologic response with low toxicity in several of the patients. The researchers were able to visualize melanoma tumors using CD8⁺ T cell PET imaging and confirmed that the radioactive PET tracer was in the resected tumors using autoradiography. “The long-term goal is to see whether this approach can inform mechanisms of response and resistance of new immunotherapies in development,” said Dr. Postow. This novel imaging technique can potentially be used as an on-treatment biomarker which can help guide treatment decision making and determine pathologic response to treatment.

Jesse Wilson, PhD – Colorado State University
Michael Postow, MD – Memorial Sloan Kettering Cancer Center
IndIstry roundtable

Combating Melanoma Brain Metastases and Leptomeningeal Disease

Melanoma is the third most common source of brain metastases, exceeded only by lung and breast cancer. In addition, metastatic melanoma cells have the highest propensity for settling in the brain out of any solid tumor. Melanoma also has one of the highest rates of leptomeningeal disease (LMD), a cancer in the cerebrospinal fluid (CSF) and the membranes that surround the brain and spinal cord. With the advent of targeted drug therapy, checkpoint immunotherapy, and targeted radiation therapy the median survival of patients with melanoma who have central nervous system (CNS) metastases (inclusive of both brain metastases and LMD) has improved. However, only certain groups of patients respond. “About half of the patients with metastatic melanoma are still dying and the majority of them have died because of uncontrolled CNS disease,” said Dr. Michael B. Atkins, of the Georgetown-Lombardi Comprehensive Cancer Center and Chair of MRA’s Medical Advisory Panel. “CNS disease represents a principal unmet need in our treatment armamentarium for patients with metastatic melanoma.”

Considerable work is still needed to fully understand where CNS metastases originate and how they progress, in order to identify better treatment strategies. To address these issues, MRA convened a roundtable discussion of approximately 35 representatives from industry, academia, and the US Food and Drug Administration (FDA) during MRA’s 2023 Scientific Retreat that was co-chaired by Dr. Atkins and MRA’s Chief Science Officer, Dr. Joan Levy. The participants were charged with evaluating the current standard of
care for melanoma patients with CNS metastases, identifying compelling basic and translational science questions to address to improve our understanding of CNS metastasis, and proposing inclusive clinical studies to advance new treatment options for patients with these tumors.

Treatment of Melanoma Brain Metastases: What We Know & Remaining Questions

“Patients who have brain metastases, who have no neurologic symptoms and have small tumors that are not in critical parts of the brain, may be treated with systemic therapy,” said Dr. Harriet Kluger of Yale University. “We often will treat these patients with the combination of ipilimumab + nivolumab based on the high response rate and clinical benefit observed in two Phase II multi-center trials, one led by Drs. Hussein Tawbi of MD Anderson and Kim Margolin of the St. John’s Cancer Center, and the other led by Dr. Georgina Long of the Melanoma Institute of Australia,” added Dr. Kluger.

However, for patients with symptomatic brain metastases, the standard of care is far less clear. Many of these patients are treated with steroids to reduce swelling in the brain and manage any adverse events. This is a delicate balance, because steroids and immunotherapies have conflicting therapeutic actions. Steroids are used for their anti-inflammatory activity while immunotherapies act to ramp up an immune response. The typical approach has been to get patients off steroids before using immunotherapy, but there is a lack of data to support this, said Dr. Allison Betof Warner of Stanford University. “There is something different about patients with symptomatic brain metastases, and just getting off steroids and treating them like an asymptomatic patient is not the only solution.”

Dr. Margolin added, “In the first line of treatment you approach symptomatic brain metastatic patients in a highly individualized manner depending on what treatments they have had before, what tumors they have in the brain and in other areas of the body, and how symptomatic these tumors are.”

Can Brain Metastases Be Prevented?

Dr. Eva Hernando of the New York University School of Medicine commented that we used to think that we could go to the primary tumor and develop ways to stop them from spreading to other places in the body. However, emerging data suggests that most primary tumor cells can spread right away and can remain dormant in the brain for long periods of time. “One of the major challenges is the need to stop the melanoma tumor cells that have already reached the brain before they come out of dormancy and become actively metastatic tumors,” said Dr. Hernando. “This is a tall task, but it is important for the research community to focus on this unmet need.”

Leptomeningeal Disease Needs Better Criteria for Diagnosing and Treating

Just as with brain metastases, melanoma also has one of the highest incidences of LMD among solid tumors. Overall survival for patients with melanoma who have been diagnosed with LMD is measured in weeks to a few months.
“The biology of LMD is fundamentally different from that of brain metastases, and we need to think about that distinction. They are not the same,” said Dr. Betof Warner. A major challenge in treating patients with LMD, she added, is just getting a reliable diagnosis, due to a lack of clear diagnostic and response criteria. “Part of that challenge is getting all of us—medical oncologists, neurologists, radiation oncologists—to agree that the patient has LMD so we can actually treat them,” she said.

Responses to treatment may be very different between patients that have brain metastases and those with LMD. The microenvironments are quite distinct and therefore we should not think of the two as the same diseases. “LMD is a much smaller group of patients with a fundamentally distinct biology,” said Dr. Georgina Long of Melanoma Institute of Australia. “It’s harder to study because it’s almost like a different organ site than CNS metastasis to the brain. We need more biological information to be able to distinguish between the two.”

Clinical Trials Need to Include More Patients with CNS Metastases

The roundtable participants agreed that more patients with CNS metastases must be included in melanoma clinical trials, and that trial designs need improvements to make them more inclusive. The FDA did a review and the agency concluded that many of the common clinical trial eligibility exclusion criteria for cancer trials were historical in nature, and unnecessarily restrictive. So, in 2020 and 2021 the FDA issued broad guidance on how trial sponsors could change clinical trial inclusion criteria to be more inclusive to patients with CNS metastases. The FDA recognized that this is a special patient population that has not been historically included in clinical trials due to a hesitancy of including them in a primary analysis based on how they do clinically. However, the agency notes to sponsors that by including these patients we are able to capture really important information that is contributing to our growing understanding of how to address this population with unmet needs.

Due in part to this new guidance from the FDA, trial sponsors are now including patients with both asymptomatic and symptomatic brain metastases in clinical trials through separate subgroups with customized endpoints. Dr. Rohini Singh of Merck commented that their melanoma umbrella trial (KEYMAKER-U02) is evaluating immune checkpoint inhibitor pembrolizumab-based combinations in various patient settings. The brain metastasis sub-study is testing pembrolizumab in combination with lenvatinib (which inhibits the formation of new blood vessels) and MK-1308 (a CTLA-4 checkpoint inhibitor) in patients with metastatic melanoma with “active” brain metastases. “To enroll more patients with symptomatic brain metastases,” noted Dr. Singh, “we had to revise and broaden the inclusion criteria to accommodate patients that were either [treatment] naïve or exposed to immune checkpoint therapies to be able to better evaluate the effectiveness of these novel combinations across different settings.”

Several academic investigators and company representatives described trials that are ongoing or soon to launch which are inclusive of melanoma patients with brain metastases, both asymptomatic and symptomatic. Highlights of such studies include next generation checkpoint immunotherapies, TIL therapies, and different types of targeted therapies. As Dr. Suzanne Topalian of Johns Hopkins Medical Center and Chair of MRA’s Scientific Advisory Panel suggested, “it would be useful to hear more about kinase inhibitors that are able to cross the blood brain barrier, as this would be potentially important for patients whose melanomas have targetable mutations.”

Both Dr. Betof Warner and Dr. Richard Williams of Kinnate Biopharma agreed, but having the ability to measure drug
concentrations in the CSF or CNS tissue would be useful when pursuing targeted therapy approaches especially with kinase inhibitors. “We don’t know why these patients are developing resistance so early if we don’t know what the concentration of the drug is in the CSF,” said Dr. Betof Warner.

Dr. Levy also reminded participants that MRA’s Clinical Trial Navigator (CureMelanoma.org/ClinicalTrials) is a great resource to identify trials that include patients with brain metastases.

**Basic and Translational Research Can Improve Treatment for Patients with CNS Metastases**

Basic and translational researchers are continuing to explore solutions to better understand the biological distinctions between metastases in the CNS and other sites. They are also hard at work identifying new targets and better treatment options for patients with CNS metastases. Dr. Keiran Smalley of the H. Lee Moffitt Cancer Center said that it is important to understand how the CNS microenvironment influences therapeutic responses. For example, he noted far lower immune infiltrates and clearance of immune cells in the brain. “It clearly isn’t the same as other organs.”

Dr. Hernando added that a potential source of new targets can emerge from studies of other cancer types. “We’re seeing certain shared mechanisms between different cancer types that also metastasize to the brain,” she said. Dr. Hernando also emphasized the need for researchers to share their study models, “there are not many faithful models of brain metastasis.”

Dr. Benjamin Izar of Columbia University said that there are genomic features that can vary between metastases to the brain compared to other parts of the body. Brain metastases have more unstable chromosomes—a hallmark of cancer that is associated with aggressive behavior and immune evasion. The brain microenvironment may be particularly susceptible to this process. “So far it is just an association,” he commented. He also agreed with the need to support more work to create models of brain metastases, noting that they are very difficult to develop. He concluded by adding that the models would be useful to validate some of the interesting genomic and non-genomic findings and potential targets identified in CNS metastases from his and other studies.

Dr. Levy concluded the session by noting that MRA has awarded close to $9M for basic and translational research on CNS metastases across all types of MRA grant mechanisms in the U.S. and abroad. She will bring back insight from this panel to inform future MRA funding opportunities to continue to support more research in this critically important area.

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1 https://www.fda.gov/media/121317/download
2 https://www.fda.gov/media/141507/download
A panel of experts convened to offer guidance on negotiating translational science.

Bridging the Gaps From the Lab to the Clinic

The journey from a fantastic laboratory discovery to a drug or device that can extend and improve the lives of patients with melanoma is long and arduous. It can take years, even decades. While the road is paved with good intentions, it is also lined with colleagues to persuade, investors to please, expenses to pay, and many regulations to adhere to.

A panel of experts was convened during MRA’s 2023 Scientific Retreat to offer guidance on negotiating the nuts and bolts of translational science, based on their personal experiences as entrepreneurial scientists and facilitators. Dr. Louise Perkins, MRA’s chief science officer emerita moderated the discussion and welcomed the panelists: Dr. Elizabeth Ottinger, National Center for Advancing Translational Sciences (NCATS); Dr. Antoni Ribas of the University of California, Los Angeles; Dr. Caroline Robert of the Institute Gustave Roussy; and Dr. Kai Wucherpfennig, of the Dana-Farber Cancer Institute.

Assembling the Right Team is Crucial

The panelists unanimously agreed that assembling a motivated and dedicated multidisciplinary team is the number one challenge for moving an idea forward. “The closer you get to the clinic, the more it becomes team science,” said Dr. Wucherpfennig. “You need to build a team and really work collaboratively.”

Dr. Robert stressed the importance of finding the right people for each phase of the project. “You need a person with a really specific background who you trust and will
understand the science but can also raise money,” she said. “It took us a year to find the right structure.”

Every winning team also needs an enthusiastic cheerleader. “Every drug that made it to the clinic and later got approved had a strong champion,” said Dr. Wucherpfennig. He cited the example of Dr. James Allison, who advocated for years for his revolutionary immune checkpoint inhibitor. You will need a strong advocate for the science within the company to shepherd the technology through the multiple layers of review that will ultimately lead to the decision on whether the molecule will move forward.

So how do you find the right people? “You have to kiss a lot of frogs,” said Dr. Wucherpfennig. “If you talk to a lot of people, someone will get excited.” Dr. Wucherpfennig’s initial contacts were academic collaborators. He also recommended talking to attendees at scientific meetings and members of scientific advisory boards. Dr. Robert said that the venture capitalists she was working with introduced her to some of their many contacts, which helped significantly.

Dr. Ottinger, Acting Director, Therapeutic Development Branch (TDB) at NCATS, said that the NCATS model is based on team science forming collaborations between biomedical researchers, clinicians, industry partners, and regulatory agencies. NCATS, a research center of the National Institutes of Health (NIH), has the specific mission of supporting translational science at all levels. “Our branch can take a lead molecule, optimize and advance it through preclinical development to move it forward to regulatory filing and testing in the clinic,” said Dr. Ottinger. Although TDB is an intramural branch of NCATS, it works with extramural collaborators and partners to drive a project forward. “We’ve had collaborators from all over the world,” said Dr. Ottinger. “It’s really about the science that they bring in, building the research plan with clearly defined milestones, and having a strong emphasis on project management to execute the plan.”

NCATS provides in-kind resources and in-house support for early preclinical efficacy and toxicity testing, drug formulation and/or pharmacodynamic studies to understand how best to deliver a drug to patients and to determine whether the drug hits its target altogether. NCATS can also help support contracting for late-stage work needed to move the drug into the clinic. This support helps minimize risks along the discovery and development pathways all the way through filing the Investigational New Drug application with the FDA to begin clinical stage testing.

**Taming the Urge to Control Allows the Team to Flourish**

Once the perfect team comes together, “accept that you are not in control anymore,” said Dr. Robert, who splits her time 50/50 between the clinic and her translational lab.

Dr. Wucherpfennig said that the key is to “not really think of your molecule as ‘my discovery,’ but to build the team and work together.” His team recently started a Phase I trial and Dr. Wucherpfennig’s role is to serve as an advisor. “I’m involved when I need to be, but it’s the people in the company who are actually running the show day-to-day. Founders who tightly control a project often constrain the growth of the company in the end.”

**Being Overly Secretive Will Not Help the Process**

There was a time about 10-15 years ago when the drug discovery field was hyper-competitive and researchers were
overly protective of their intellectual property, said Dr. Perkins. It was an era when researchers did not talk to their competitors about what they were doing and the hurdles they faced. But this wariness changed as researchers came to appreciate the value of sharing their work. “I don’t think it’s good to be too secretive,” said Dr. Ribas, adding that the data must be robust.

Dr. Wucherpfennig said that publishing the data is very important for moving something into the clinic. “Potential team members want to see the quality of the data. Investors want to see that an idea is widely accepted by the community.”

**Funding Scientific Discoveries Can Be Challenging**

“Sometimes an idea is so powerful from the beginning that people will want to be part of it and raise money,” said Dr. Ribas. He added that programs at NIH and that certain states, like Texas and California, can help with funds early on, until the time is right to license or create a company.

Dr. Robert said that it was “quite easy” to find the first $6 million to start development, but after that, much more capital is needed and acquiring it became more difficult. “Every round of fundraising for us was tough,” said Dr. Wucherpfennig. “It took a lot of work. And as you get closer to the clinic, the amount of money needed grows exponentially.”

Which projects attract the most funding? Initial investors and venture capitalists are more likely to put money into therapeutics rather than diagnostics due to projected profit margins, said Dr. Ribas. His team had patented a number of biomarker targets that they believed would be good diagnostic tools for immunotherapy, “but ultimately, nobody was interested,” he said.

Dr. Ribas also noted that much of the work in a small company can be outsourced. “If you’re a small startup, you’re not going to make bioreactors that can make antibodies.” Contract Research Organizations (CROs) can manufacture an antibody to meet the specifications, and philanthropy or government programs can fund the work. “You do not need to do everything in house to be successful,” said Ribas.

**Not Every Pioneer Wants to Be an Entrepreneur**

“Starting a company is not the only way to take ideas to the clinic,” said Dr. Wucherpfennig. “Many universities have incubators, or you can collaborate with pharma and biotech.” He cited a colleague who discovered an interesting molecule with potential for clinical use. Although the colleague wanted to see his findings advance, and to ultimately benefit patients, he did not want to launch a startup himself. In this case, a collaboration with a biotech or pharma company would be a better fit. There may be different approaches depending on the type of therapeutic.

**Help is Out There**

Dr. Ottinger said that NCATS is working on developing programs about their translational process and has discussed having translational post-docs that can be trained in specific areas of drug development, while also doing basic research. Dr. Perkins mentioned a new monthly journal, Med, published by Cell Press, that focuses on clinical and translation research that could also be a useful resource.

At the close of the session, Dr. Wucherpfennig commented on the perception that academic work involves just doing laboratory research, publishing, and then moving on to the next project. “But if an idea is really powerful, I think you want to see it to the next level,” he said. “I don’t think that’s really different for academic researchers. Our purpose has always been to change the future of medicine.”
MRA’s Melanoma Exchange Patient and Advocate Forum, held in-person in Washington DC and virtually on March 9, 2022, brought together hundreds of melanoma patients, survivors, advocates, and their loved ones to provide lay-friendly, state-of-the-science education, promote collaboration and networking across the melanoma community.

The forum brought 500 people together for the in-person and simulcast program. Participants left with practical tips and strategies to get the most out of their care while navigating the challenges of melanoma diagnosis, treatment, and beyond.

Videos from the 2023 Melanoma Exchange Patient and Advocate Forum are available at CureMelanoma.org/Forum
The dream of transforming melanoma from the deadliest skin cancer into a curable one is on the cusp of becoming a reality—thanks to recent advances made in research over the past decade. While the rate of new melanomas has increased every year since 1975, the good news is that deaths attributed to the disease are decreasing faster than all other cancers, said Dr. Michael Atkins of Georgetown University and Chair of MRA’s Medical Advisory Panel.

A major revolution in melanoma treatment took place in 2011 with the success of immune checkpoint inhibitors. These drugs block certain “checkpoint” proteins that allow immune cells to kill cancer cells. This breakthrough was followed by the development of agents that target the most common mutations found in melanoma, and new strategies to reduce the likelihood of melanoma returning after surgery for patients at high risk. In his presentation focused on melanoma treatments and clinical trials at MRA’s 2023 Patient Forum, Dr. Atkins discussed the evolution of the melanoma treatment landscape and reviewed new and possibly upcoming therapeutic options. In a later presentation, Dr. Elizabeth Buchbinder of the Dana-Farber Cancer Institute showed how positive clinical research findings and advances in immunotherapy are translating into promising future melanoma therapies that can save even more lives.

Immunotherapy Options Continue to Grow for Melanoma

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Immunotherapy Continues to Revolutionize Melanoma Treatment

Immunotherapy empowers the body’s own immune system to kill cancer. “It’s like machine-gunning the tumor,” said Dr. Atkins. “An activated immune system can
target many different mutated proteins simultaneously, and the responses can deepen and grow over time—eliminating the last tumor cells and ultimately leading to cures.” Melanoma is one of the tumors that are most responsive to immunotherapy, particularly with the anti-PD-1 (i.e., programmed cell death 1) agents such as pembrolizumab and nivolumab, said Dr. Atkins.

But which agent to choose? The two checkpoint immunotherapies most commonly used in melanoma—pembrolizumab and nivolumab—are essentially very similar in efficacy, so it can be a “Coke vs. Pepsi” type of choice, said Dr. Atkins. Treatment selections are largely based on factors such as dosage schedule, time to approval, marketing, provider preference, and the cost of the drug. A patient might choose one treatment over another, for example, because fewer clinic visits are needed—making it more convenient in their day-to-day life.

The real advances in immunotherapy came with the introduction of combination therapy, said Dr. Atkins. In 2015, two different checkpoint immunotherapies were combined for the first time in the CheckMate 067 study. The study found that the combination of nivolumab, an anti-PD-1 agent, and ipilimumab, an anti-CTLA-4 agent, was better than either therapy alone in terms of overall survival. This response has enabled patients to achieve their goal of ending treatment while having the benefits of their therapy persist. “My oncology clinic has changed into a virtual travel agency,” said Dr. Atkins. “Patients freed from their therapy are traveling the world, ticking off items from their bucket lists, and attending milestone events like weddings, graduations, and the like that they would never have thought possible—certainly not prior to 2011.”

One reason why the responses are so durable is that the nivolumab + ipilimumab combination works in the central nervous system, at least for patients with asymptomatic brain metastases, said Dr. Atkins. For an in-depth account of a patient’s journey with immunotherapy for melanoma with brain metastases, Dr. Atkins recommended a book written by one of his patients, The Neuroscientist Who Lost Her Mind: My Tale of Madness and Recovery, by Barbara K. Lipska.

Combining targeted therapy with immunotherapy can sometimes offer additional benefits, said Dr. Atkins. Targeted therapies identify and attack certain proteins with gene mutations in tumors that control the growth of cancer cells. The BRAF and MEK mutations are currently the most common targets for melanoma therapy. BRAF/MEK targeted therapies appear to be a good second-line treatment after immunotherapy but do not work as well when used before checkpoint immunotherapy, said Dr. Atkins. Targeted therapies also have some ongoing toxicities and are given continuously, except when used before or post-surgery to reduce the likelihood of melanoma recurring. Another option is to administer immunotherapy simultaneously with targeted therapy. Therapy that combines BRAF/MEK inhibitors with nivolumab/ipilimumab may be useful for patients with aggressive disease, but the approach has not really caught on in the medical community, said Dr. Atkins.
Anti-PD-1 checkpoint immunotherapies serve as the basis for many types of combination regimens, with thousands of active clinical trials using PD-1 inhibitors as a backbone. However, questions remain, said Dr. Buchbinder. “We still have patients who develop diabetes, diarrhea, adrenal insufficiency, and other long-term problems with PD-1 inhibitors,” she said. “So thinking about which patients really need this—especially before or following surgery—is important.” Biomarkers may help with these predictions, she added. “I think we’ll be hearing more about circulating tumor DNA, which is being used in other cancers, such as lung cancer, to detect tumor regrowth earlier than scans are able to.”

Most recently, the combination of nivolumab and relatlimab, an antibody that blocks the immune checkpoint protein LAG-3 (lymphocyte-activation gene 3), represents an alternative frontline therapy option for patients with advanced melanoma, said Dr. Atkins. This combination was FDA-approved in 2022 based on results of the RELATIVITY-047 trial that demonstrated superior progression-free survival compared with nivolumab alone.

**Adjuvant and Neoadjuvant Therapies Can Decrease Cancer Mortality**

One of the best ways to reduce deaths from melanoma is to give adjuvant therapy (administered after surgery) or neoadjuvant therapy (administered before surgery) to patients who have ‘high risk’ melanoma, said Dr. Atkins.

Dr. Buchbinder shared recently published research showing that three cycles of pembrolizumab given before surgery and 15 cycles given after—what doctors call neoadjuvant therapy—resulted in a better event-free survival (meaning fewer patients saw their melanoma recur) than giving 18 cycles after surgery (adjuvant therapy). “Most of us are now giving neoadjuvant therapy when we can in clinic,” said Dr. Buchbinder. “But many questions remain. What treatment is really best in the neoadjuvant space? Should we be doing combinations? Triplets? How do we use the information in the neoadjuvant setting to look at what happens after the treatment is given?” Research continues in these areas.

**New Immunotherapies in Development Continue to Show Promise for Melanoma**

Checkpoint immunotherapies are not the only immune-related approaches being studied for the treatment of melanoma. Dr. Buchbinder described several innovative immune-based approaches currently in development.

**Cancer Vaccines.** “The role of vaccines in the treatment of melanoma is another exciting area to watch,” said Dr. Buchbinder. Although vaccines are generally thought of as preventive therapy, there are also therapeutic vaccines that train the immune system to fight off abnormal proteins, such as those linked with cancer cells including melanoma. “When a tumor develops, genetic changes take place within the tumor that result in new proteins called neoantigens, which are specific to that tumor,” said Dr. Buchbinder. Researchers are using DNA and RNA sequencing to identify an individual patient’s neoantigens for inclusion in a
personalized vaccine—supported in part by MRA—called NeoVax. Early clinical trials have shown that a regimen of NeoVax and PD-1 blockade was effective in patients with melanoma, bladder cancer, and non-small cell lung cancer, said Dr. Buchbinder.

Another therapeutic vaccine approach involves mRNA vaccines, similar to those developed for COVID-19. “Instead of giving a little piece of protein, we can give RNA that causes the cells to create that protein,” said Dr. Buchbinder. “The immune system can then react against the protein and build an immune response.” The mRNA-4157/V940 trial is looking at treating patients with Stage 3 or 4 melanoma with a combination of pembrolizumab and a personalized mRNA vaccine, and comparing the results to pembrolizumab alone, said Dr. Buchbinder.

Preliminary results showed that the risk of death was reduced for the combination compared with the single agent, she said, noting that the final full data report is pending.

Other trials are studying the effects of off-the-shelf mRNA vaccines—designed using key mRNA sequences found in most melanomas—when combined with PD-1 inhibitors. These trials are also reporting encouraging results.

Tumor-Infiltrating Lymphocyte (TIL) Therapy. Another type of immunotherapy uses TIL cells harvested from the tumor itself to fight the cancer. “We take cells from the melanoma and give them back to the patients with some chemotherapy and immunotherapy,” said Dr. Buchbinder. “It’s a pretty complicated therapy that requires inpatient admission.” TIL therapy may be a very good second-line option, she added, noting that clinical trial results indicate effectiveness even after many different lines of therapy have been tried—including chemotherapy, targeted therapies, triplet therapy, and others. “The responses were durable and long-lasting,” said Dr. Buchbinder, noting that most of the side effects occurred when patients were in the hospital—where they can be closely monitored. Toxicity did not continue afterwards.

In conclusion, treatment options for melanoma have dramatically changed over the last decade, and the progress only continues to accelerate. Dr. Buchbinder said that we can also expect to hear more in the near future about topics such as cytokine therapies, adoptive cell transfer, and oncolytic virus therapies. “There’s tons of exciting research going on,” she said, “but none of this could happen without patients willing to go on trials and work with us. That really is the most important piece for helping all patients at all stages of their disease.”
Living Well Despite Melanoma

Well-being, comfort, and good emotional health are daily concerns for people living with melanoma. Patients, advocates, clinicians, and researchers alike are asking—even demanding—that these quality-of-life issues become a larger part of the conversation. “Focusing on quality of life is good for all of us,” said Dr. Lorenzo Cohen of the MD Anderson Cancer Center and co-author of the book, *Anticancer Living*. Dr. Cohen was the first presenter on a panel discussion at the 2023 Melanoma Exchange Patient Forum focused on how managing stress, eating a healthy diet, and staying active can help improve your quality of life before, during, and after a melanoma diagnosis. And, based on emerging research, the same factors that can improve your quality of life may actually improve the way your body responds to melanoma treatment. “At the end of the day, we all want to thrive,” he said.

**The Mix of Six**

“And it’s not just about feeling better,” said Dr. Cohen. “You also want to create an inhospitable environment for cancer to grow.” To do this, Dr. Cohen recommended focusing on the “Mix of Six,” a half-dozen key areas that can impact the biology of cancer and play a role in cancer prevention and control. They include:

- social support,
- stress management,
- sleep,
- physical activity,
- diet, and
- avoiding environmental toxins.

Emerging research suggests that the same factors that improve your quality of life may actually improve the way your body responds to melanoma treatment.
Three in particular—stress, diet, and exercise—influence the biological processes that determine the extent that mutated cells continue to grow and threaten our lives, said Dr. Cohen. He focused his talk on stress management and diet, while Dr. Allison Betof Warner of Stanford University discussed current research on the benefits of exercise for patients with cancer, including melanoma.

**Managing Stress May Reduce the Spread of Cancer**

Stress is a common reaction to a life-threatening illness, such as melanoma, and its challenges. Although the fight-or-flight response helps us in the short term, it’s extremely damaging when this response becomes chronic, said Dr. Cohen. Chronic stress can disrupt relationships, interfere with sleep, and influence our metabolism and how we process food. Stress hormones, particularly norepinephrine and cortisol, can influence the tumor microenvironment and actually encourage cancer growth.

Stress-reducing interventions—such as cognitive behavioral therapy, yoga, meditation, and tai chi—have been well-studied and are actually included in the cancer care guidelines for managing symptoms for patients with many cancers, including melanoma, said Dr. Cohen. “They also impact our biology.” He cited a 6-week study conducted at the University of California Los Angeles of patients with Stage 2 and 3 melanoma. The data showed that a structured cognitive therapy program not only resulted in better quality of life and fewer mental health symptoms, but also in improved cell-mediated immunity, which is relevant for controlling melanoma. The effects were even more pronounced at 6 months, along with improvements in disease-free and overall survival at 10-year follow-up.1

**Foods Can Influence Cancer Growth and Responses to Therapy**

Over the past 50 years, the average American’s eating habits have become increasingly unhealthy. In contrast to this societal shift, evidence-based research supports recommendations for eating more legumes, whole grains, and nuts, and reducing consumption of animal proteins—particularly red meat.

Dr. Cohen discussed a recently published study that followed immunotherapy responses of patients treated with checkpoint immunotherapy for melanoma. The results showed that the closer the patients’ diet mirrored a Mediterranean diet, which emphasizes fruits and vegetables, whole grains, seafood, nuts and legumes, and olive oil, the higher their probability of responding to immunotherapy.2

Immunotherapy responses are also influenced by the microbiome. Dr. Cohen shared a recent study, supported by MRA, that looked at how lifestyle factors, including the microbiome, can influence immunotherapy responses. Dr. Cohen served not only as an investigator for this study, but also as a patient with melanoma, which he learned he had in 2018—the same year he and the team were awarded funding from MRA. The results of the study showed that patients on a high-fiber diet, which acts as a prebiotic to improve the microbiome, had a higher probability of responding to treatment and better survival rates. Surprisingly, patients who did best were not taking a probiotic with their high-fiber diet.3 “To improve the microbiome, the majority of your plate needs to be plant-based, whole foods,” said Dr. Cohen.

**Exercise Can Ease Cancer Symptoms and May Affect Responses to Therapy**

“Movement as medicine is not a new concept,” said Dr. Betof Warner, who is studying how exercise affects tumor growth and immunotherapy. “Since the days of Socrates, we’ve known that
moving the body is good for us, but this concept was not formally studied until about 40 years ago.”

Patients with cancer had been told for many years—including now—that they should relax, take it easy, and be gentle to their bodies. However, studies in the mid-1980s showed the benefits of exercise for women receiving high-dose chemotherapy for breast cancer. The findings helped launch the field of “exercise oncology,” an area that has grown exponentially, especially since the early 2000s, said Dr. Betof Warner. The American College of Sports Medicine (ACSM) recently published consensus guidelines based on data showing that exercise is safe during and after cancer treatment. These guidelines have made their way into the guidelines for symptom management issued by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN).

“For symptom management, it’s not surprising that exercise is beneficial,” said Dr. Betof Warner. “But what about from a cancer outcomes perspective?” Although exercise has been heavily studied and linked with decreases in cancer-specific and all-cause mortality in a variety of cancers (e.g., breast, colon, and prostate), early studies of patients with melanoma did not show similar results. However, Dr. Betof Warner noted, these studies did not control for the fact that people do most of their physical activity outside in the sun, which increases the risk of melanoma.

“There are many mechanisms through which exercise can affect a tumor,” said Dr. Betof Warner, “but it can be challenging to tease out individual biologic effects.” People who exercise also tend to have other good health behaviors, such as eating better, sleeping more, and wearing sunscreen. Therefore, researchers like Dr. Betof Warner are using mouse models to study the specific effects of exercise on melanoma. Results so far have shown that sedentary mice have larger tumors than mice that exercise, an effect that disappears in immune-deficient mice. “This tells me that the immune system is critical for mediating the exercise effects on tumor growth,” said Dr. Betof Warner.

Many questions remain before a clinician can write a prescription for exercise, said Dr. Betof Warner. How much? How often? What intensity? Is a 20-minute walk sufficient? Is weight training better than aerobic exercise? “I can’t answer those questions for you today,” she said. “This is what I’m spending my time working on.”

Dr. Betof Warner suggested that patients should check out the ACSM’s web page on Exercise in Medicine (exerciseismedicine.org), which provides guidance and links to exercise rehabilitation programs for patients with cancer by zip code.

The session concluded with comments by panelist Bill Evans, a patient advocate with metastatic melanoma who described himself as a “husband, father of two children, fourth grade teacher, and competitive cyclist.” Cycling was an integral part of Evans’s identity and routine before his diagnosis—and he did not want that to change just because of melanoma. Evans said that early on, it was hard to figure out how much exercise he could do during therapy when few data were available. “But I found a balance. Or the balance found me,” he said. A sleep monitor and heart rate tracker helped him, along with a healthy diet and a dedicated oncology team. “It’s been an amazing journey.”

Good communication is always challenging but can be especially so when you are undergoing treatment for melanoma. That’s because navigating our modern healthcare system is often an exercise in decoding complex jargon and knowing the right questions to ask while managing stress and other strong emotions. “Communication is hard—whether you’re a patient, clinician, nurse, or administrative person who answers the phone,” said Nadia Jabri, a patient advocate and caregiver for her mother who passed away due to melanoma. Jabri joined Dr. Anna Pavlick, an oncologist at Weill Cornell Medicine, and Kristina Baum, another patient advocate, to discuss why communication matters in melanoma care and how to improve it. They provided tips, tricks, and strategies to make sure patients and caregivers are proactive partners with their care team.

**Improving Communication With Your Melanoma Care Team**

“Communication is hard—whether you’re a patient, clinician, nurse, or administrative person who answers the phone.”

NADIA JABRI, PATIENT ADVOCATE

Good communication is always challenging but can be especially so when you are undergoing treatment for melanoma. That’s because navigating our modern healthcare system is often an exercise in decoding complex jargon and knowing the right questions to ask while managing stress and other strong emotions. “Communication is hard—whether you’re a patient, clinician, nurse, or administrative person who answers the phone,” said Nadia Jabri, a patient advocate and caregiver for her mother who passed away due to melanoma. Jabri joined Dr. Anna Pavlick, an oncologist at Weill Cornell Medicine, and Kristina Baum, another patient advocate, to discuss why communication matters in melanoma care and how to improve it. They provided tips, tricks, and strategies to make sure patients and caregivers are proactive partners with their care team.

**Speak Up!**

“It’s essential to tell your clinician how much you want to know,” said Dr. Pavlick. “Every patient has different needs about the amount of information they want. Some don’t want details. Others want to learn everything.” Jabri added that
sometimes a patient wants to know everything but doesn’t always have the right words to even ask a question. In cases like this, the panelists reminded patients and caregivers that sometimes it takes multiple attempts to get your point across—and that’s okay because ultimately, it’s your life or the life of your loved one that is at stake. “You have to start the conversation, even if it isn’t pretty,” says Jabri. “You may have to repeatedly remind the clinician that you want to know everything and have them proactively inform you,” she said. “You have the right to know what is happening and to have it explained in a way that you can fully understand.”

Robust communication with the care team is especially critical when participating in clinical trials, said Baum, a melanoma survivor. “Things that seem small to you may actually be a big deal.” While participating in a Phase 1 clinical trial, Baum started having headaches and nausea, which she at first attributed to her stressful job on Capitol Hill. When she finally decided to take the initiative and report the symptoms to her medical team, she learned that she was having a rare adverse response to the experimental therapy called “autoimmune meningitis.” Basically, her immune system recognized her brain as foreign and began attacking it. Because Baum spoke up early, her care team was able to manage the reaction and she had no permanent damage. “Reporting any and all side effects to your care team is so important,” emphasized Jabri. “When in doubt, just report it—you aren’t bothering them.”

Baum’s favorite piece of advice came from a research nurse who told her not to be afraid of being a jerk. “She was absolutely right,” said Baum. “You have to take control and be persistent and consistent. I learned what that looks like.”

Write Questions in Advance of Your Appointment and Have a Game Plan for Each Visit

“I’m a big advocate of lists,” said Dr. Pavlick. “I tell everybody to write down their questions, because once you get to the appointment it’s easy to forget what you wanted to ask.”

In another panel discussion held later that day focused on Living with Melanoma, Ken Billett, a patient advocate and melanoma survivor, suggested bringing a pen and paper to each visit to write down the answers—and even a computer, laptop, or tape recorder, if that works better for you. “Your appointments are your best opportunity to understand what is happening to your body, with your treatment, and what you can expect around the bend,” said Billett.

Jabri suggested sending questions to the provider by email before the visit. “Some clinicians may look them over and some may not. But it signals to your doctor that you have questions in a specific area and can allow them to prepare or make additional time to address them,” said Jabri. “If you propose the idea, they may be open to it. In the end, it will make their job easier.”
Baum also recommended asking for help managing stress and anxiety, which is often a big part of a melanoma journey. This anxiety often appears in the types of questions patients ask their doctors. For example, early in her melanoma journey, she wrote a list of 16 questions, took them to her oncologist, and realized she was asking the same question 16 different ways: Am I dying? “That was my anxiety talking,” she said. “Being depressed or anxious about what you’re dealing with is super normal. Support is out there and you’re not alone.”

**Bring a Loved One or Caregiver to Your Appointments**

“Four ears are better than two,” said David Marx, a patient advocate on the Living with Melanoma panel. Marx found it helpful to have his wife accompany him on visits. “Sometimes I might not be paying attention, or she might not be paying attention but together: we are a team.”

Caregivers or loved ones can also ask questions or report symptoms that the patient is reluctant to bring up. Jabri said that in her situation, she and her mother discussed symptoms and other challenges that they wanted to discuss with her doctor before each visit. But at the appointment, her mother would often say that everything was just fine. Jabri realized this was her mother’s way of trying to be a “good patient,” and not raising any flags.

Dr. Pavlick said that if a caregiver has questions that the patient doesn’t want to discuss, she will ask the patient for permission to talk with the caregiver alone. Dr. Pavlick will ask the patient to have a seat in the waiting room while she answers the caregiver’s questions. “Making sure your support system knows what to expect is important,” said Dr. Pavlick. “No one faces melanoma alone.”

**Recap What You Heard, Ask if that’s Right, and Know How to Follow Up**

Jabri said that she would often go to appointments worried that she wouldn’t be able to write answers fast enough, understand the answers, or read her writing afterward. Fortunately, her provider was open to following up by email. Dr. Pavlick also encourages this, noting that it allows her to clarify information in writing. “I’ll often learn that the patient didn’t understand what I thought they understood,” she said. “I’ll forget that they may not know the difference between a CT scan and a PET scan. When you don’t understand something—that’s okay and normal—but please communicate that. Don’t be embarrassed. It’s our job to explain what’s happening in a way you can understand.”

After a clinical visit, Jabri and her mother always planned to debrief together. They would go to a restaurant and discuss what they heard so that they could both be on the same page. “And often we weren’t,” she said. “Two people always hear things differently, so this became a helpful routine for us.”

At the conclusion of the session, Jabri said that patients and caregivers need to “go to school” to learn how to communicate with not just one clinician but multiple clinicians over time. She suggested checking for resources at a local institution that can help with navigating the health care system. A social worker, patient navigator, or psychologist, for example, can help connect the dots with your entire medical team, including multiple specialty providers.

Baum said that the most important thing is to trust your provider and medical team. “If you don’t trust them, then find someone else,” she said. Dr. Pavlick agreed. “Make sure it’s the person that you trust with your life,” she said, noting that with Zoom, it’s easy to get second opinions. Dr. Pavlick has patients all over the country and will have calls with them together with their local doctors.

Patients and caregivers must also keep in mind that clinicians are not taught communication skills in medical school, said Jabri. “Many doctors do not know everything about dealing with end-of-life issues or what hospice is like,” she said. “Hopefully, we’ll have more conversations as equal stakeholders and come up with better ways to talk with each other. We’re all in this together.”

David Lombard, MD, PhD – University of Miami
Wednesday, March 8

7:30am-5:00pm Grant Review Committee Meeting (by invitation)
12:00-5:30pm Melanoma Patients, Advocates & Foundations Forum
   Chair: Cody Barnett | MRA Senior Director of Communications & Patient Engagement
4:00-8:00pm Retreat Registration open
5:30-6:00pm Sponsor Toast/Reception
6:00-7:30pm Opening Reception
7:00-9:30pm Friends of MRA Dinner [GRC and invited guests only]

Thursday, March 9

6:30am-6:00pm Registration
7:30-8:45am General Breakfast
7:30-8:45 am Young Investigators Breakfast (by invitation): Mentorship and Lab Personnel Management
   Andrew Aplin | Thomas Jefferson University
   Marcus Bosenberg | Yale University
   Elizabeth Patton | University of Edinburgh
   Ashi Weeraratna | Johns Hopkins University
9:15-9:45am OPENING REMARKS DAY 1
   Marc Hurlbert | MRA Chief Executive Officer
   Jamie Goldfarb | Patient Advocate
   Ken Billett | Patient Advocate
   Joan Levy | MRA Chief Science Officer
9:15-9:45am KEYNOTE LECTURE 1
   Georgina Long | Melanoma Institute Australia
   Zero deaths from melanoma – Progress to date, prospects for the future, systemic therapy and beyond
9:45-11:55am SCIENTIFIC SESSION 1
   Artificial Intelligence and Imaging in Melanoma Detection, Prediction and Prognosis
   Chair: Maria Wei | University of California, San Francisco
9:45-10:10am Albert Chiou | Stanford University
   AI-Augmented melanoma triage and diagnosis: interim update on this prospective multi-site study
10:10-10:30am Jesse Wilson | Colorado State University
   Image translation networks for noninvasive biopsy and dermoscopy screening
10:30-11:00am BREAK
### 11:00-11:25am
**Iman Osman** | New York University  
*Developing a predictive tool using machine learning algorithm in melanoma*

### 11:25-11:50am
**Pratip Bhattacharya** | University of Texas M.D. Anderson Cancer Center  
*Hyperpolarized MRI to interrogate pH in immunotherapy resistant and responding melanoma models in vivo*

### 11:50am-12:00pm
**TRANSITION TO LUNCH**

### 12:00pm-1:20pm
**NETWORKING LUNCH AND GENERAL ROUNDTABLES**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Facilitator/Institution</th>
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<tbody>
<tr>
<td>Acral + Mucosal Melanoma Patient Registry</td>
<td>Mentoring/mentorship</td>
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<td>Biomarkers – ‘liquid biopsy’, ctDNA, tumor biomarkers</td>
<td>Metastasis and tumor dormancy</td>
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<td>Brain metastasis and leptomeningeal disease</td>
<td>Microbiome</td>
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<td>Clinical trials – patient recruitment and engagement, trial design</td>
<td>Neoadjuvant and adjuvant therapy</td>
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<td>Dermatology fellows</td>
<td>Prevention (primary prevention)</td>
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<td>Diversity – Women &amp; Underrepresented groups in melanoma research and care</td>
<td>Starting a company/venture philanthropy</td>
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<tr>
<td>Early Detection &amp; Diagnosis (AI, imaging, machine learning)</td>
<td>Targets &amp; drug discovery for new treatments</td>
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<tr>
<td>Genomics – Role of genetics, genomics &amp; epigenetics</td>
<td>Tumor microenvironment</td>
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<tr>
<td>irAE – understanding immune-related adverse events</td>
<td>Vaccines and cell-based therapies</td>
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### 1:30-3:00pm
**SCIENTIFIC SESSION 2**

**Novel Treatment Strategies for Melanoma and Improving Treatment Responses**  
**Chair: Tanisha Jackson** | MRA Scientific Program Director

### 1:30-1:55pm
**Michael Postow** | Memorial Sloan Kettering Cancer Center  
*CD8+ cell imaging during Neoadjuvant ImmunoTherapy (The C-IT Neo Trial)*

### 1:55-2:15pm
**Lixin Wan** | Moffitt Cancer Center and Research Institute  
*An atypical way to sustain wild-type BRAF signaling in melanoma*

### 2:15-2:35pm
**Gatien Moriceau** | University of California, Los Angeles  
*PDXs to discover targets and to model therapeutics*

### 2:35-2:55pm
**Matthew Vesely** | Yale University  
*Colocalization of VISTA and CD11b myeloid cells is associated with poor outcomes in melanoma*

### 2:55-3:25pm
**BREAK**

### 3:25-4:25pm
**SCIENTIFIC SESSION 3**

**Rare Melanomas**  
**Chair: Joan Levy** | MRA Chief Science Officer

### 3:25-3:45pm
**C. Daniela Robles-Espinoza** | National Autonomous University of Mexico  
*Genomic analysis of acral melanoma in Latin American patients*

### 3:45-4:05pm
**Rolando Perez-Lorenzo** | Columbia University  
*CK2 inhibition in Acral Melanoma*
4:05-4:25pm J. Silvio Gutkind | University of California, San Diego
Targeting signaling vulnerabilities in uveal and cutaneous melanoma: new multimodal precision therapies

4:25-5:10pm

SCIENTIFIC SESSION 4

Highlighting MRA Young Investigator Awardees
Chair: Rachel Fischer | MRA Associate Director, Scientific Program & Registry

4:25-4:35pm Zachary Buchwald | Emory University
Immune niches containing stem-like T cell in brain metastases control disease and are modulated by SRS

4:35-4:45pm Tobias Bald | University Hospital Bonn
Loss of CD226 in T cells drives resistance to melanoma immunotherapy

4:45-4:55pm Jeremy Logue | Albany Medical College
Piezo1 conspires with INF2 to promote confined migration in invasive melanoma cells

4:55-5:05pm Haizhen (Jen) Wang | Medical University of South Carolina
Targeting PTPs for CDK6 induced immunotherapy resistance in melanoma

5:05-5:10pm CLOSING REMARKS DAY 1
Tanisha Jackson | MRA Scientific Program Director

5:15-6:15pm

MRA BOARD MEETING

5:15-6:45pm

POSTER SESSION I
Dermatology Fellows, Young Investigators, Pilot Awardees, and Sponsors
Light refreshments, all retreat attendees encouraged to attend

7:00-9:30pm Dinner | Charlie Palmer Steak, 1101 Constitution Ave, NW, Washington DC
Transportation provided

Friday, March 10

6:30-10:00am Registration open

7:00-8:50am Breakfast and Poster Session II: Young Investigator and Pilot Awardees

7:30-9:00am Industry Roundtable Breakfast (by invitation only)

9:00-9:05am OPENING REMARKS DAY 2
Rachel Fischer | MRA Associate Director, Scientific Program & Registry

9:05-9:35am KEYNOTE LECTURE 2
Sohail Tavazoie | The Rockefeller University
A hereditary basis for melanoma metastasis and its experimental and clinical therapeutic implications

9:35-11:30am SCIENTIFIC SESSION 5
Discovery Research to Identify New Melanoma Therapies
Chair: Genevieve Boland | Massachusetts General Hospital

9:35-9:55am Neta Erez | Tel Aviv University
Systemic instigation of neuroinflammation by LCN2 facilitates brain metastasis
9:55-10:15am  Alfonso Bellacosa | The Research Institute of Fox Chase Cancer Center
Enhancing immunotherapy with novel epigenetic modulators that induce a proinflammatory response

10:15-10:40am  BREAK

10:40-11:05am  Jamie Spangler | Johns Hopkins University
Tumor-targeted cytokine/antibody fusion proteins to treat melanoma

11:05-11:30am  Sarah Slavoff | Yale University
Getting a handle on undruggable proteins in melanoma with bicycles

11:30am-12:30pm  PANEL DISCUSSION
Translation of New Therapeutics and Diagnostics from the Lab to the Clinic
Moderator: Louise Perkins | MRA CSO Emerita

Panelists:
Elizabeth Ottinger | National Center for Advancing Translational Sciences
Antoni Ribas | University of California, Los Angeles
Caroline Robert | Institut Gustave Roussy
Kai Wucherpfennig | Dana Farber Cancer Institute

12:30-12:45pm  CLOSING REMARKS: Stephanie Kauffman | MRA President and Chief Operating Officer

12:45-1:45pm  Lunch and Departures

12:45-6:30pm  Lunch and MRA & Seerave Foundation Melanoma & the Microbiome Workshop (by invitation only)

6:30-9:30pm  MRA & Seerave Foundation Melanoma & the Microbiome Workshop — Dinner

Saturday, March 11

8:30am-1:30pm  MRA & Seerave Foundation Melanoma & the Microbiome Workshop (by invitation only)
11:30-11:45am  Registration & Check in*

11:45-1:00pm  Networking Roundtables with Lunch*

1:00-1:10pm  WELCOME REMARKS

Stephanie Kauffman | President & COO, Melanoma Research Alliance (MRA)
Cody Barnett, MPH | Senior Director of Comms & Patient Engagement, MRA

1:10-1:50pm  The Melanoma Standard of Care: Building a Shared Foundation
The melanoma treatment landscape has dramatically changed in the last decade. This opening talk will give participants a shared foundation to ground the full program.

Michael Atkins, MD | Georgetown University

1:50 - 2:30pm  On the Horizon Emerging Therapies & Clinical Trials to Watch
Today, the melanoma research landscape has never been more dynamic. In fact, more than 500 clinical trials are actively enrolling patients with melanoma.

Elizabeth Buchbinder, MD | Dana-Farber Cancer Institute

2:30 - 2:40pm  BREAK

2:40 - 3:15pm  Melanoma & Brain Mets: Where We Stand
Learn more about melanoma brain metastases and leptomeningeal disease (LMD), how they are treated, and about ongoing research into this urgent area of unmet patient need.

Omid Hamid, MD | The Angeles Clinic

3:15 - 4:10pm  Lost in Translation: Improving Communication With Your Care Team
Communication between you and your care team is absolutely critical. Get tips on how to communicate effectively from diagnosis, to beyond.

Kristina Baum | Patient Advocate
Anna Pavlick, DO | Weill Cornell Medicine
Nadia Jabri | Patient Advocate
4:10 - 5:00pm  **Maximizing Quality of Life & Practicing Wellness Despite Melanoma**  Learn how managing stress, eating a healthy diet, good sleep, and staying active can help improve your quality of life despite melanoma. You’ll also hear about exciting advances in non-invasive imaging that could make skin biopsies a thing of the past.

**Allison Betof Warner, MD, PhD** | Stanford University  
**Lorenzo Cohen, PhD** | MD Anderson Cancer Center  
**Bill Evans** | Patient Advocate  
**Alexander Witkowski, MD, PhD** | Oregon Health & Science University

5:00 - 5:55pm  **Panel Discussion: Living with Melanoma**  Get tips and strategies from this diverse panel of people who have all been impacted by melanoma.

**Ken Billett** | Patient Advocate  
**Pat Janiak** | Patient Advocate  
**David Marx** | Patient Advocate  
**Joan Levy, PhD** | Chief Science Officer, MRA

5:55 - 6:00pm  Closing & Wrap-up

6:00 - 7:30pm  Patient, Advocate, & Researcher Reception*

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**Download Meeting Materials:**  
SCAN THE ABOVE QR CODE OR CUREMELANOMA.ORG/FORUM-MATERIALS
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