Breaking the Barrier:
Getting Beyond 50% Long-term Survival for Patients with Advanced Melanoma

Highlights from the 2020 Melanoma Research Alliance Scientific Retreat
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Each year, the Melanoma Research Alliance looks forward to hosting the annual Scientific Retreat. The 2020 Retreat took place from February 26-28 in Washington, DC. The gathering brought together key members of the melanoma community — researchers, clinicians, patients and their loved ones, as well as representatives from industry, government, scientific journals, and other foundations — for three days of scientific presentations, conversations, and learning.

This year’s Retreat featured presentations from 20 researchers, including a keynote lecture from Nobel Laureate and MRA Scientific Advisory Panel member Jim Allison. Central to these presentations, and to the Retreat as a whole, was engaging the melanoma community around the question of how to maintain innovation to improve outcomes for patients. Innovation led to the approval of 12 new treatments in the past decade and pushed survival rates to five years or more for nearly 50% of advanced melanoma patients on combination immunotherapy — but how can this promise be realized for the other half of melanoma patients?

Scientific sessions focused on novel therapeutic approaches, understanding melanoma initiation and metastasis, as well as a special session on acral melanoma, among others, highlighted the innovative approaches being taken by MRA-funded researchers that continue to raise the bar for patients who do not respond to the currently approved therapies. Research presented, which was largely unpublished, demonstrated that approaches such as treating patients with systemic therapy at earlier stages of disease, using artificial intelligence (AI) to improve the accuracy of melanoma diagnosis, and designing studies so clinical data can advance laboratory studies and vice versa have the potential to lead to better outcomes for patients in the near future.

Beyond the scientific presentations, the Retreat featured the Melanoma > Exchange Advocates Forum where patients, their family members, and caregivers had the opportunity to gather with experts to learn about the latest advances in treatment, the importance of animal models to propel research forward, and tools for how to separate hope from hype in the media coverage of melanoma and cancer treatment more broadly. The Forum also featured a guest appearance by U.S. Surgeon General Jerome Adams, who highlighted the importance of advancing melanoma prevention and early detection efforts.

The program also included a breakfast for MRA Young Investigator Awardees focused on the importance of mentorship in scientific research, a poster session where MRA-funded researchers had the opportunity to present their work, and two topic-focused networking sessions. MRA also hosted an Industry Roundtable discussion focused on how industry, researchers, clinicians, and regulatory officials can work together to improve survival outcomes for melanoma patients not benefitting from currently approved therapies. MRA’s goal is that the conversations and collaborations sparked by these events will continue to accelerate progress in melanoma prevention, detection, diagnosis, and treatment.

The science presented and ensuing discussions help MRA set its priorities in the coming year. We are delighted to share highlights from the 2020 Scientific Retreat with you, which we are sure will lead to critical advances for melanoma patients in the near future.

Sincerely,

Marc Hurlbert, PhD
Chief Science Officer

Kristen L. Mueller, PhD
Senior Director, Scientific Program
Maintaining Momentum:
Advancing Treatment Approaches, Understanding Patients’ Holistic Needs, and Preventing New Melanomas
The last decade has been one of substantial progress and hope for many melanoma patients, researchers, and clinicians. With 12 new therapeutic approaches now approved to treat melanoma, many advanced-stage patients are seeing their tumors shrink or disappear, and are experiencing renewed hope for a brighter future. Given this exceptional progress, researchers, clinicians, patients and their caregivers, as well as representatives from industry, biotech, non-profits, and government gathered at the 2020 MRA Scientific Retreat to hear updates on the latest research, to discuss how to keep this incredible momentum going into the next decade, and to build new collaborations.

Raising the Bar to Help More Melanoma Patients

While some newly approved treatments are helping far more patients with advanced melanoma hit the five-year survival threshold, there are still too many patients who don’t respond to these treatments, and others who may respond, but don’t maintain a durable response. The bar has been raised for many, but further work is needed to raise the bar for more melanoma patients.

Driving this need home, Grace Wenzel provided opening remarks via an address delivered from her hospital bed, recorded the night before the Retreat. Twenty-three-year-old Grace relayed how current treatments

On May 8, 2020 — two months after delivering the opening remarks at the MRA Scientific Retreat — Grace Wenzel passed away due to complications from melanoma. Grace’s advocacy for melanoma research, prevention, and early detection continues to inspire. She will always be a cherished member of the MRA family.
put her melanoma into remission for several months, but now were no longer working. She pleaded with researchers to continue to strive towards a melanoma cure. “I have no idea what things are going to look like for me even one week from now. But I am determined to keep fighting.”

Delivering the Retreat’s opening scientific keynote, Jedd Wolchok of Memorial Sloan Kettering Cancer Center started by saying, “We are determined and by Grace’s side to help find better answers to her disease.” He and other researchers at the retreat reported on exciting results that they think will help maintain the amazing momentum. By assessing ways to improve existing therapies, including using them in combination or using them in patients with earlier stages of disease, as well as exploring totally new treatment avenues, researchers are optimistic that fewer patients will find themselves in circumstances similar to Grace. While many researchers focus on treatment, others are pursuing ways to prevent new melanomas or to detect them at an earlier stage. The hope is that by the end of this decade, if not sooner, patients like Grace will not be in the hospital, but will instead be leading normal lives after successful melanoma treatment. Better yet, there may be fewer melanoma patients altogether because of successful and widespread melanoma prevention programs.

The Treatment Landscape

**Immunotherapies, Combinations & Dosing:** Currently, thousands of clinical trials are testing new combinations of immunotherapies in melanoma and other cancers. Most build on already approved checkpoint immunotherapies by adding to them vaccines and other new agents designed to rally more components of the immune system to enhance overall response. Others combine them with standard chemotherapy, targeted therapy, or radiation therapy. “Combination therapy will be necessary for immunotherapy to achieve its full potential,” Wolchok stressed. The experimental combination therapies build on the greater understanding of immune responses to tumors that has blossomed from basic research. “These are rational immunotherapy combinations based on rational preclinical science, rather than just throwing things out and seeing what sticks because there are too many possible combinations to try,” Wolchok noted.

He added that investigators are also becoming more refined in the dosing of immunotherapies as they gain a better understanding of how the therapies work on a molecular level. Given the severe adverse reactions often caused by immunotherapies, “There shouldn’t be a one-size-fits all assumption about dosing,” he said. Wolchok described one study (NCT03122522) testing “adaptive dosing” that uses an innovative imaging agent to detect how patients are responding after just two doses of combination ipilimumab + nivolumab therapy. Building on the understanding that responses to combination ipilimumab + nivolumab often continue even if ipilimumab is discontinued, continuation of the combination therapy in the trial was based on whether a response to therapy is seen after just two doses. Only patients who do not appear to be responding well — as detected by medical imaging — continue to receive combination therapy. Patients whose tumors are

“There shouldn’t be a one-size-fits-all assumption about dosing.”

— Jedd Wolchok
Bringing Currently Approved Therapies to Earlier Stage Patients:
Researchers are also focused on treating earlier stage melanoma with drugs currently approved only for advanced melanoma patients. Treating patients with systemic therapy prior to surgery — termed neoadjuvant therapy — may reduce the chance of recurrence, which is supported by clinical trial data, although these trials are early stage and have enrolled only small numbers of patients. Learn more about neoadjuvant therapy here: [www.CureMelanoma.org/ NeoAdjuvantWorkshop](http://www.CureMelanoma.org/NeoAdjuvantWorkshop)

responding switch to nivolumab only. This approach offers the potential to further mitigate some adverse events. Wolchok also highlighted that researchers are developing sensitive genetic tests that can detect whether melanoma cells are still present in the blood of patients who appear to be in remission (often referred to as liquid biopsies), and therefore may warrant continued treatment despite no evidence of disease.

Novel Therapies that Reduce Off-Target Effects: Other researchers, such as Rizwan Haq of the Dana-Farber Cancer Institute, are striving to find a way to design targeted therapies that avoid harmful effects on healthy cells. Molecularly targeted treatments inhibit growth-promoting enzymes called kinases, but in many cases, healthy cells also depend on these enzymes, leading to toxic side effects. Haq's team identified a compound that inhibits an enzyme required for the survival in both melanoma and healthy cells. However, this drug is uniquely active in melanoma cells since it requires a chemical reaction to turn it ‘on’ that can only happen in tumor cells. Although further testing is needed, the compound could inhibit a kingpin growth pathway for melanoma cells not targeted by current drugs, without causing undue harm to normal cells. Haq found the compound suppressed the growth of melanoma cells in mice without causing harmful side effects for the animals, but these findings have yet to been verified by human tests. Haq noted that similar inhibitors for other growth promoting pathways in melanoma could be developed into safer drugs if they also are activated in this manner.

Immunotherapy Beyond Checkpoints: Investigators are also pursuing personalized treatments that rely on removing tumor-killing T cells from a patient, expanding them in culture, and then reinjecting them back into the patient, often referred to as TILS (Tumor-Infiltrating Lymphocytes). Similarly, another “adoptive T cell” approach is to remove a patient’s T cells and genetically engineer them to hone in and attack tumor cells better. Both types of experimental treatments are currently being tested in clinical trials and may be especially useful to treat patients with rare subtypes of melanoma, which tend not to respond as well to current therapies.

Scientists are also exploring ways to call more types of anti-tumor immune cells to action. Spread of a tumor after responding to immunotherapies often occurs due to the outgrowth of tumor cells that lack the highly specific antigens T cells have been trained to attack. Immune cells called neutrophils and natural killer cells may be able to prevent such escape, Wolchok and Nick Huntington of Monash University both reported. This may be particularly true for so-called ‘heterogeneous tumors,’ which are composed of cells sporting different antigens on their surface — meaning that cells within the same tumor or in
different tumors in the same person may look different to the immune system. Checkpoint immunotherapies work by releasing the breaks on T cells, spurring them to action. But as Wolchok noted, “T cells by themselves are only enough to kill tumors when you don’t have to worry about heterogeneity. When you do, you need the neutrophils for an anti-tumor response. Neutrophils are underappreciated—they are considered poor stepchildren in immunotherapy—but they deserve our attention.”

Using a mouse melanoma model, Wolchok presented data suggesting that neutrophils create an inflammatory environment that works in conjunction with T cells to eliminate heterogeneous tumors.

Natural killer (NK) cells may also be a key target to pursue as studies in mice reveal that these cells prevent melanoma from metastasizing when injected intravenously, presumably by being less selective than T cells in attacking tumor cell antigens. Huntington pointed out that although T cells outnumber NK cells in tumors, there are more NK cells that can specifically recognize and target melanoma cells in tumors, compared to T cells. Underscoring a potentially tumor-fighting role for these cells, patients with high numbers of NK cells tend to have more favorable outcomes. Because they drive T cells and other immune cells to infiltrate the tumor, he added, NK cells are likely to make melanoma more responsive to already approved immunotherapies. Huntington’s recent research has revealed key molecules that control natural killer cells’ ability to target and kill tumor cells, and efforts are underway to develop drugs that act on these molecules so as to create a new type of immunotherapy for melanoma that could be used singly or with already approved treatments.

Thorsten Mempel of Massachusetts General Hospital reported on another way to potentially enhance existing immunotherapies. He found a molecular pathway in mice for converting T regulatory cells — immune cells that typically suppress an immune response to tumors — into T cells that promote tumor killing. If these findings can be translated into a safe drug that stimulates this pathway, it could be used to enhance current immunotherapies by lifting another brake on the immune system.

**Improving Treatment Outcomes with Lifestyle Changes**

**How Lifestyle Can Impact Treatment:** Though immense progress with new treatments has been made, and further research offers additional hope, it is widely understood that treatment is only one part of the equation. Lorenzo Cohen, a melanoma survivor and research psychologist at the University of Texas MD Anderson Cancer Center stressed the need to focus research on lifestyle factors that can help improve patient response to treatments. “Love, support, sleep, exercise, and diet impact all the cancer hallmarks we’re trying to harness as drug developers,” Cohen pointed out. He cited studies indicating that chronic stress suppresses immune responses, while exercise increases immunity.

Diet is also important to melanoma patients receiving immunotherapies as preliminary studies show patients with the highest fiber in their diet are more likely to

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“Engaging patients is key to maximizing the benefits of treatment and getting the best long-term response.”

— Lorenzo Cohen
more public health measures aimed at preventing sunburns, including increasing shade in playgrounds, recreation areas, and other public spaces, and increasing public education efforts about sun safety so that sun protection becomes a habit. “No matter how many great drugs there are for melanoma, that won’t change the fact that for every person we cure, 10 more are going to get it,” he stressed.

Bringing Melanoma Prevention to the Forefront:
Even more progress could be made if melanoma was prevented from occurring to begin with, Susan Swetter of Stanford University pointed out. Noting that sunburns heighten the risk of developing melanoma, she said “If we enacted a comprehensive prevention program aimed at reducing ultraviolet light exposure, we could reduce melanoma by 20 percent and reduce $3 billion of costs in treating melanoma.” Swetter noted that unlike in European countries, sunscreen ingredients haven’t been improved in the US in the past several decades, and there are no full-spectrum sunscreens on the market. She pointed out that research is underway to develop other agents beyond sunscreen to prevent melanoma that reduce the damage induced by sunburns.

US Surgeon General Jerome Adams suggested restricting access to tanning facilities is also key to reducing melanoma incidence. He pointed out that although some tanning facilities have been limited by local or state laws, a national law in this regard is still needed. “As glad as I was that there was top notch research to help my wife deal with a deadly melanoma, I still wish I could have gone back in time and told her not to get into that tanning bed,” he said at the MRA Patient and Advocate Forum.

Adams recently updated the Surgeon General’s 5-year plan to emphasize prevention of skin cancer, but he reported that a million high school students continue to use indoor tanning devices, and each year half of adults and high school students get sunburned. He suggested

United States Surgeon General Jerome Adams
Basic Research:

Understanding what Triggers Melanoma and its Spread to Identify New Treatment Targets
remendous progress has been made in understanding the basic biology needed to trigger melanoma and fuel its growth and progression. These findings have led to the targeted therapies we have today for melanoma patients that target the proteins BRAF and MEK (with BRAF mutations are seen in about half of cutaneous melanomas). But because not everyone responds to these treatments and those that do tend to relapse, researchers continue to probe deeper, finding new molecular culprits that could lead to novel and more effective melanoma treatment strategies. Some of these new potential drug targets were revealed at MRA's 2020 Scientific Retreat.

**How Melanocytes Turn into Melanomas**

Lorenz Studer of Memorial Sloan Kettering Cancer Center has been investigating the process by which melanocytes, a type of cell that resides in the skin, turn into melanomas using both human stem cells and zebrafish models of melanoma. Studer has identified parallels between how stem cells differentiate — or transform — into melanocytes and how melanocytes can morph into melanomas. His studies reveal that similar genetic programs operate in both of these cellular processes and identified a particular protein that leads to changes in melanocyte metabolism, growth, and movement that enables the transformation of these cells into a melanoma. Melanoma patients whose
primary tumors express high amounts of this protein have worse outcomes. Although more validation studies are still needed, these studies point to a novel drug target that may prevent tumor formation. Studer suggested that other factors similar to the one he uncovered could play key roles in enabling melanoma to persist. “This is just the beginning as there could also be other similar factors needed for tumor maintenance that could be targeted by treatment,” Studer stressed.

Research conducted by Elaine Fuchs at the Rockefeller University is also focused on how melanomas initiate. In particular, she is studying the melanocyte stem cells — these are cells of the skin that perpetually self-renew, creating cells that eventually mature into melanocytes — the cell type that gives rise to melanomas. Fuchs thinks studying these stem cells may be important because her studies on squamous cell carcinoma — another type of skin cancer — have revealed that the stem cells of the skin that give rise to those tumors are often treatment resistant and contribute to relapse and metastasis. Tumors are often surrounded by blood vessels and attract immune cells. Fuchs’ studies show that these inputs can cause the tumor's stem cells to be active and invasive. “We think that the tumor stem cells also enter these blood vessels and cause metastasis,” Fuchs offered. Fuchs’ early studies suggest something similar may be happening with melanoma. She continues to explore this with the hopes of developing compounds that can block the signals that activate the stem cells, thereby preventing metastatic spread, disease relapse, or recurrence.

The Role of RNA in Melanoma Formation

Other researchers are exploring sections of the genetic RNA machinery in our cells and how they might contribute to melanoma. RNA is best known for being the intermediary between the DNA that makes up our genes and the proteins that these genes give rise to. But there is a lot of RNA in cells that does not participate in this process, and for a longtime, scientists thought it was unimportant for cellular functions — so much so that it was often referred to as “junk” RNA. But now it appears that these “junk,” or more accurately ‘noncoding,’ regions of RNA are rife with specific variations that appear to govern the initiation, growth, and even the spread of tumors, including melanomas. “I hope I can convince you that these noncoding regions are not garbage,” stressed Eleonora Leucci of the KU Leuven during her presentation.

She found a noncoding RNA molecule abbreviated SAMMSON that is expressed by most melanomas, but not normal melanocytes, and that promotes melanoma growth and survival. When Leucci blocked SAMMSON in melanoma cells, most died, including both BRAF mutant and non-BRAF mutant cells, suggesting SAMMSON may represent a broad drug target for melanoma. Reducing SAMMSON expression increased the effectiveness of BRAF/MEK inhibitors in melanoma mouse models, and even worked to slow the growth of tumor cells resistant to BRAF/MEK inhibition. These findings suggest that a compound that targets SAMMSON could be effective in melanoma patients in combination with BRAF-targeted treatment, and because SAMMSON is not found in normal cells, this compound may cause few serious side effects. “This would be beautiful,” Leucci said, but added that
unfortunately, there are no agents targeting SAMMSON that are approved yet in the clinic.

Interestingly, SAMMSON acts on some of the same cellular signaling pathways that a specific class of FDA-approved compounds do, leading Leucci to suspect they might also be effective in killing melanoma cells. Testing this in mice by combining the compounds with BRAF/MEK inhibition, as well as with immunotherapy, suggests this may be a promising therapeutic strategy; however, more follow-up studies are needed before testing this in patients.

Florian Karreth of the Moffitt Cancer Center also focuses his research on the noncoding regions of RNA, in this case on regions that are thought to indirectly fine-tune protein production and play a role in melanoma growth and progression. He found one short stretch of RNA, called miR-29, that when inactivated enhanced production of melanoma tumors in mice. Further analysis revealed that loss of miR-29 promotes melanoma because it leads to increases in the production of protein MAFG, which is normally shut off by miR-29. “Melanoma cells are addicted to miR-29 inactivation and overproduction of MAFG,” Karreth said. He also found three genes that affect the activity of miR-29 and other short noncoding regions of RNA. When these genes were overactive, they promoted melanoma metastasis in mice. “Understanding the mechanisms of non-coding RNAs has the potential to uncover novel targets for therapy,” Karreth stressed.

All this basic research on what causes melanoma to start, and then eventually progress, has the potential to lead to more effective melanoma treatments, but translating these findings into something usable in the clinic can take many years, noted Rizwan Haq of the Dana-Farber Cancer Institute. At the Patient and Advocate Forum, he pointed out the lack of new melanoma treatments in what some call a drought period between 1975 to 2010, prior to the explosion of new treatments in the decade following. He stressed that “If we look at the pre-clinical lab work that directly led to the development of these therapies approved since 2010, it was [conducted] during this so-called drought. Research is the engine we need to support in order to drive the next generation of innovation and treatment.”

“Research is the engine we need … to drive the next generation of innovation and treatment.”
— Florian Karreth
Advancing Acral Melanoma Research: New Drug Targets for Rare Types of Melanoma
Patients with acral melanoma, a rare subtype of the disease that develops in the nailbeds, palms, or soles of the feet are particularly underserved by today’s treatments. For example, the BRAF mutations found in about 50% of cutaneous melanoma cases are only seen in approximately 25% of patients with acral melanoma. Thus, only a small subset of patients with acral melanoma are treated with targeted therapies such as combination BRAF/MEK inhibitor drugs. Patients with acral melanoma also tend not to respond as well to checkpoint immunotherapies. So, raising the bar on improving outcomes for all advanced melanoma patients will, in part, depend on developing new treatments for acral and other rare subtypes of melanoma like uveal and mucosal melanoma. Those treatments, in turn, will depend on more research on these subtypes that deepens our understanding of what causes them or enables them to flourish. “We need to extend the advances in cutaneous melanoma to other subtypes that respond less robustly,” stressed Richard Carvajal of Columbia University during a panel discussion at the 2020 MRA Scientific Retreat.

Fortunately, recent studies on acral melanoma that were presented at the 2020 MRA Scientific Retreat are showing promising findings.
This research reveals some of the unique genetic flaws underlying this type of melanoma and how they interact with other factors in the body to trigger tumors and their growth. These basic research findings suggest new drug targets that could be particularly effective for patients with this melanoma subtype.

Richard White of Memorial Sloan Kettering Cancer Center shared findings — based on an innovative zebrafish model — that help explain why acral melanoma only occurs on the hands and feet. He created this model by giving the fish the same genetic defects found in acral tumor samples. Strikingly, he found these fish develop melanoma tumors predominantly in their fins, which are evolutionarily related to limbs in people. These findings suggest the cells that generated them are stamped early in development with a molecular signature unique to the fin/limb position in the body to which they migrated. That signature is retained and dictates unique molecular signaling pathways and susceptibilities for their particular locale on the edges of the body. “Something in the microenvironment in the fin or limb synergizes with the gene signatures common to acral melanoma to drive this type of melanoma,” White stressed.

Building on knowledge of the gene that plays a role in localizing acral melanoma development to the fin/limb, White noted that when he knocked out the gene’s activity in his zebrafish, they no longer developed melanoma on their fins or on any other part of their body. “Targeting this gene may offer new therapeutic opportunities in acral melanoma,” White concluded.

Boris Bastian’s research at the University of California, San Francisco suggests that proteins involved in the repair of DNA may be another target for future acral melanoma treatments. Bastian’s genetic analyses of acral patient tumors suggest that many of these rare melanomas may also be triggered by major genetic rearrangements due to DNA breaks that aren’t repaired due to mutations in genes that carry out this function in cells. Because repairing DNA — even if the job is imperfect — is critical for cell survival, cells use multiple processes to do this. Bastian thinks that blocking the remaining functional DNA repair pathway in acral melanoma may prove to be its Achilles heel, and is currently conducting laboratory experiments to explore this hypothesis more thoroughly.

Ruth Halaban of Yale University and Aaron Newman of Stanford University reported on their discovery of another potential drug target for acral melanoma—a gene located in a specific stretch of DNA that tends to be duplicated multiple times in acral melanoma. In studies of acral melanoma cells cultured in the lab, suppressing this gene reduced tumor growth. Little is known about the role of this gene in melanoma, and so Halaban and Newman are also working to identify how it contributes to acral melanoma initiation and progression.
Proteins in cells that control the activation of certain cancer-causing genes may also play a role in acral melanoma. In her genetic and tissue studies of acral melanoma, Phyu Aung of the University of Texas MD Anderson Cancer Center found a flawed genetic activation pattern, called DNA methylation, of six genes that was linked to a worse prognosis in patients. She also found a subtype of acral melanoma that tended to have more T cells in tumor samples, suggesting it might respond better to existing immunotherapies.

The research updates presented at the 2020 MRA Scientific Retreat revealed many promising molecular leads for acral melanoma. Developing new experimental drugs, testing their safety and effectiveness among acral melanoma patients will be challenging given the relative rarity of this melanoma subtype. Acral melanoma is estimated to account for just 5% of all melanomas worldwide. “We need to figure out how to get the most information out of a small group of patients,” Carvajal stressed. To do this, he suggested not further subdividing the small numbers of patients with acral melanoma into control and treatment arms, but rather comparing patients who are given an experimental treatment to how patients similar to them did in the past without such treatment. These can be achieved through patient registries, or prospective cohorts of patients with rare melanomas. He also suggested conducting multi-center clinical trials to capture enough numbers of these rare patients. Determining the best approach for bringing new therapies to patients with rare melanoma subtypes will require innovative science and input from regulatory officials, such as those at the U.S. Food and Drug Administration.

Melanoma clinical trials are research studies involving human volunteers that are designed to answer specific questions about new treatments for melanoma. The answers gained through the research helps doctors find new ways to improve outcomes for people with melanoma. Without patient volunteers our entire medical research process would stop.

MRA’s “Fight Back Give Back” campaign highlights the importance of clinical trials in driving progress towards curing melanoma.

Learn more about clinical trials at CureMelanoma.org/ClinicalTrials.
Dr. James Allison
and the Path to More Effective Immunotherapies
hen MRA co-founder and Board Chair Debra Black introduced James Allison of the University of Texas MD Anderson Cancer Center at MRA’s 2020 Scientific Retreat, she described him as the man “who changed the way cancer patients are treated forever.” This fitting introduction is due to Allison’s pioneering work to mainstream the use of checkpoint immunotherapy as a tool in the arsenal against cancer; joining the likes of chemotherapy, radiation, and surgery. Dr. Allison and Tasuku Honjo were jointly awarded the 2018 Nobel Prize in recognition of their groundbreaking work on CTLA-4 and PD-1 checkpoint immunotherapies, respectively. These treatments release the brakes on T cells’ response to tumors and have proven effective in treating, if not curing, millions of patients with advanced cancers.

“There’s been a paradigm shift,” said Allison’s collaborator and wife Padmanee Sharma, also of MD Anderson. “It opened up a whole new field. Back in the 1990s, everyone laughed when we said we wanted to do cancer immunotherapy and only a handful of people attended sessions devoted to that at cancer research meetings. But then the field exploded with checkpoint immunotherapy.”
From Dark Horse to Game-Changer

Decades before Allison began collaborating with Sharma, he had been conducting basic research on how the immune system works, with a major focus on T cells. Then in the mid-1990’s, he was shocked when he went to check on mice given antibodies that blocked a recently discovered immune-suppressing protein called CTLA-4 found on the surface of T cells. The antibody had cured the mice of their cancers. “I was expecting anti-CTLA-4 to slow tumors a little bit, but the tumors completely melted,” said Allison in an interview with the Journal of Clinical Investigation.

Inspired by those findings, and his brother who had been recently diagnosed with advanced prostate cancer, Allison doggedly pursued collaborators to develop his antibody into a drug that eventually would be called ipilimumab (Yervoy). But most major drug companies he approached were skeptical due to the poor track record of experimental cancer treatments that relied on the immune system to kill tumors. Despite seeing promising results in the lab, almost none of these treatments ended up working in patients, and of those that did, only a tiny fraction of patients benefited.

But ipilimumab proved to be a game-changer. Clinical tests of the drug showed it provided long-term complete remissions, which some call cures, in about one out of five patients with advanced melanoma. These were unprecedented findings — particularly because these responses were seen in patients with advanced disease — nearly all of whom would have failed to respond to treatments available to treat them at that time. Ipilimumab was approved in 2011 for advanced melanoma, followed shortly afterwards by drugs targeting another immune checkpoint called PD-1, discovered by Honjo. Checkpoint inhibitors have since been shown effective in treating many different types of cancers, including lung, kidney, colorectal, and bladder cancer.

CTLA-4- and PD-1-Targeting Immune Checkpoint Therapies Affect T Cells in Different Ways

But that is just the beginning of the story on checkpoint immunotherapies, Allison and Sharma stressed. They and many other investigators continue to search for more immune checkpoints that can be blocked, and thousands of clinical trials of various combinations of new and already approved immunotherapies are underway. “I never dreamed my research would take the direction it has,” Allison said in an MD Anderson Cancer Center press release. “It’s a great emotional privilege to meet cancer patients who’ve been successfully treated with immune checkpoint blockade. They are living proof of the power of following our urge to learn and to understand how things work.” But Allison also stressed, “We need these drugs to work for more people. Our clinical success has outrun our scientific knowledge of how these drugs work and how they might best be combined with other therapies.
to improve treatment and reduce unwanted side effects. We need more basic research to do that.”

At the 2020 MRA Scientific Retreat, Allison reported on the abundant basic research findings on checkpoint blockers he and his colleagues have garnered recently. These reveal major differences in how anti-CTLA-4 and anti-PD-1 drugs affect an immune response to tumors, and why combining both types of drugs is especially effective. Allison found that blocking CTLA-4 affects the early stages of T cell activation and causes a wide range of new anti-tumor immune T cells to proliferate and become active. Blocking CTLA-4 also boosts production of the immune-stimulating protein, interferon-gamma. In contrast, blocking PD-1 acts on a different subset of T cells that do not produce interferon, and doesn’t create new subsets of T cells. In addition, although anti-PD1 treatment expands these mature anti-tumor T cells, it also expands the number of so-called ‘exhausted’ T cells that cannot kill tumor cells. But when the two treatments are combined in laboratory studies, there is no expansion of exhausted T cells, and instead the combination activates a wider range of tumor-killing T cells subtypes and boosts interferon production. Understanding how each drug affects the immune system may allow for the design of improved versions of CTLA-4 and PD-1 antibodies, or new immunotherapy drugs altogether.

Exploring New Combinations

“We need to improve survival by doing combination therapy,” Allison stressed. He noted that in addition to combining anti-CTLA-4 treatments with anti-PD1 treatments, agents targeting other aspects of the immune response could also enhance current cancer immunotherapies. He and Sharma found a striking increase in T cells expressing the immunostimulatory protein ICOS in the tumors and blood of patients responding well to ipilimumab. Higher levels of ICOS were linked to greater survival among melanoma patients, and when a vaccine targeting ICOS was given to mice with melanoma, along with anti-CTLA4 treatment, it increased the effectiveness of CTLA-4 blockade. “There are many other immune checkpoints besides CTLA-4 that contribute to immune resistance pathways and we need to understand where and when they play key roles,” Sharma said.

Fortunately, many investigators in addition to Sharma and Allison are devoted to uncovering this information in their labs, now that such basic immunology research has proven its worth in leading to effective treatments for advanced cancers. “Improving survival with immunotherapies can be done,” Allison said. “And understanding the molecular mechanisms gives us a handle on how to do it.”

“Improving survival with immunotherapies can be done...
Understanding molecular mechanisms gives us a handle on how to do it.”
— James Allison
Industry Roundtable

Bringing Industry Together to Break the Barrier
Although the media tend to highlight patients such as President Jimmy Carter, whose metastatic melanoma seems to have been cured by a cancer immunotherapy, Dr. Patrick Hwu opened the Industry Roundtable Breakfast discussion at the 2020 MRA Scientific Retreat by noting a 21-year old patient with advanced melanoma he recently treated who only survived three months. “We gave him everything we could, including immunotherapy and it was tragic,” Hwu said. The patient was typical of those with a high burden of rapidly progressing disease who tend not to respond to the newer targeted and immunotherapies that have proven so effective in others with metastatic melanoma. “We haven’t raised the mark for these patients,” Hwu stressed.

Response rates have also not improved much over the past 10 years for most patients with rare melanoma subtypes, such as those with tumors that crop up in the eye, mucosal membranes, or the hands and feet. For these reasons, the MRA brought together key experts from drug and biotech companies, the Food and Drug Administration (FDA), and academia at the Annual Industry Roundtable to explore how to improve the long-term survival rate for the half of patients with advanced melanoma who do not respond to currently available treatments. Among
the suggested options were developing new tests or types of imaging to predict a patient’s response to treatment, improving clinical trial designs and patient access to them, and conducting additional basic science research to answer remaining unanswered questions such as how existing treatments work, why only some patients respond to them, and why others relapse.

Identifying Biomarkers to Predict Response

If new and more predictive biomarkers could be identified to help assess which patients would respond best to which treatment, patients who have little chance of success with certain treatments could be quickly funneled into alternative treatment options or to clinical trials of experimental therapies that might be more effective. Marc Theoret of the FDA pointed out that such ‘biomarker’ tests could possibly enable enriching a clinical trial population with patients at high risk of progressing, making it easier to detect a clinical benefit of an agent or combination of agents in this high-risk population. By enriching a patient population through use of a biomarker, it is possible to accelerate the clinical trial process for these patients.

Although investigators are currently testing levels of an enzyme called LDH and other potential biomarkers of high-risk patients unlikely to respond to current therapies, as well as biomarkers and imaging tests that can indicate an early lack of response to immunotherapies, clinicians don’t know yet “who to give what,” Hwu noted. Federico Monzon of Castle Biosciences pointed out that such diagnostics have not yet been developed because of a lack of knowledge of molecular defects, akin to mutant BRAF, predicting response to certain treatments, and especially for immunotherapies. Similarly, biomarkers to detect early response to immunotherapies, before tumors can be seen to shrink using traditional imaging tests, are lacking. Howard Kaufman of Replimune stressed that “we need to put more biomarker studies in all our industry and academic investigations to help guide targeting the specific defects in individual patients.”

Dr. Suzanne Topalian of Johns Hopkins University noted the utility of clinical trials in which therapeutic agents are given to melanoma patients before their tumors are surgically removed — termed neoadjuvant therapy. These studies enable researchers to compare before and after treatment tumor samples for molecular or cellular signals or patterns indicating response or lack of a response, which may then serve as biomarkers for future patients. Such neoadjuvant treatment in patients with early-stage melanomas might also help prevent them from progressing to more advanced and difficult to treat stages. Hwu suggested giving neoadjuvant treatment to patients with Stage 2 melanoma because more people die from melanomas originally diagnosed in this thin-lesion stage than those diagnosed with thicker tumors that are generally treated more aggressively. This is because there are a much greater number of melanoma patients with thin as opposed to thick lesions at diagnosis. But mandating such biopsies is difficult to do for studies supported by the National Cancer Institute because there often is no additional funding set aside for tissue removal and analysis, one participant noted. “Where do we get that funding for biomarkers and correlative science?” was asked by many participants.
MRA’s Industry Roundtable

Each year, at the MRA Scientific Retreat, representatives of each biotech and pharma sponsor are convened together with key opinion leaders, and government representatives to discuss, and hopefully advance, current challenges in the field. In 2020 — the Roundtable included representatives from 26 companies, and was focused on improving long-term survival for patients with advanced melanoma.

Expanding our Knowledge of the Tumor-Targeting Immune Response

The development of some diagnostic tests will also hinge on gaining a more granular understanding of the immune response to tumors and how it differs between patients that respond to immunotherapies and those that don’t. As Antoni Ribas of the University of California, Los Angeles noted, some patients may not respond to checkpoint immunotherapies because tumor-killing T cells present in their blood may not be able to reach the tumor. These patients might respond better to a drug that directs these T cells to tumors. “Patients who don’t respond to anti-PD-1 therapy might get a response to another immune-based therapy,” he said. Professor Richard Marais of the Cancer Research UK Manchester Institute added “We need a better understanding of what is happening in the tumor microenvironment. If we understand why those T cells are not doing their job, we can tackle it better with treatments.”

Topalian suggested being even broader in our pursuit of basic information about an immune response to tumors so as to break the 50-percent barrier. “What is preventing
advances is a lack of scientific knowledge. We’re still focusing on T cells and antigens, but we don’t know the whole story.” She noted that researchers in the past have not provided enough focus on the important role antibody-producing B cells play in an immune response to tumors that recent studies are now highlighting. “We need to leap into a completely new area of knowledge,” she stated.

Kellie Malloy of OncoSec Medical noted several efforts to enhance currently approved immunotherapies, including intratumor vaccines that don’t appear to have any overlapping toxicities with approved checkpoint inhibitors. “They offer a different immune-targeting pathway and we have to bring every tool and type of ammunition to the fight,” she stresses.

Improving clinical trial designs

Malloy and others also suggested improving clinical trial designs so that multiple agents can be tested simultaneously in adaptive trials, similar to the I-SPY trial in breast cancer patients. This trial enabled nonresponding patients to be switched to new experimental treatment arms within the same trial based on their early response results. Caroline Robert of Gustave Roussy Institute also stressed that improvements could be made with the approved treatments we already have by improving clinical trial designs to better test how to use existing options in combination, with alternative doses, or sequencing to compare their effectiveness. Such trials can be challenging to forge though, Hwu noted, because they require the cooperation of multiple drug companies.

Greater cooperation in the arena of sharing patient data in the public domain could also help move the field forward, Michael Meyers of Syndax pointed out.

Focusing on the Biology of Rare Melanoma Subtypes

MRA’s Chief Science Officer, Marc Hurlbert, and others stressed the need to focus on patients with rare subtypes of melanoma that tend to not respond well to current therapies. Steven Lemery of the FDA pointed out that patients with uveal melanoma, which develops in the eye, have difficulty accessing clinical trials because the drug industry expects a lower response rate from them. He suggested including these patients in trials as a preplanned subset, but not including them in the primary analysis of results, may be one way forward for this rare melanoma subtype. If a secondary analysis finds that people with the more common cutaneous melanoma as well as those with uveal melanoma respond to a treatment, labeling could then be expanded to include the latter group. Charlotte Ariyan of Memorial Sloan Kettering Cancer Center stressed that not all forms of melanoma share the same pathology and “the more we do basic science research on these subtypes, the more drug companies will develop agents to target them.” Hwu agreed that, “we need to nail down the basic science and biological understanding for rare subtypes of melanoma.”

Expanding Clinical Trial Enrollment

Another participant noted that key to improving outcomes in melanoma is having more melanoma patients participate in clinical trials of new treatments, but that many trials have trouble accruing sufficient numbers of patients. Accrual for immunotherapy trials could be expanded,
the participant said, if patients with autoimmune disorders are no longer automatically excluded from participating. Such exclusions were historically thought to be warranted because patients can develop severe autoimmune conditions in response to therapies that rev up their immune systems; but given that clinicians have become more adept at managing these immune-related adverse events, such exclusions may no longer be warranted, especially for melanoma patients with no other options.

Breaking the barrier – making long-term survival possible for even more patients with advanced melanoma — will require all stakeholders to continue their life-saving work needed to improve existing and to develop altogether new approaches to treating melanoma. Better understanding the melanoma biology and immune response, improving clinical trial designs, and keeping rare melanoma subtypes at the forefront are key strategies that will carry the melanoma community through the next decade of research.
Young Investigators
Lead the Path Forward
Advancing Immune Checkpoint Therapy and Exploring Nanotechnologies
Since issuing its first research award in 2008, the Melanoma Research Alliance has held steadfast to the belief that pulling early career scientist with novel ideas into the field of melanoma could provide substantial impact on innovation and help drive the field forward. Since 2008, MRA has invested nearly $20 million through 115 Young Investigator awards as of the end of 2019, and an additional 79 young investigators were supported within Team Science Awards.

Among MRA’s inaugural class of Young Investigators, Dr. Padmanee Sharma has demonstrated what early investment can do for both the field and an investigator. Dr. Sharma was funded in 2008 as she worked to further the understanding of checkpoint immunotherapy well before there had been an FDA approval for such treatments. Twelve years later, at the 2020 MRA Scientific Retreat, Dr. Sharma provided a keynote lecture on investigating the response and resistance mechanisms to immune checkpoint therapy, a field she has helped to advance. This work has led to her to identify several potential new drug targets to test in combination with ipilimumab, some of which are currently in clinical trials.
Young Investigators Lead the Path Forward

The innovation and novel approaches brought in by Young Investigators, were further highlighted at the 2020 Retreat in a talk given by Dr. Ashish Kulkarni of the University of Massachusetts, a 2017 Young Investigator Award recipient who is applying his engineering training to develop new melanoma treatments and imaging techniques.

Supporting the Next Generation of Melanoma Researchers

Young Investigator Awards, which are given to scientists within four years of their first academic faculty appointment, attract early career scientists with novel ideas into melanoma research. This seed funding comes at a critical time for these researchers, who are just starting to establish their own independent research labs and focus areas. Such funding typically grows researchers’ careers by allowing them to hire personnel and generate data needed to attract more traditional sources of funding, like that from the National Institutes of Health. By providing an early runway towards melanoma research with guaranteed funding, MRA’s Young Investigator Awards help to steer promising talent towards a career focused on melanoma.

Dr. Sharma, From the Clinic to the Lab and Back Again

Sharma’s novel idea, which ended up being instrumental in advancing checkpoint immunotherapies, was to do what she calls “reverse translation.” Sharma begins this process by observing things in the clinic. She then brings these observations back to the lab in order to test new hypotheses needed to further understand how patients respond to cancer immunotherapies and uncover ways to improve them. For example, long before the FDA approved the checkpoint immunotherapy ipilimumab (Yervoy) for melanoma patients, Sharma experimentally treated bladder cancer patients with it before removing their tumors surgically. This enabled her to examine how the tumors responded to the treatment, and if there was a response, to assess what immune components were causing that response. Through this work, Sharma discovered that T cells (a type of immune cell) that expressed a protein called ICOS increased in the tumors of patients responding to ipilimumab, and that this correlated with improved survival of melanoma patients. These findings led Sharma to hypothesize that ICOS was important for effective anti-tumor immune responses to ipilimumab. She then tested this idea in the lab using mouse models and found it to be true. Now a combination therapy of ipilimumab and an experimental agent that acts on ICOS is in clinical testing for use in patients with many different types of cancers, including melanoma.

A similar clinic-to-lab and back again research approach has allowed Sharma to uncover other key players in the anti-tumor immune response and led her to be involved in more than 100 clinical trials at MD Anderson Cancer Center that have enrolled over 4000 patients. “Multiple immune checkpoints exist and are dynamic in their expression and should be evaluated in both pre- and on-treatment human tumor samples to guide therapeutic decisions. We need to understand where and when they play a key role,” Sharma said. She also stressed, “Pre-surgical and tissue-based clinical trials provide a feasible platform to study clinical and biologic effects in patients, which provide insights into mechanisms that can be targeted for rational combination therapies.” Since receiving her MRA Young Investigator Award in 2008, Sharma has received large grants from the National Cancer Institute, the American Cancer Society, and other major funders.
Dr. Kulkarni, Engineering Better Melanoma Therapies

Ashish Kulkarni also has received major grants from the American Cancer Society and the Cancer Research Institute since receiving his MRA award in 2017. With a background in chemistry and biomedical engineering, he aims to use nanotechnologies to both create new cancer immunotherapies as well as to reveal within days whether these drugs are working. Although just two years into running his own lab, Kulkarni has made substantial progress on both goals thanks to his MRA Young Investigator Award that provided his first funding as an independent investigator. He used sophisticated computer modeling to design a self-assembling nanoparticle compound that latches onto a key receptor jutting out of the surface of macrophages, immune cell that can suppress anti-tumor immunity. The nanoparticles block the receptor, thereby limiting the immunosuppressive functions of the macrophages’, allowing them to engulf and digest tumor cells. Thanks to the computer modeling, he was able to design a compound that can be delivered at greater and longer-lasting concentrations to tumor cells without increasing concentrations in healthy tissues, all of which makes it more likely the nanoparticles will be safe and effective in human patients. In a melanoma mouse model, “Just a single dose gave significant antitumor activity,” Kulkarni stressed. If he continues to get good results with additional testing, this pioneering approach to designing and developing new drugs has potential to change how drug development is done.

Kulkarni also created nanoparticles that activate an imaging agent, causing telltale fluorescence when there is a response to the PD1-targeted immunotherapy in mice. “It’s exciting that it can distinguish in real time between responders and non-responders,” Kulkarni said, noting that his probe could be used in MRI imaging if initial promising findings on it are confirmed through further testing.

Going Beyond Funding to Support its Young Investigators

Recognizing that in addition to funding, mentoring is a crucial component to furthering a research scientist’s career, a mentorship commitment from a senior investigator is required for all MRA Young Investigator Award applicants. MRA also provides its own form of mentoring by fostering connections and providing career-focused information at its annual Young Investigators Breakfast. These breakfasts have featured editors from top scientific journals providing tips on navigating the publishing process, presentations on how to collaborate productively with colleagues, and information on non-traditional funding sources. In 2020, the Young Investigators Breakfast had a presentation on mentoring by Kelly Diggs-Andrews, a Master Facilitator with the National Research Mentoring Network. “Mentoring is essential and there is a host of research that shows strong mentoring relationships enhance identity, a sense of belonging, and self-efficacy, persistence, research productivity, higher career satisfaction, and enhanced recruitment of women and minorities,” she stressed during her presentation.

Beyond its Young Investigator Breakfasts, MRA offers other mentoring and collaboration opportunities at its annual scientific retreats. Sharma, for example, received instrumental input during a previous Scientific Retreat that helped her design better experiments, projects, and compete for more advanced grants. “MRA is a core group who will always help to move the field forward,” Sharma said.
Melanoma > Exchange Patient & Advocate Forum

When melanoma comes into your life, your life will never be the same, whether you recognize it as such or not. No one knows this feeling better than other people who’ve experienced it firsthand. This is why MRA’s Melanoma > Exchange Advocate Forum is always such a charged, passionate, and powerful experience.

In 2020, the forum brought almost 150 patients, survivors, and loved ones together with world-renowned melanoma clinicians and researchers. In addition, for the first time ever, over 700 registered to join us through the event livestream.

Participants – virtual and those joining us in person – walked away 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 2020 Melanoma > Exchange Advocate Forum are now available at CureMelanoma.org/Forum
Despite the tremendous progress made in melanoma treatments over the last 10 years, with 2 FDA-approved treatments blossoming to 14 and many metastatic melanoma patients experiencing remissions that are starting to look like cures, only about half of such patients respond favorably to current treatments. No one knows this better than 23-year-old Grace Wenzel, who spoke at the MRA’s 2020 Scientific Retreat via a video filmed from her hospital bed. Diagnosed in October, 2018 with Stage 4 melanoma, she had all the innovative treatments so far approved by FDA, including combination immunotherapies, to which she didn’t respond, and combination targeted therapies, which quickly shrank her tumors but stopped being effective in May of 2019.

The Current Landscape of FDA-Approved Treatments — The Successes & Remaining Hurdles

Why don’t the new melanoma treatments provide a lasting benefit for some patients like Grace, and what is being done to improve them? Rizwan Haq, an MRA-funded physician-scientist at Dana-Farber Cancer Institute, broadly addressed both questions as he provided the opening lecture at MRA's Melanoma > Exchange Patient & Advocate Forum.
To set the stage, Dr. Haq outlined the two broad categories of treatment approaches predominantly used in the United States today for patients with advanced melanoma. One approach called ‘targeted therapy’ turns off the molecular switches that drive melanoma tumor growth. Currently, targeted therapies are only effective in melanoma patients whose tumors have a genetic defect in the protein BRAF. The other treatment approach releases the breaks on the patient’s immune system to respond to tumors, and is called ‘immune-based therapies’ or ‘immunotherapy.’ Some immunotherapies are given systemically, while others are injected directly into accessible melanoma tumors.

Targeted therapies quickly put most patients with BRAF mutant melanoma into remission, but over time cancer usually becomes resistant to targeted treatments by finding other molecular pathways to fuel its growth. So, most patients tend to see their tumors recur within months to years after starting targeted therapies — although about 20% of patients experience durable benefits from combination targeted therapy. Researchers are avidly pursuing multiple strategies to overcome this drug resistance, including simultaneously targeting additional molecular switches for tumor growth, creating more powerful drug inhibitors for existing switches, or giving targeted therapies intermittently rather than continuously. The latter strategy has generated more durable responses in mice and is currently being tested in the clinic, as are clinical trials examining altogether new combinations of these molecularly targeted therapies.

Patient responses generated by immunotherapies tend to be more durable than those from targeted therapies, but a sizable portion of melanoma patients still do not respond to them at all. Researchers are starting to understand why, uncovering that the effectiveness of these therapies appears to depend on specific factors related to the tumor, the patient’s immune system, and even microbes in a patient’s gut. Some patients’ tumors lack the molecular knobs current immunotherapy drugs grab on to kill tumor cells. Other patients’ tumors may lack enough T cells in the vicinity of the tumor, or enough foreign particles called antigens made by tumor cells that the immune system uses to recognize and attack. Studies in mice also show that microbes in patients’ gut influence response to immunotherapies in ways we are just beginning to understand.

Overcoming Hurdles: The Next Decade of Melanoma Treatments

Picking up where Dr. Haq left off, a panel of world-renowned melanoma experts from across the United States shared how researchers are devising new agents and approaches to overcome the limitations of existing therapies presented by Haq. The panel, moderated by MRA-funded investigator, Dr. Marlana Orloff, featured panelists Dr. Antoni Ribas, Dr. Stephanie Goff, Dr. James Moon, Dr. Kenneth Grossmann, and Dr. Georgia Beasley and highlighted emerging treatment approaches that may help more patients experience better outcomes.

Cancer-Fighting Vaccines

One type of immune-enhancing treatment currently being tested in the clinic is a vaccine injected directly into tumors that can spur an antitumor response even in tumors not treated directly. “It trains the immune system to recognize and attack melanoma no matter where it appears and no matter how much later it appears,” says Dr. Antoni Ribas, an MRA-funded physician-scientist from the University of California, Los Angeles. The vaccines being studied are comprised with either viral or bacterial proteins recognized and known to jumpstart the immune response. In some vaccines, these proteins are inserted into viruses that attack cancer cells. James Moon, an MRA-funded investigator from the University of Michigan, reported on another type of tumor vaccine he
is developing in collaboration with the company Evoke to enhance response to current immunotherapies. This “personalized” vaccine is comprised of new antigens produced by patients’ tumors that are then combined with immune-stimulating agents. “We’re getting exciting results in mice and humans,” Moon said, noting that the vaccine is being given to Stage III patients along with existing immunotherapies following surgery in a clinical trial aimed at preventing relapse.

**Tumor Infiltrating Lymphocytes**

Another personalized approach to treating melanoma is being explored at the National Cancer Institute, Dr. Stephanie Goff reported. There, she and her colleagues are harvesting tumor-attacking T cells from advanced melanoma patients and multiplying them in culture. After giving these patients extensive chemotherapy that temporarily destroys their bone marrow, creating a blank slate for new immune cells, they then inject patients with these cultured tumor-infiltrating T cells. So far, the investigators have treated 40 cancer patients with a response rate of about 40%, even if these patients previously did not respond to any of the approved immunotherapies. “So, something different is going on there. If the first line of drugs doesn’t work, these tumor-infiltrating lymphocytes still can, but we’re still trying to sort out who are the right patients to treat with it,” she said.

James Moon of the University of Michigan and Antoni Ribas of the University of California Los Angeles (UCLA)

**“Not all melanomas are created equal.”**

— Marlana Orloff

**Individualized Approaches Driven by Biology**

In his framing remarks, Dr. Haq noted that the best choice between available treatment options will likely differ between patients. This highlights the need to understand patients’ specific immune responses to tumors and to have diagnostic tests that can elucidate them. Investigations have revealed some promising findings in this regard that could come to the clinic soon. Marlana Orloff, a rare-melanoma specialist from Thomas Jefferson University, also highlighted how diverse melanoma tumors are, even when derived from the same patient. She stressed we have to understand this diversity to make progress with treatments. “Not all melanomas are created equal—even patients with the same size tumors respond differently, and tumors in the brain and liver are more difficult to treat than those found elsewhere,” Orloff stressed.

The panelists also stressed that a better understanding of the unique molecular defects that cause or fuel the growth of rare melanoma subtypes that form in the eye, mucous membranes, and on the hands and feet should lead to more effective treatments. “There’s much more room for improvement,” said Orloff, noting that responses in mucosal melanoma to existing immunotherapies are only half what they are for cutaneous melanomas. Current treatments aren’t as effective for rare melanoma subtypes largely because the underlying biology that causes and feeds these melanomas is just so different than that of melanomas that form on sun-exposed skin. Agents targeting some of the specific mutations found in these rare subtypes are currently in clinical trials but are complicated by the wide range of such mutations.
Novel Combinations

Perhaps more effectiveness can be achieved by combining immunotherapies with targeted therapies. Researchers are showing encouraging early results by combining PD-1 checkpoint immunotherapy with BRAF/MEK targeted therapies, according to Dr. Grossmann, from the University of Utah Huntsman Cancer Institute. But he noted that the long-term benefits of these approaches are not known yet, and there is an increased possibility of side effects with combination therapy, which might be reduced by giving treatments sequentially rather than simultaneously. A better understanding of what causes side effects can also lead to their amelioration, studies in patients have shown, Grossmann noted.

Moving to Earlier Stages of Disease Through Adjuvant & Neoadjuvant Therapy

Currently, patients with no evidence of disease following surgery to remove melanoma are eligible for adjuvant therapy — or the use of systemic therapy to reduce the likelihood of relapse. Another option, that might be even more effective, is to administer systemic treatment before surgery in early-stage patients at high risk of recurrence. “Treating patients at earlier stages makes sense because there is less cancer there to kill so it’s like you are climbing a hill rather than a mountain,” said Dr. Georgia Beasley of Duke University. Initial findings suggest that such neoadjuvant treatment can slash the chance of recurrence in half, she reported. By shrinking tumors before surgery, it can also make them easier to remove, with the added benefit that investigators can assess if the treatment given is working by analyzing removed tumor tissue. Risks with this strategy are that cancer could spread during the pre-surgery treatment period and that some patients who receive it will suffer serious side effects of treatment without any additional benefits. “This is an exciting experimental strategy that we’re doing with a lot of patients in clinical trials,” Beasley said.

Haq concluded his presentation by stressing “Research is the engine that will drive advances and gains in treatment.” Orloff added, “Patients often ask why aren’t things moving faster and I feel their frustration, but good science takes time and we want to make sure we’re doing it right for the patient’s sake.” These sentiments were echoed by Grace as she ended her remarks, stressing, “Be determined to keep asking and searching. And be determined to keep fighting to find a cure.”

“Treating patients at earlier stages makes sense … You are climbing a hill rather than a mountain.”
— Georgia Beasley
Separating Hope From Hype
Melanoma research has undoubtably transformed what it means to be diagnosed with melanoma. For many patients facing melanoma, research has become synonymous with hope, and for good reason. In the last decade alone 12 therapeutic approaches have earned FDA approval giving patients, families, and clinicians new tools to treat melanoma. Up from 5-10% of patients in 2007, today about half of patients with advanced disease respond to available treatments; some may even be cured.

But there can be a fine line between hope and hype, especially today when news — both true and inflated — travels instantly via the internet and social media. As MRA President and CEO Michael Kaplan stressed in his opening remarks at the 2020 Melanoma > Exchange Patient & Advocate Forum, “Patients and their advocates need to understand what is real science now and what is just hot air.” To help in this regard, the MRA brought together oncologist Jason Luke of the University of Pittsburgh and medical journalist Liz Szabo of Kaiser Health News for an informative — and grounding — discussion on how to separate...
hype from hope, and the problems that can arise when the fine line separating the two is overstepped.

“There are real consequences to giving people false hope and inappropriate expectations that affects their care, comfort, and decisions about how they want to spend the rest of their lives,” noted Szabo. This is especially true in melanoma where the differences between patients who do exceptionally well and those who get little or no benefit from available treatment approaches is still poorly understood. Luke added, “Hope is good, but hype can be a barrier to reasonable expectations.”

Hype can be fueled at almost all levels, by scientists who need to out-compete others for grant funding to continue their work, by universities who want to highlight important work done on their campus, by government officials who want to herald the next great thing, pharmaceutical companies who have to please shareholders and hit sales targets, and journalists that “play the role of cheerleader because it gets them on the front page of a newspaper or on the 6 ’o clock news,” Szabo noted. “Almost everyone has some motivation to hype,” she said, including patients and their families.

To separate hope from hype, Szabo suggested paying attention to the source of information about a new treatment, and relying more on reputable sources such as the American Cancer Society, the National Cancer Institute, the Food and Drug Administration, and the Melanoma Research Alliance. “Joe’s cancer blog is not where I would go for information,” Szabo said. She also stressed that “Misinformation spreads faster than the coronavirus. If it seems too good to be true then it probably is. A red flag for snake oil is a treatment that supposedly works for every kind of disease because that is never true.”

Szabo also cautioned against being seduced by articles that only highlight one patient who is doing amazingly well on an experimental treatment. “You need to know the denominator— is this one out of two people who do great on the treatment or only one out of 1000?” she said.

Dr. Luke added that because President Jimmy Carter did so well on his immunotherapy for melanoma, people assumed that everyone would.

Unfortunately, the sobering reality is that while more patients are responding than ever before, the majority of patients with late stage melanoma are unlikely to respond as well as President Carter.

Szabo noted that even when a clinical trial is generating positive results, these results may not apply perfectly to the general population because older and sicker people are historically excluded from participating in clinical research. Although eligibility criteria for clinical trials has slowly evolved towards being more inclusive of patients with diabetes, heart disease or other health conditions besides cancer, or those with metastases in their brain — these patients have historically not been included in clinical studies. “You don’t want to say no to progress, but you need to be realistic,” she stressed.
Luke pointed out that scientific progress tends to be slow, sometimes taking close to a decade from the time an experimental agent shows initial promise in the laboratory to the time it can be used in patients. He suggested that “if you read an article showing results only in animals and you can’t figure out how it would change what you would do now, then it probably can’t.

We’re excited about the treatments we may have in the future, but these are not options we can grab and use now. We need to focus on what we can do here and now.”

The good news for patients and families who are navigating the surge in information focused on promising research is that they aren’t facing this alone. Luke recommended that patients work together with their doctors and care team to assess any information about new treatment approaches or emerging research to put it into the context of their current treatment plan. What is hyped today may be discarded tomorrow when more results come in, both Luke and Szabo stressed. “Just because it’s new doesn’t mean it will be better,” Szabo noted, pointing out that for every successful new drug, there may be a thousand experimental drugs that fail.

That being said, both Luke and Szabo suggested patients consider participating in a clinical trial if that appears to be their best treatment option, and they have the resources and the energy to do so. But patients and their families should also ask questions to understand the additional hassles — such as extra tests, visits to the doctor, etc. — and how likely these may work for them. A clinical trial may require patients to travel out of their area for treatment or to reside for long periods of time away from home, with no guarantee that the experimental therapy will work. “They can go the clinical trial route, but the reason a treatment is in a research trial is because we haven’t proven anything yet,” Luke noted.

Luke tries to be forthright in his discussions with patients about clinical trials. “I first tell them why a clinical trial will be horrible before I tell them why I am excited about it,” he said. “Expectation management is very important.” Szabo agreed, saying “You don’t want to give [patients] false hope that makes them disappointed and creates a lost opportunity to have end-of-life conversations.”

Part of that false hope can stem from poor communication between doctors and patients or incorrect assumptions about what words like ‘respond’ mean in the context of cancer care. “If your doctor tells you your tumor is likely to respond to a treatment, that doesn’t mean it will be cured by the treatment,” Szabo noted.

For example, in one study of patients with advanced lung or colorectal cancer researchers found that most of the participants mistakenly thought the chemotherapy they were being given solely to help relieve their symptoms — what doctors call palliative care — was going to cure them of their cancer. She also gave the example of a good friend of hers who died in the ICU from metastatic breast cancer because she continued taking a treatment that was unlikely to work and made her very sick. “If you only have weeks left, you may not want to travel to a hospital but instead travel to see a mountain or that brother you haven’t seen in years,” she said, adding, “I’ve lost dear friends to cancers so it makes me committed to not hyping cancer treatments.”

Separating Hope From Hype

“If it seems too good to be true then it probably is.”

— Liz Szabo
Agendas
Wednesday, February 26

7:30am- 5:00pm  Grant Review Committee Meeting (by invitation).........................Salon I
12:00-5:30pm   Melanoma Patients, Advocates & Foundations Forum..................Salon IV
4:00-8:00pm    Retreat Registration open...................................................Foyer of Penn Avenue Terrace
6:00-7:30pm    Opening Reception............................................................Penn Avenue Terrace

Thursday, February 27

6:30am-6:00pm  Registration.............................................................................Foyer of Salon III & IV
7:00-8:15am    General Breakfast.................................................................Salon II
7:00-8:15 am   Young Investigators Breakfast (by invitation) .......................Salon I
8:30-8:45am    Opening Remarks Day 1.........................................................Salon III & IV

Michael Kaplan, MRA President & CEO
Marc Hurlbert, MRA Chief Science Officer
Grace Wenzel, Patient Advocate

8:45-9:15am    Lecture
Jedd Wolchok, Memorial Sloan Kettering Cancer Center: Maintaining innovation: New directions in melanoma research

9:15-11:25am  Session 1: Novel therapeutic approaches for treating melanoma
Chair: Ronit Satchi-Fainaro, Tel-Aviv University

9:15-9:40
Thorsten Mempel, Massachusetts General Hospital: CARMA1 in control of regulatory T cell function in melanoma

9:40-10:05
Elaine Fuchs, The Rockefeller University: How skin stem cell biology can guide us to the basis for tumor relapse

10:05-10:20  Break

10:20-10:40  Nick Huntington, Monash University: Therapeutic modulation of natural killer cell response to growth factors in melanoma

10:40-11:00  Rizwan Haq, Dana-Farber Cancer Institute: Melanoma selective cytotoxicity achieved through a novel switchable kinase inhibitor

11:00-11:25  Richard White, Memorial Sloan Kettering Cancer Center: Why tumors appear where they do: positional memory in the pathogenesis of acral melanoma

11:25-11:55am  Lecture: Padmanee Sharma, University of Texas MD Anderson Cancer Center: From the clinic to the lab: Investigating response and resistance mechanisms to immune checkpoint therapy
11:55am-12:05pm  Transition to lunch

12:05-1:05pm  Networking Lunch and General Roundtables #1..................Salon I & II
Seating at roundtables limited by prior registration. Additional tables with open seating available for general networking and/or scheduled meetings. Topics are:

1. Acrail melanoma;
2. AI/imaging/diagnostics;
3. Brain metastasis and leptomeningeal;
4. Cell therapy (ACT, TIL, etc);
5. Clinical trials: multi-site and patient recruitment;
6. Founding your own company;
7. IO-understanding immune-related adverse events;
8. Microbiome;
9. MRA dermatology fellows;
10. Neoadjuvant and adjuvant treatments;
11. Overcoming resistance to IO/targeted therapies;
12. Pediatric and young adult melanoma;
13. Predictive, diagnostic & prognostic biomarkers;
14. Prevention & early detection;
15. Role of genetics, genomics, & epigenomics;
16. Single-cell technologies sequencing and imaging;
17. Targets: finding/validating new targets & drug discovery;
18. Treatment: combos, sequencing, and duration of treatment;
19. Tumor microenvironment;
20. Vaccines & intralesional therapies.

12:00-2:00pm  Scientific Advisory Panel meeting and lunch (by invitation)..............The Senate Room

1:05-1:20pm  Transition to general session room (Salon III & IV)

1:20-2:30pm  Session 2: Understanding melanoma metastasis
Chair: Ashani Weeraratna, Johns Hopkins University

1:20-1:45  Eva Hernando, New York University: Melanoma-secreted Amyloid Beta Suppresses Neuroinflammation and Promotes Brain Metastasis

1:45-2:05  Florian Karreth, Moffitt Cancer Center: MicroRNA deregulation in melanoma progression

2:05-2:30  Carmit Levy, Tel Aviv University: Identification of novel regulators of melanoma brain metastasis

2:30-2:50pm  Break

2:50-4:00pm  Session 3: Special Focus — Acrail Melanoma
Chair: Nick Hayward, QIMR Berghofer Medical Research Institute

2:50-3:15  Boris Bastian, University of California, San Francisco: The genetics of acrail melanoma

3:15-3:35  Phyu Aung, University of Texas MD Anderson Cancer Center: Acrail melanoma – histologic and molecular studies

3:35-4:00  Ruth Halaban, Yale University and Aaron Newman, Stanford University: Recurrent patterns of structural variation promote tumorigenesis in acrail melanoma

4:00-4:30pm  Lecture: James Allison, University of Texas MD Anderson Cancer Center: Immune checkpoint blockade in cancer therapy: Historical perspective, new opportunities, and prospects for cures

4:30-4:35  Closing Remarks Day 1
Kristen Mueller, MRA Senior Director, Scientific Program

4:45-6:15pm  Young Investigator, Dermatology Fellow, and Pilot Awardee Poster Session...............................................................Penn Avenue Terrace
All retreat attendees encouraged to attend

4:45-5:45pm  ACS-MRA grant awardees reception (by invitation).................State Room
Friday, February 28

6:30-10:00am Registration open .................................................................Foyer of Salon III & IV

7:00-8:30am Networking Breakfast and General Roundtables #2..............Salon I & II
Seating at roundtables limited by prior registration. Additional tables with open seating available for general networking and/or scheduled meetings. Topics are:

1. Clinical trials: Benefits and impediments to Phase 1 trials; 10. Role of genetics, genomics & epigenomics in melanoma;
2. Founding your own company; 11. Surgery: current and emerging methods of surgical treatment;
4. Heterogeneity and phenotype switching 13. Tumor metabolism and metabolomics;
5. IO – understanding immune-related adverse events; 14. Tumor microenvironment;
7. Overcoming resistance to IO/targeted therapies; 16. Uveal & mucosal melanoma;
9. Prevention & early detection – melanoma initiation;

7:00-8:30 am Industry Roundtable Breakfast (by invitation) .........................Salon FG

8:40-8:45 am Opening Remarks Day 2 ..........................................................Salon III & IV
Kristen Mueller

8:45-9:15 am Lecture: Christian Blank, Netherlands Cancer Institute:
Neoadjuvant approaches for treating melanoma

9:15-10:25am Session 4: Understanding melanoma initiation to improve patient outcomes
Chair: Sheri Holmen, Huntsman Cancer Institute at University of Utah

9:15-9:35 Eleonora Leucci, Katholieke Universiteit Leuven: LncRNAs as modulators of protein synthesis rewiring in melanoma

9:35-10:00 Lorenz Studer, Memorial Sloan Kettering Cancer Center: Cell of origin as a driver of heterogeneity in melanoma

10:00-10:45 Break

10:45-11:30am Session 5: Novel approaches for diagnosing melanoma and assessing therapeutic efficacy
Chair: Christin Burd, Ohio State University

10:45-11:05 Ashish Kulkarni, University of Massachusetts, Amherst: Nanoscale Approaches for Targeting Tumor-associated Macrophages

11:05-11:30 Joann Elmore, University of California, Los Angeles: The importance of applying AI to assess histologic features to improve melanoma diagnosis

11:30am-12:15pm Panel Discussion: Maintaining the momentum: New directions in melanoma research
Moderator: Michael Atkins, Georgetown University, Chair of MRA Medical Advisory Panel

• Susan Swetter, Stanford University
• Suzanne Topalian, Johns Hopkins University, Chair of MRA Scientific Advisory Panel,
  MRA Board of Directors
• Richard Carvajal, Columbia University

6:30-9:00 pm Reception and Dinner ...............................................................Zaytinya, 701 9th St NW
Dress: Casual
Reception: 6:30-7:00pm; Dinner 7:15pm
• Marisol Soengas, Spanish National Cancer Research Center
• Lorenzo Cohen, University of Texas MD Anderson Cancer Center

12:15pm-12:30pm  Closing Remarks
  Michael Kaplan and Marc Hurlbert

12:30-1:30pm  Lunch and Departures .................................................................Salon II

12:30-6:00 pm  Lunch and Melanoma Models Workshop (Chaired by Dr. Liz Patton and Dr. Glenn Merlino)
  (by invitation) .......................................................................................Salon I
Melanoma > Exchange
Patient & Advocate Forum  February 26, 2020

12:00-1:00pm  Lunch & Networking

1:00-1:10pm   Welcome Remarks
Michael Kaplan – President & CEO, Melanoma Research Alliance

1:10-1:30pm   Who We Are & Why We Are Here

1:30-2:20pm   The Melanoma Treatment Landscape
Learn where we are, where we’ve been, and where research is taking us.
Rizwan Haq, PhD, MD – Dana-Farber Cancer Institute

2:20-2:30pm   Break

2:30-3:30pm   Is it Hope or Hype?
We’ve all see headlines proclaiming the imminent cure for cancer, only to be let down after
reading just a few lines. Learn how to separate hype from hope.
Jason Luke, MD – University of Pittsburgh
Liz Szabo – Kaiser Health News

3:30-4:00pm   Ask the Expert: Animal Models
What role do animal models play in developing next-generation melanoma therapies?
Liz Patton, PhD – University of Edinburgh

4:00-4:15pm   Break

4:15-5:45pm   Looking Beyond 2020 – The Next Decade of Melanoma Treatment
The melanoma treatment landscape has more options than ever. Hear from experts on emerging
approaches gaining steam in clinical trials and the clinic.
Georgia Beasley, MD – Duke University
Stephanie Goff, MD – National Cancer Institute
Kenneth Grossman, MD, PhD – University of Utah
James Moon, PhD – University of Michigan
Antoni Ribas, MD, PhD – University of California Los Angeles
Moderator: Marlana Orloff, MD – Thomas Jefferson University

5:45-6:00pm   Closing & Wrap-up

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

Keep the conversation going on the Melanoma > Exchange online discussion community.
CureMelanoma.org/Community
<table>
<thead>
<tr>
<th>Name</th>
<th>Role and Affiliation</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dave Adams</td>
<td>Wellcome Sanger Institute <a href="mailto:da1@sanger.ac.uk">da1@sanger.ac.uk</a></td>
<td></td>
</tr>
<tr>
<td>Rhoda Alani</td>
<td>Professor and Chair Boston University School of Medicine <a href="mailto:alani@bu.edu">alani@bu.edu</a></td>
<td></td>
</tr>
<tr>
<td>Kimberly Albertson</td>
<td>Patient Advocate <a href="mailto:berlybbsmichael1@icloud.com">berlybbsmichael1@icloud.com</a></td>
<td></td>
</tr>
<tr>
<td>James Allison</td>
<td>Chairman, Department of Immunology; UT MD Anderson Cancer Center <a href="mailto:jallison@mdanderson.org">jallison@mdanderson.org</a></td>
<td></td>
</tr>
<tr>
<td>Niroshana Anandasabapathy</td>
<td>Associate Professor of Dermatology, Attending Physician Well Cornell Medicine <a href="mailto:niroananda@gmail.com">niroananda@gmail.com</a></td>
<td></td>
</tr>
<tr>
<td>Ana Anderson</td>
<td>Associate Professor Harvard Medical School <a href="mailto:aanderson@rics.bwh.harvard.edu">aanderson@rics.bwh.harvard.edu</a></td>
<td></td>
</tr>
<tr>
<td>Margaret Anderson</td>
<td>Board of Directors Melanoma Research Alliance</td>
<td></td>
</tr>
<tr>
<td>Andrew Aplin</td>
<td>Associate Director Thomas Jefferson University <a href="mailto:andrew.aplin@jefferson.edu">andrew.aplin@jefferson.edu</a></td>
<td></td>
</tr>
<tr>
<td>Frederic Appelmans</td>
<td>Global Marketing Director Amgen <a href="mailto:fappelma@amgen.com">fappelma@amgen.com</a></td>
<td></td>
</tr>
<tr>
<td>Victoria Aranda</td>
<td>Senior Editor Nature <a href="mailto:v.aranda@us.nature.com">v.aranda@us.nature.com</a></td>
<td></td>
</tr>
<tr>
<td>Charlotte Ariyan</td>
<td>Attending Memorial Sloan Kettering Cancer Center <a href="mailto:ariyanc@mskcc.org">ariyanc@mskcc.org</a></td>
<td></td>
</tr>
<tr>
<td>Maryam Asgari</td>
<td>Associate Professor Massachusetts General Hospital <a href="mailto:masgari@partners.org">masgari@partners.org</a></td>
<td></td>
</tr>
<tr>
<td>Michael Atkins</td>
<td>Deputy Director Georgetown University <a href="mailto:mba41@georgetown.edu">mba41@georgetown.edu</a></td>
<td></td>
</tr>
<tr>
<td>Phyu Aung</td>
<td>Associate Professor UT MD Anderson Cancer Center <a href="mailto:paung@mdanderson.org">paung@mdanderson.org</a></td>
<td></td>
</tr>
<tr>
<td>Michael Axelson</td>
<td>Head of Clinical Research Tempus <a href="mailto:michael.axelson@tempus.com">michael.axelson@tempus.com</a></td>
<td></td>
</tr>
<tr>
<td>Shirin Bajaj</td>
<td>Resident Physician NYU Langone Medical Center <a href="mailto:shirin.bajaj@nyulangone.org">shirin.bajaj@nyulangone.org</a></td>
<td></td>
</tr>
<tr>
<td>Anand Balasubramani</td>
<td>Associate Editor Science Immunology <a href="mailto:abalasubramani@aaas.org">abalasubramani@aaas.org</a></td>
<td></td>
</tr>
<tr>
<td>Riyue Bao</td>
<td>Co-Director of Cancer Bioinformatics UPMC Hillman Cancer Center <a href="mailto:baor@upmc.edu">baor@upmc.edu</a></td>
<td></td>
</tr>
<tr>
<td>Boris Bastian</td>
<td>Professor UCSF <a href="mailto:boris.bastian@ucsf.edu">boris.bastian@ucsf.edu</a></td>
<td></td>
</tr>
<tr>
<td>Kristina Baum</td>
<td>Communications Director White House Office of Science and Technology Policy <a href="mailto:baum.kristina@gmail.com">baum.kristina@gmail.com</a></td>
<td></td>
</tr>
<tr>
<td>Georgia Beasley</td>
<td>Assistant Professor of Surgery, co-director Duke Cancer Institute Melanoma Program <a href="mailto:georgia.beasley@duke.edu">georgia.beasley@duke.edu</a></td>
<td></td>
</tr>
<tr>
<td>Barbara Bedogni</td>
<td>Associate Professor University of Miami <a href="mailto:bxb602@miami.edu">bxb602@miami.edu</a></td>
<td></td>
</tr>
<tr>
<td>Valerie Behan</td>
<td>Scientific Program Manager Rising Tide <a href="mailto:valerie.behan@risingtide.ch">valerie.behan@risingtide.ch</a></td>
<td></td>
</tr>
<tr>
<td>Emily Bernstein</td>
<td>Professor Icahn School of Medicine at Mount Sinai <a href="mailto:emily.bernstein@mssm.edu">emily.bernstein@mssm.edu</a></td>
<td></td>
</tr>
<tr>
<td>Corine Bertolotto</td>
<td>INSERM <a href="mailto:Corine.Bertolotto@unice.fr">Corine.Bertolotto@unice.fr</a></td>
<td></td>
</tr>
<tr>
<td>Ben Black</td>
<td>Board of Directors Melanoma Research Alliance</td>
<td></td>
</tr>
<tr>
<td>Debra Black</td>
<td>Co-Founder and Chair Melanoma Research Alliance</td>
<td></td>
</tr>
<tr>
<td>Leon Black</td>
<td>Co-Founder Melanoma Research Alliance</td>
<td></td>
</tr>
<tr>
<td>Christian Blank</td>
<td>Professor, Group Leader Netherlands Cancer Institute <a href="mailto:c.blank@nki.nl">c.blank@nki.nl</a></td>
<td></td>
</tr>
<tr>
<td>Kim Blenman</td>
<td>Associate Research Scientist Yale University <a href="mailto:kim.blenman@yale.edu">kim.blenman@yale.edu</a></td>
<td></td>
</tr>
<tr>
<td>Gideon Bollag</td>
<td>CEO Plexxikon <a href="mailto:gbollag@plexxikon.com">gbollag@plexxikon.com</a></td>
<td></td>
</tr>
</tbody>
</table>
Greg Friberg  
Vice President Global Development  
Amgen  
gfriberg@amgen.com

Dean Frohlich  
Scientific Review Officer  
Conquer Cancer Foundation  
dean.frohlich@conquer.org

Elaine Fuchs  
Investigator, Rebecca C. Lancefield  
Professor  
HHMI, The Rockefeller University  
fuchslb@rockefeller.edu

Gina Fusaro  
Development Team Lead  
Bristol-Myers Squibb  
gfusaro@celgene.com

Thomas Gajewski  
Professor  
University of Chicago  
tgajewsk@medicine.bsd.uchicago.edu

Christine Garrison  
President  
The White Aisle Foundation  
thewhiteaisle@comcast.net

Eduard Gasal  
Global Program Clinical Development Head  
Novartis Pharmaceuticals  
eduard.gasal@novartis.com

Evris Gavathiotis  
Professor  
Albert Einstein College of Medicine  
evrippidis.gavathiotis@einstein.yu.edu

Tamar Geiger  
Principal Investigator  
Tel Aviv University  
geiger@post.tau.ac.il

Lincy George  
Global Therapeutic area Lead - Regulatory Affairs  
Novartis Pharmaceuticals  
lincy.george@novartis.com

David Gerber  
Professor  
UT Southwestern Medical Center  
david.gerber@utsouthwestern.edu

Jeffrey Gershenwald  
Professor  
UT MD Anderson Cancer Center  
jgershen@mdanderson.org

Michael Goldberg  
CEO  
STIMIT  
michael@stimittx.com

Foster Gonsalves  
Vice President, Drug Development & Strategy  
Rgenix Inc.  
foster.gonsalves@rgenix.com

Mark Gorman  
Patient Advocate  
mgormanss@mac.com

Nancy Gough  
Consultant  
BioSerendipity, LLC  
ngough@bioserendipity.com

Susanna Greer  
Director, Clinical Cancer Research and Immunology  
American Cancer Society  
Susanna.Greer@cancer.org

Skip Grinberg  
Patient Advocate  
Meyergrinberg@gmail.com

Kenneth Grossmann  
Associate Professor  
Huntsman Cancer Institute  
kenneth.grossmann@hci.utah.edu

Samantha Guild  
Executive Director  
AIM at Melanoma  
sguild@aimatmelanoma.org

Ray Gustin  
Partner  
Drake Capital  
ray.gustin4@gmail.com

Ruth Halaban  
Senior Research Scientist  
Yale University  
ruth.halaban@yale.edu

Allan Halpern  
Chief, Dermatology Services  
Memorial Sloan Kettering Cancer Center  
halperna@mskcc.org

Omid Hamid  
Dir, Melanoma Oncology; Chief, Clinical Research  
The Angeles Clinic and Research Institute  
ohamid@theangelesclinic.org

Brent Hanks  
William Dalton Family Assistant Professor of Medical Oncology  
Duke University  
hanks004@mc.duke.edu

Rizwan Haq  
Assistant Professor  
Dana-Farber Cancer Institute  
rizwan_haq@dfci.harvard.edu

Liz Patton of University of Edinburgh
J. William Harbour  
Professor and Vice Chairman  
University of Miami  
harbour@med.miami.edu

Christine Harhaj  
Director  
PhRMA  
charhaj@phrma.org

Nicholas Hayward  
Senior Scientist  
QIMR Berghofer Medical Research Institute  
nicholas.hayward@qimrberghofer.edu.au

Maitreyee Hazarika  
Senior Medical Officer  
US Food & Drug Administration  
maitreyee.hazarika@fda.hhs.gov

Simon Heidegger  
Senior Scientist  
Klinikum rechts der Isar, Technical University Munich  
simon.heidegger@tum.de

Daisy Helman  
Board of Directors  
Melanoma Research Alliance

Shawn Helms  
President & CEO  
Helms Hope Foundation  
shawn@helmshope.org

Meenhard Herlyn  
Professor and Program Director  
The Wistar Institute  
herlynm@wistar.org

Eva Hernando  
Associate Professor  
New York University School of Medicine  
Eva.Hernando-Monge@nyulangone.org

Jack Hidary  
Radimmune Therapeutics  
jack@hidary.com

Shannon Hines  
Staff Director, Appropriations Committee  
U.S. Senate  
Shannon_Hines@appro.senate.gov

Frank Stephen Hodi  
Director, Melanoma Disease Center & Center for Immuno-Oncology  
Dana-Farber Cancer Institute  
stephen_hodi@dfci.harvard.edu

Sheri Holmen  
Professor  
University of Utah  
sheri.holmen@hci.utah.edu

Dave Hoon  
Professor Director  
John Wayne Cancer Institute  
hoond@jwci.org

Thomas Hornyak  
Associate Chief of Staff for Research & Development  
VA Maryland Health Care System/Univ. of Maryland  
thomas.hornyak@va.gov

Timothy Hsiao  
Director of Scientific Affairs  
ASTRO  
timothy.hsiao@astro.org

Ku-Lung Hsu  
Assistant Professor of Chemistry and Pharmacology  
University of Virginia  
kenhsu@virginia.edu

Leah Hubbard  
Program Director  
National Cancer Institute  
leah.hubbard@nih.gov

Willy Hugo  
Assistant Adjunct Professor  
UCLA  
hwilly@mednet.ucla.edu

Siwen Hu-Lieskovan  
Assistant Professor of Medicine, Director of Solid Tumor Immunotherapy  
Huntsman Cancer Institute  
siwen.hu-lieskovan@hci.utah.edu

Nick Huntington  
Immunotherapy Head  
Monash University  
huntington@wehi.edu.au

Marc Hurlbert  
Chief Science Officer  
Melanoma Research Alliance  
mhurlbert@curemelanoma.org

Adam Hurlstone  
Senior Lecturer  
University of Manchester  
adam.hurlstone@manchester.ac.uk

Patrick Hwu  
Head, Division of Cancer Medicine  
UT MD Anderson Cancer Center  
phwu@mdanderson.org

Kimberly Irvine  
Patient Insight & Advocacy Officer  
OncoSec Medical  
kirvine@oncosec.com

Rubina Ismail  
Medical Director  
Amgen  
rismail@amgen.com

Fumito Ito  
Associate Professor of Surgery  
Roswell Park Cancer Institute  
fumito.ito@roswellpark.org

Burkhard Jansen  
Chief Medical Officer  
DermTech  
bjansen@dermtech.com

Russell Jenkins  
Assistant Professor  
Massachusetts General Hospital  
rwjenkins@partners.org

Prakash Jha  
Medical Officer  
US Food & Drug Administration  
Prakash.Jha@fda.hhs.gov
Lucia Jilaveanu  
Associate Professor  
Yale University  
lucia.jilaveanu@yale.edu

Sabrina Joseph  
Senior Scientific Program Officer  
ASTRO  
sabrina.joseph@astro.org

Nikhil Joshi  
Assistant Professor  
Yale University  
nikhil.joshi@yale.edu

Mizuho Kalabis  
Oncology Clinical Director  
Merck & Co.  
mizuho.kalabis@merck.com

Michael Kaplan  
President & CEO  
Melanoma Research Alliance  
mkaplan@curemelanoma.org

Florian Karreth  
Assistant Member  
H. Lee Moffitt Cancer Center  
florian.karreth@moffitt.org

Charles Kaufman  
Assistant Professor  
Washington University in Saint Louis  
ckkaufman@wustl.edu

Howard Kaufman  
Replimune  
howard.kaufman@replimune.com

Alissa Keegan  
Senior Medical Scientist  
Amgen  
akeega01@amgen.com

Denise Kellen  
Board of Directors  
Melanoma Research Alliance

Priscilla Kelly  
Editor  
SCIENCE  
pkelly@aaas.org

Shaheen Khan  
Assistant Professor  
UT Southwestern Medical Center  
shaheen.khan@utsouthwestern.edu

Nikhil Khushalani  
Vice Chair and Senior Member, Cutaneous Oncology  
H. Lee Moffitt Cancer Center  
nikhil.khushalani@moffitt.org

Donna Kimbark  
Program Manager  
CDMRP-Melanoma Research Program  
donna.m.kimbark.civ@mail.mil

Enko Kiprilov  
Senior Medical Director  
Pfizer  
enko.kiprilov@arraybiopharma.com

John Kirkwood  
Usher Professor of Medicine, Dermatology, and Translational Science  
UPMC Hillman Cancer Center  
kirkwoodjm@upmc.edu

Libby Kistler  
Patient Advocate  
opkva117@gmail.com

Michael Klowden  
CEO  
Milken Institute

Sebastian Kobold  
Attending Physician, Professor  
Klinikum der Ludwig-Maximilians-Universität München  
sebastian.kobold@med.uni-muenchen.de

Larissa Korde  
Head, Breast Cancer and Melanoma Therapeutics, Clinical Investigations Branch, National Cancer Institute  
larissa.korde@nih.gov

Clemens Krepler  
Clinical Director  
Merck & Co.  
clemens.krepler@merck.com

Art Krieg  
Chief Scientific Officer & Founder  
Checkmate Pharmaceuticals  
akrieg@checkmatepharma.com

Esther Krofah  
Senior Director  
FasterCures, a Center of the Milken Institute  
ekrofah@mileninstitute.org

Ashish Kulkarni  
Assistant Professor  
University of Massachusetts Amherst  
akulkarni@engin.umass.edu

Rajan Kulkarni  
Assistant Professor  
Oregon Health & Science University  
kulkarni@ohsu.edu

Ann Kurowski  
Vice President, Regulatory Affairs  
Alkermes  
an.kurowski@alkermes.com
Benjamin Larimer  
Assistant Professor  
University of Alabama Birmingham  
blarimer@uab.edu

Theresa LaVallee  
VP, Translational Medicine and Reg. Affairs  
Parker Institute for Cancer Immunotherapy  
tlavallee@parkerici.org

Sancy Leachman  
Professor & Chair, Department of Dermatology  
Oregon Health & Science University  
leachmas@ohsu.edu

Evan Lipson  
Associate Professor, Medical Oncology  
Johns Hopkins University  
elipson2@jhmi.edu

Sixue Liu  
Postdoctoral fellow  
UCLA  
sxliu0130@gmail.com

Roger Lo  
Professor, Associate Chief, Program Director  
UCLA  
rolo@mednet.ucla.edu

John Loffredo  
Associate Director, Clinical Biomarker Lead  
Bristol-Myers Squibb  
joh.loffredo@bms.com

David Lombard  
Associate Professor of Pathology  
University of Michigan  
davidlom@umich.edu

Buddy Long  
CEO  
Elios Therapeutics  
buddy.long@perseuspci.com

Michal Lotem  
Head, Center for Melanoma and Cancer Immunotherapy  
Hadassah University Hospital  
mlotem@hadassah.org.il

Jason Luke  
Associate Professor of Medicine  
UPMC Hillman Cancer Center  
lukejj@upmc.edu

Amanda Lund  
Associate Professor  
Oregon Health & Science University  
lunda@ohsu.edu

Kim Lyerly  
Professor  
Duke University  
kim.lyerly@duke.edu

Paul Macklin  
Associate Professor  
Indiana University  
macklinp@iu.edu

Umar Mahmood  
Professor of Radiology  
Massachusetts General Hospital  
umahmood@mgh.harvard.edu

Kellie Malloy Foerter  
Chief Clinical Development Officer  
OncoSec Medical  
kmalloy@oncosec.com

Steve Mao  
Editor-in-Chief  
Cancer Cell, Cell Press  
stevemaodallas@gmail.com

Richard Marais  
Director  
Cancer Research UK Manchester Institute  
richard.marais@cruk.manchester.ac.uk

Kim Margolin  
Professor/Physician  
City of Hope  
kmargolin@coh.org

Jean-Christophe Marine  
Professor  
VIB KULeuven Center for Cancer Biology  
jeanchristophe.marine@kuleuven.vib.be

Melanie Massenzio  
Marketing Director  
Novartis Pharmaceuticals  
melanie.massenzio@novartis.com

Mark McLaughlin  
Professor  
West Virginia University  
mcloughlin@hsc.wvu.edu

Martin McMahon  
Professor and Sr. Director  
Huntsman Cancer Institute  
martin.mcmahon@hci.utah.edu

Young Investigator, Pilot, and Dermatology Fellow Awardee Poster Session
Sapna Patel  
Physician  
UT MD Anderson Cancer Center  
sppatel@mdanderson.org

Margie Patlak  
Science writer  
Margie Patlak, Inc.  
margiepatlak@gmail.com

Elizabeth Patton  
Programme Leader and Reader  
MRC Human Genetics Unit, University of Edinburgh  
e.patton@igmm.ed.ac.uk

Anna Pavlick  
Professor of Medicine and Dermatology  
NYU Langone Medical Center  
anna.pavlick@nyumc.org

Guangyong Peng  
Professor  
Saint Louis University  
gpeng@slu.edu

Weiyi Peng  
Assistant Professor  
University of Houston  
wpeng2@central.uh.edu

George Peoples  
Chief Medical Officer  
Elios Therapeutics  
georgepeoples2@hotmail.com

Rolando Perez-Lorenzo  
Associate Research Scientist  
Columbia University  
rp2522@cumc.columbia.edu

Louise Perkins  
President  
BioPharmata Consulting  
imperkins@aol.com

Connie Pfeiffer  
Head, US Oncology Advocacy & Prof Relations  
Bristol-Myers Squibb  
constance.pfeiffer@bms.com

Neil Pfister  
Radiation Oncology Resident  
Emory University  
neil.pfister@emory.edu

Elena Piskounova  
Assistant Professor  
Weill Cornell Medicine  
elp2025@med.cornell.edu

David Polsky  
Professor of Dermatology  
NYU Langone Medical Center  
david.polsky@nyumc.org

Lara Porzak  
President  
Lara Porzak Photography  
lporzak@gmail.com

Poulikos Poulokakos  
Associate Professor  
Icahn School of Medicine at Mount Sinai  
poulikos.poulikakos@mssm.edu

Christine Pratilas  
Associate Professor of Oncology  
Johns Hopkins University  
cpratl1@jhmi.edu

Richard Prejean  
Senior Director, Team Lead  
Pfizer  
Richard.Prejean@arraybiopharma.com

Enrica Quattrrocchi  
Mayo Clinic  
quattrocchi.enrica@mayo.edu

Shah Rahimian  
VP of Clinical Development and Medical Lead  
Idera Pharmaceuticals  
srahimian@iderapharma.com

Ofer Reiter Agar  
Fellow  
Memorial Sloan Kettering Cancer Center  
reiterao@mskcc.org

Jon Retzlaff  
Chief Policy Officer, & VP, Science and Government Affairs  
AACR  
jon.retzlaff@aacr.org

Antoni Ribas  
Professor of Medicine  
UCLA  
aribas@mednet.ucla.edu

David Rickles  
Chief Science Officer  
Radimmune Therapeutics  
drickles@radimmune.com

Todd Ridky  
Asst. Professor  
University of Pennsylvania  
ridky@pennmedicine.upenn.edu

Caitlin Riley  
Patient Advocate  
crileyri@gmail.com

Caroline Robert  
Head of Dermatology  
Gustave Roussy  
caroline.robert@gustaveroussy.fr

Gavin Robertson  
Professor  
Penn State College of Medicine  
gpr11@psu.edu

C. Daniela Robles-Espinoza  
Assistant Professor  
National Autonomous University of Mexico  
drobles@iligh.unam.mx

Kristen Mueller, Senior Director, Science Program
Keiran Smalley  
Professor and Director  
H. Lee Moffitt Cancer Center & Research Institute  
keiran.smalley@moffitt.org

Maria Soengas  
Professor  
Spanish National Cancer Research Centre  
msoengas@cnio.es

Jonathan Sokoloff  
Board of Directors  
Melanoma Research Alliance

David Solit  
Attending Physician  
Memorial Sloan Kettering Cancer Center  
solidt@mskcc.org

Vernon Sondak  
Chair, Department of Cutaneous Oncology  
H. Lee Moffitt Cancer Center & Research Institute  
vernon.sondak@moffitt.org

Howard Soule  
Executive Vice President and Chief Science Officer  
Prostate Cancer Foundation  
hsoule@pcf.org

Alan Spatz  
Professor/Director of Pathology  
McGill University Health Centre  
alan.spatz@mcgill.ca

Neil Spiegler  
Executive Director  
Peggy Spiegler Melanoma Research Foundation  
NSpiegler@aol.com

Stefani Spranger  
Assistant Professor  
MIT  
spranger@mit.edu

Mark Stewart  
Vice President, Science Policy  
Friends of Cancer Research  
mstewart@focr.org

Edward Stites  
Assistant Professor  
Salk Institute for Biological Studies  
estites@salk.edu

Erica Stone  
VP of Oncology  
GigaGen  
estone@gigagen.com

Lorenz Studer  
Physician  
Memorial Sloan Kettering Cancer Center  
studerl@mskcc.org

Ryan Sullivan  
Assistant Professor  
Massachusetts General Hospital  
russullivan7@mgh.harvard.edu

Lu Sun  
Assistant Project Scientist  
UCLA  
lusun@mednet.ucla.edu

Qi Sun  
Postdoctoral fellow  
NYU Langone Medical Center  
qi.sun@nyulangone.org

Susan Swetter  
Professor of Dermatology; Director, Pigmented Lesion and Melanoma Program, Stanford Cancer Institute  
Stanford University  
sswetter@stanford.edu

Yuval Tabach  
Senior Lecturer  
Hebrew University  
yuvaltab@ekmd.huji.ac.il

Mary Tagliaferri  
Chief Medical Officer  
Nektar Therapeutics  
mtagliaferri@nektar.com

Elizabeth Tarka  
Chief Medical Officer  
Idera Pharmaceuticals  
ltaarka@iderapharma.com

Walter Tatarowicz  
Senior Medical Science Liaison  
Eisai, Inc.  
Walter_Tatarowicz@eisai.com

Janis Taube  
Director of Dermatopathology  
Johns Hopkins University  
jtaube1@jhmi.edu

Marc Theoret  
Deputy Director (Acting), Office of Oncologic Diseases; Acting Associate Director, OCE  
US Food & Drug Administration  
marc.theoret@fda.hhs.gov

Magdalena Thurin  
Program Director  
National Cancer Institute  
thurinm@mail.nih.gov

Roberto Tinoco  
Assistant Professor  
UC Irvine  
rtinoco@uci.edu

Suzanne Topalian  
Professor of Surgery and Oncology  
Johns Hopkins University  
stopali1@jhmi.edu

Olivia Tournay Flatto, PhD  
President  
Pershing Square Foundation  
otflatto@persq.org
Jedd Wolchok  
Chief, Melanoma & Immunotherapeutics  
Memorial Sloan-Kettering Cancer Center  
wolchokj@mskcc.org

James Wooldridge  
Chief Medical Officer  
Checkmate Pharmaceuticals  
jwooldridge@checkmatepharma.com

Xu Wu  
Associate Professor  
Massachusetts General Hospital  
xwu@cbrc2.mgh.harvard.edu

Kai Wucherpfennig  
Chair of Dept of Cancer Immunology & Virology  
Dana-Farber Cancer Institute  
kai_wucherpfennig@dfci.harvard.edu

Adam Yakovich  
Senior Director, Medical Affairs  
Replimune  
adam.yakovich@replimune.com

Qin Yan  
Associate Professor  
Yale University  
qin.yan@yale.edu

Iwei Yeh  
Associate Professor  
UCSF  
iwei.yeh@ucsf.edu

Vashisht Yennu Nanda  
Assistant Professor  
UT MD Anderson Cancer Center  
vynanda@mdanderson.org

Alexia-Ileana Zaromytidou  
Chief Editor  
Nature Cancer  
a.zaromytidou@nature.com

Hassane Zarour  
Professor  
UPMC Hillman Cancer Center  
zarourhm@upmc.edu

Li Zhou  
Associate Scientist  
Henry Ford Health System  
lzhou1@hfhs.org

Jiyue Zhu  
Professor  
Washington State University  
jiyue.zhu@wsu.edu

Robin Zimmerman  
Scientific Research Advocate  
Oregon Health & Science University  
robin@wearesolsurvivors.org

Jonathan Zippin  
Associate Professor  
Weill Cornell Medicine  
jhzippin@med.cornell.edu

Leonard Zon  
Director, Stem Cell Program  
Boston Children’s Hospital  
zon@enders.tch.harvard.edu
As the largest non-profit funder of melanoma research, MRA has dedicated $123 million to date in support of the fight against melanoma.