2019 SCIENTIFIC RETREAT

RESEARCH IS HOPE

Highlights from the Melanoma Research Alliance 11th Annual Scientific Retreat.

Melanoma Research Alliance

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LETTER FROM CHIEF SCIENCE OFFICER AND SCIENTIFIC PROGRAM DIRECTOR

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One of the highlights for the Melanoma Research Alliance (MRA) each year is hosting the Annual Scientific Retreat. The 2019 Retreat was held February 25-27, in Washington, D.C. One reason this is such a special event for MRA is that it brings together key stakeholders from across the melanoma research community, including academic researchers; representatives from industry, government and non-profits; and patients and their loved ones for three days of scientific presentations, conversations, and learning.

This year's Retreat included presentations from 20 researchers that focused on the latest discoveries in melanoma prevention, diagnosis, and treatment. At the Melanoma > Exchange Advocates Forum, melanoma patients and caregivers gathered with experts to learn about the latest scientific advancements as well as engage in critical conversations around advocacy and survivorship. Woven through these sessions and other supporting events was a sense of community and the shared mission of working together to defeat this deadly disease and give patients the best outcomes possible.

The research presentations touched on the incredible progress made over the past decade in melanoma treatment and highlighted how much more work is necessary so that all patients can benefit from available therapies. Topics discussed included overcoming treatment resistance to both molecular and immunotherapies, as well as advances in personalized vaccines as a therapeutic strategy for melanoma. Presentations on novel animal models and technologies for melanoma treatment and diagnosis showed how zebrafish could be used to identify promising drug candidates and how applying data analysis techniques from astronomy may reveal new insights about why some melanomas respond to immunotherapy while others do not. A talk about Oregon's War on Melanoma campaign highlighted exciting, large-scale efforts in melanoma prevention. Finally, a closing panel discussion shed light on how advances in artificial intelligence may impact melanoma diagnosis, prognosis, and treatment. Together these presentations offered an exciting, and in-depth picture of the current state of research and illuminated a path toward improved prevention, diagnosis, and treatment of melanoma.

Accompanying programs, such as the Industry Roundtable provided an opportunity for representatives from industry, government, and academia to discuss the development of neoadjuvant therapies for melanoma in a structured way. A panel discussion at the Young Investigators Breakfast provided insights for obtaining funding from non-traditional (i.e., non-NIH) sources. New additions to the program included a poster session for currently funded Pilot and Young Investigator awardees and a topic-focused networking lunch. Together, these events provided opportunities for diverse stakeholders to engage in discussions that are sure to accelerate progress in the field.

The research presented and information exchanged at this event help inform MRA's priorities for the coming year. We are honored to host such an interactive forum and are excited to share the highlights of MRA's 2019 Scientific Retreat with you.

Sincerely,

Marc Hurlbert, Ph.D.
Chief Science Officer

Kristen L. Mueller, Ph.D.
Scientific Program Director

SETTING THE STAGE:
RESEARCH SAVES LIVES

"Rusty shouldn't have survived a year after being diagnosed with Stage 4 melanoma in 2006," began Heather Davis at the opening session of the 2019 MRA Scientific Retreat. The room, bursting with melanoma researchers, industry partners, survivors, and patients was instantly rapt.

"He shouldn't have survived his first clinical trial, second, or fifth. But he did. His life included a series of uncanny miracles – of radical scientific innovations that appeared at the exact moment when they could be applied to him—affording him year-after-year of life that without he would never have known," she continued.

Heather then shared that Rusty Cline's string of miracles ended after 12 years. Twelve years that he arguably should never have had.

She told the crowd that Rusty's life was a testament to the incredible progress of melanoma research and the contributions of people in this very room. That his death was a reminder that more – much more – remains to be done.

Heather's call to action was the perfect start to the 2019 MRA Scientific Retreat. Over the course of three days more than 300 people from across the melanoma research ecosystem would gather together at this invitation-only event to exchange ideas, report on scientific progress, celebrate achievements, and mourn the losses.

Over the course of three days, attendees discussed everything from new treatment approaches such as RNA-based vaccines, strategies to fight back against treatment resistance, and hurdles to testing neo-adjuvant therapies in melanoma.

Investigators also shared progress made and challenges encountered when harnessing new technology to further their research goals, be it advancing prevention or developing

Louise Perkins, Michael Klowden, and Michael Kaplan

Melanoma > Exchange Advocate Forum

Preceding the retreat, MRA held its annual Patient and Foundations Forum, newly christened the Melanoma > Exchange Advocate Forum. The Forum brought people together from across the United States – survivors, patients, loved ones, industry, government, and the research community – to learn from one another, get support, and leave empowered. **Learn more on page 19**.

new treatments. From artificial intelligence, innovative imaging strategies, and altogether new models for studying melanoma – presenters and participants alike explored the deep collaborations within and across specialties focused on melanoma.

"Please know, above all else, that there is hope in every single thing you do," Heather told the crowd. "Every hour logged, experiment failed, trial endured, datum analyzed, adverse event suffered, is an act of composition: ultimately leading to another joyous story of hope that will be told, another living song that will be sung."

Alan Hunter Shain

TREATING MELANOMA PATIENTS BEFORE SURGERY

With the advent of targeted and immunotherapies, the past decade has seen tremendous advances for patients facing late stage melanoma. But can these new therapies benefit patients with early stage melanoma, where spread of disease has yet to be observed? Typically, such patients have their tumors surgically removed, and then watch and wait. Over 90% will never see their tumors come back or spread to other sites, but is there a way to prevent recurrence in those patients that will eventually go on to relapse?

One approach currently being tested in clinical trials, termed neoadjuvant therapy, is to treat early stage patients with targeted or immunotherapy before surgical removal of their tumor. In theory, such a treatment could rid the body of any microscopic tumors or circulating tumor cells that cannot be detected by our scans, but can cause the melanoma to recur and become metastatic given sufficient time. Advantages of this approach are that patients with early stage disease tend to respond better to cancer therapies than those with metastatic disease, and treating patients with other anti-cancer drugs like chemotherapy or anti-hormonal therapy before surgery has been shown to shrink tumors in other malignancies, although not necessarily to improve survival. Moreover, for immunotherapy, there are reasons to suspect that treatment before surgery might be particularly effective by virtue of there being more tumor cells present to help prime the immune cells to recognize and attack the target.

Nageatte Ibrahim

Marc Theoret and Ashley Ward

Over 40 thought leaders came together for this discussion at the 2019 MRA Scientific Retreat to explore and discuss key issues central to developing and safely applying neoadjuvant therapies for melanoma. Participants included representatives from academia, FDA, industry, National Cancer Institute, and MRA. The session was moderated by MRA Board Member Suzanne Topalian of Johns Hopkins University and MRA Chief Science Officer Marc Hurlbert. Among the topics discussed were how best to test neoadjuvant therapy, how to determine which patients would benefit most from such treatment, and whether such treatment might even preclude the need for surgery.

Topalian noted that “it’s the right time to talk about neoadjuvant therapy in melanoma” given that it has been the focus of nearly 40 clinical trials. Most of these trials are ongoing, and a few have recently reported favorable results. But Marc Theoret and Patricia Keegan of the FDA cautioned that most of these studies were done in academic settings on small numbers of patients. They stressed the need for larger, industry-supported trials, or for greater harmonization of the types of data collected in small studies so they can be combined to provide a more robust assessment of neoadjuvant therapy in melanoma. Both Keith Flaherty of Massachusetts General Hospital and Gregory Friberg of Amgen suggested NIH fund larger, more robust trials, and provide a means to combine such data across trials

But the harmonization across studies required to pool data is more difficult than it seems. For example, how do you best measure immunotherapy response? Typically, tumor regression is measured – but this may not be appropriate given that tumors treated with immunotherapy frequently expand before shrinking, presumably due to the influx of immune cells. Topalian and others suggested devising new indicators of response. One such

correlate could include pathological tumor response, which has been used as a clinical correlate of response for neoadjuvant trials in breast cancer. Tumor samples with 10% or fewer viable tumor cells may serve as an early indicator that patients are responding to neoadjuvant therapy. Dermatopathologist Janis Taube of Johns Hopkins University noted that she and her colleagues have developed a new scoring system for evaluating pathological responses to immunotherapies and stressed that full cross-sections of tumors are needed to evaluate those responses and should be collected during clinical trials.

Ashley Ward of FDA emphasized the need to validate the utility of using pathological response as a surrogate for endpoints like overall survival or progression-free survival. Such validation would likely be necessary for approving any drugs in the neoadjuvant setting. Kellie Malloy of OncoSec Medical indicated that carrying out such trials would be a challenge for industry due to the needed length of trials, numbers of patients needed to enroll, and the high costs since the vast majority of early stage patients never relapse and for those that do, the tumors may not rebound for many years.

One advantage of treating patients prior to surgery is that the degree of response seen in their tumor samples may suggest their risk of relapse after surgery. If the tumor did not respond to neoadjuvant therapy at the time of surgery, they can be given another treatment after surgery, Tara Mitchell of University of Pennsylvania noted.

Thomas Gajewski and Rebecca Moss

Other participants stressed the need to strike an appropriate risk/benefit balance with neoadjuvant treatment. Many non-metastatic melanoma patients are cured by surgery alone, so additional treatment may not be warranted, especially when additional treatment carries risk of adverse reactions that in the case of immunotherapy can be lifelong. There is also the risk that while patients are on neoadjuvant therapy, their tumors may not respond and instead continue to grow, becoming too large to be surgically removed. The few studies that have been done show that most melanoma patients who receive neoadjuvant combination immunotherapy will experience immune-related adverse events, including severe autoimmune reactions, such as diabetes or an inflamed colon. “Maybe we need to back away from such aggressive treatment in the neoadjuvant setting,” Topalian said, suggesting treatment with just one immunotherapy, or having a good means for predicting which patients are at greater risk for recurrence and likely to respond to such immunotherapies.

Keith Flaherty

Current risk prediction models, which are based on how deep the tumor is and whether tumor cells have spread to the lymph nodes, "is refined for melanoma but not perfect," Topalian said. She stressed the need to select "the most likely patients for relapse."

Another question neoadjuvant treatment raises is whether its use might allow some patients, whose tumors shrink substantially, to avoid surgery altogether because their tumors will likely go on to completely disappear. "Why not just skip surgery in those cases?" Michael Atkins of Georgetown University and Chair of MRA's Medical Advisory Panel posited, especially since increasingly, except for its very early stages, melanoma is being viewed as a systemic rather than localized disease that should be treated with a systemic therapy such as immunotherapy, he said. Paul Chapman of Memorial Sloan Kettering Cancer Center agreed and added that, "We could avoid surgery if we see a major response at three weeks."

All agreed more studies need to be done, and Chapman cautioned "we don't want to speed neoadjuvant therapy approval when we haven't established that it works, because it has a lot of financial and toxicity costs." But he added the robust data about the high relapse rate for Stage 3 melanoma patients "should make us pay attention." Christian Blank of Netherlands Cancer Institute responded by pointing out that neoadjuvant therapy is less expensive than treatment given after surgery, and may be less expensive than surgery itself, since the drugs are only given for a short period of time. MRA Chief Science Officer Emerita Louise Perkins added that neoadjuvant therapy may also be preferred by patients who prefer to avoid surgery.

The discussion revealed that while neoadjuvant therapy does show great promise for early melanoma patients, many questions remain and given the potential risks involved, proceeding with caution is warranted. Exploration of the topic will continue later this year at a public workshop MRA is convening with the FDA. "This is a hot topic that is critical to MRA and to the melanoma field," Hurlbert stressed. Stay tuned.

Marc Hurlbert

Michael Atkins

MELANOMA VACCINES SHOW PROMISE

While checkpoint immunotherapies, such as ipilimumab (Yervoy), nivolumab (Opdivo), and pembrolizumab (Keytruda) have been hailed as a breakthrough in the way melanoma is treated, about half of patients do not respond. Researchers are pursuing multiple strategies to understand why this happens and to develop novel strategies to jumpstart an immune response. One approach showing promise in early clinical trials, comes in the form of a new personalized vaccine being developed by Ugur Sahin of Johannes Gutenberg-Universität Mainz and BioNTech.

Ugur Sahin

Sahin creates RNA-based personalized vaccines for each patient after analyzing tumor samples to determine which protein fragments – what researchers call neoantigens – are most likely to spur an immune response. Each vaccine includes up to 20 of these neoantigen targets and takes about six weeks to develop. The vaccine is then given to the patient by injecting it directly into a lymph node or by infusing it intravenously.

Sahin is currently testing "two flavors" in the clinic. The first, called IVAC-MUTANOME, is injected directly into a patient's lymph node where it is more likely to meet dendritic cells that can present the antigens to tumor-killing T cells, who will then home in and destroy any tumor cells harboring these proteins. So far, 13 patients with advanced melanoma have been treated with the experimental IVAC-MUTANOME vaccine. Each patient receives at least eight vaccinations over regular intervals. One concern with personalized vaccines such as these is that a patient's T cells may not react to any of the neoantigens included in the vaccine, but fortunately this was not the case. Sahin and his colleagues found that 60% of the neoantigens included in the vaccine prompted a T cell response in patients. "We saw a strong immune response against tumor antigens in all patients," Sahin stressed. The vaccine significantly reduced the cumulative rate of metastatic relapse, resulting in sustained progression-free survival. In one patient, who had a metastatic lymph node removed after being vaccinated four times, the vaccine prompted T cells to react to all 10 tumor antigens within it. IVAC-MUTANOME is currently being tested in combination with Keytruda versus Keytruda alone in a Phase II clinical trial in patients with advanced melanoma (NCT03815058). Learn more about this and other clinical trials here.

Targeted and immune-based therapies have transformed the way we treat melanoma for many patients facing advanced melanoma. However, too many patients aren't benefiting from these new approaches. Several MRA-funded investigators are hard at work developing, testing, and refining the use of therapeutic vaccines to help even more people with melanoma.

- Patrick A Ott M.D. – Dana Farber Cancer Institute
- Nicolas Chevrier Ph.D. – University of Chicago
- Nina Bhardwaj M.D., Ph.D. – Icahn School of Medicine at Mount Sinai

Learn more about these and other MRA Grant Awards at CureMelanoma.org/Grants

The second flavor of Sahin's vaccines, called Lipo-MERIT, encases the tumor antigens in a sphere of fat particles and then widely distributes them throughout the body using an intravenous infusion. In this case, the vaccine is not personalized to individual patients, rather it is composed of four antigens commonly expressed at high levels on melanoma tumors. The Lipo-MERIT vaccine is currently being tested in patients with advanced melanoma (NCT02410733). This clinical trial will enroll 115 Stage III and IV melanoma patients, including those that did not respond to checkpoint inhibitor therapies. These patients will receive eight doses delivered intravenously at regular intervals. So far, while premature, the results are promising. PET scans of patients done three hours after being given the 6th vaccine reveal a buildup of T cells in the spleen, which is a staging ground for activated T cells. Additional investigations uncovered that, "the T cells are recognizing tumor cells and doing their job killing them," Sahin said. Out of 22 patients with metastatic tumors who had progressed on checkpoint inhibitors, four patients had a partial response, eight had stable disease, and ten had progressive disease, he reported. Preliminary data in 70 patients found it caused minor flu-like symptoms that were short-lived.

While these early studies suggest that vaccine approaches such as these may one day complement currently approved checkpoint inhibitors, more work is needed to validate the efficacy and safety of this approach.

RESISTING RESISTANCE


Poulikos Poulikakos

When the new targeted and immunotherapies first started to melt away some patients' melanoma tumors, both clinical researchers and their patients were elated. But when the tumors returned months later in most patients treated with targeted therapies, and in many patients treated with immunotherapies, albeit more slowly, elation soon turned to puzzlement. Investigators grappled with why a therapy that once worked so well stopped being effective. "I'm happy to see that with some patients we reached a plateau with effective therapies, but with others, we reached a ceiling that we can't seem to go above," noted Caroline Robert of Gustave Roussey Institute at the 2019 MRA Scientific Retreat. "The major issue for these drugs is resistance."

Such resistance – termed acquired resistance by doctors – has sent many researchers scurrying back to the lab bench in an effort to uncover its cause, and new tools that may help to overcome it. Similarly, researchers are still struggling to understand why some patients do not respond to any therapy, termed primary resistance. At the MRA 2019 Scientific Retreat, several researchers reported on research funded by MRA to identify new ways to combat drug resistance, including a number of strategies that are already being tested in the clinic.

Taking Multiple Approaches to Restore PD-1 Sensitivity

For resistance to cancer immunotherapies, investigators are focusing on the battle between tumor and immune cells and what determines who will emerge victorious, noted Antoni Ribas of the University of California, Los Angeles. "By understanding molecular differences between patients who respond to immunotherapy and those that don't, we get hints of what the cancer did to escape the immune system," he said. Two weapons wielded by melanoma that Ribas discussed include disabling the molecular machinery used to present tumor proteins to T cells and decreasing sensitivity to interferons, secreted proteins that aid T cells in their attack of tumor cells.

Cancer immunotherapies release the brakes—what researchers call checkpoints—on an immune response by inhibiting PD-1 or CTLA-4 proteins that keep T cells in a non-responsive state. Once those brakes are released, an effective immune response to tumors relies on the 'presentation' of small fragments of tumor proteins – called antigens – on the surface of the tumor and immune cells. Like red flags, these presented antigens trigger T cells to hone in and destroy tumor cells. But cancer cells develop ways to evade T cells by disrupting antigen presentation in multiple ways, thereby giving the immune system the slip, Ribas reported.

Fortunately, researchers have identified multiple compounds that may provide a work-around. These compounds activate natural killer cells, which like T cells, can also kill tumors and are actually more potent when tumors disable antigen presentation. This strategy restored sensitivity of melanoma tumors to immunotherapies, and is showing promising results in early stage clinical studies.

When T cells recognize tumor cells, they release molecules called interferons. Interferons then spur the tumor to release molecules that attract additional T cells to it, increasing their antigen presentation, and slowing the tumor's growth. Not surprisingly, immunotherapy-treated tumors can acquire new mutations that cause them to lose sensitivity to interferons and resist therapy. Ribas described strategies that are showing promise in reversing this resistance, which involve giving patients a tumor-killing virus or similarly, giving them synthetic molecules that mimic a viral infection alongside immunotherapy. Both of these therapeutic strategies help to activate T cells and drive their entry into the tumor microenvironment. "It's like lighting a match to start a fire," said Ribas.

Targeting Targeted Therapy Resistance

Because tumors are constantly growing, they have very high metabolic demands and can change the way they acquire energy to support their growth. Vashisht Yennu Nanda of MD Anderson Cancer Center discovered that melanoma cells resistant to

Antoni Ribas

targeted-therapy have rewired their energy-producing pathways so that they can generate energy in a different way than tumor cells that are still sensitive to BRAF inhibitors. He then tested two different inhibitors capable of shutting down this rewired metabolism and demonstrated that melanoma tumor cells in culture and in mice regained sensitivity to targeted therapies. Yennu Nanda also found that one of the inhibitors demonstrated additive effects when used in combination with a CTLA-targeting checkpoint blockade such as ipilimumab. Besides blocking the alternative pathways resistant melanoma cells use to get energy, the inhibitors may also work because tumors are energy hogs that deprive immune cells of the fuel they need to function. These inhibitors presumably make more energy available to the immune cells.

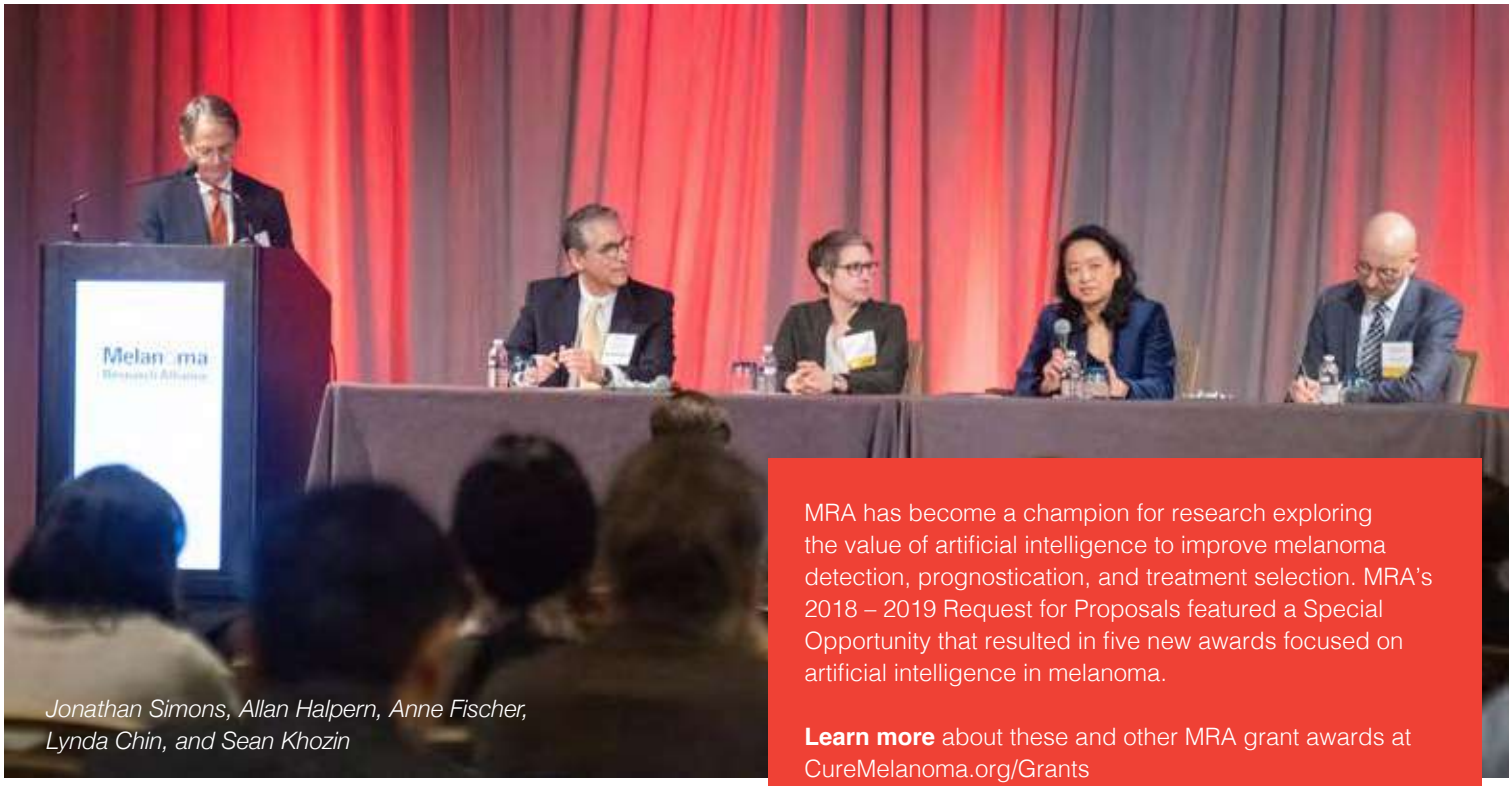
Another tactic Robert has taken to overcome resistance to targeted therapies is to target a complex of proteins she claims is “the nexus of resistance.” Despite targeted therapies killing the majority of tumor cells, often a small population of drug-resistant ‘persister’ cells remain. Robert and her team discovered that one way these cells are able to persist despite therapy is by making large scale changes to their protein expression pattern. Blocking a component of the protein complex that translates the genetic code into proteins has the potential to inhibit these protein expression changes. “We will lose if we go after each and every resistance mechanism. We have to target the smartest thing tumor cells do to adapt to treatment,” she said, which is to alter protein translation of a large suite of genes, including PD-L1, a molecule that helps to put the brakes on the immune system. “If you were a cancer cell you would do the same—hide yourself [from the immune system] and then try to find a way out” by altering the protein translation of genetic instructions, Robert said. She tested an inhibitor to this protein translation complex in melanoma cells and found that when combined sequentially with targeted therapies, it enhances tumor cell death. In theory, the inhibitor could also hamper resistance to some checkpoint therapies. Robert is currently testing the inhibitor in mice, and pointed out that a number of companies are interested in developing it into a melanoma drug.

A final strategy for preventing resistance to targeted therapies reported at the retreat is to create new targeted drugs with unique biochemical properties that are designed to avoid the main ways tumors resist them. As Poulikos Poulikakos of Mount Sinai explained, targeted therapies block the BRAF growth promoting pathway tumor cells use. In response, these cells can develop genetic changes that affect how BRAF functions in the cell. Instead of acting as a single molecule, BRAF proteins can form doublets, which are insensitive to current FDA-approved BRAF inhibitors. Consequently, Poulikakos is testing in mice with melanoma combinations of current and next-generation inhibitors that together block both the doublet and single versions of BRAF. “We are trying to provide a roadmap for next-generation targeted therapies," Poulikakos said, stressing “don’t give up on these drugs because we are not at the end of the road here. We just need rational combinations.” Such next-generation agents used singly or in combination are currently being tested in patients.

Ribas ended his presentation by stressing, “If we can understand why patients don’t respond to therapy, we can develop new treatments to overcome that resistance.” On the basis of what MRA-funded researchers presented at the retreat, we are well on our way.

Caroline Robert

CATCHING THE NEXT WAVE OF AI TO SAVE LIVES



Jonathan Simons, Allan Halpern, Anne Fischer, Lynda Chin, and Sean Khozin

MRA has become a champion for research exploring the value of artificial intelligence to improve melanoma detection, prognostication, and treatment selection. MRA's 2018 – 2019 Request for Proposals featured a Special Opportunity that resulted in five new awards focused on artificial intelligence in melanoma.

Learn more about these and other MRA grant awards at CureMelanoma.org/Grants

Besides the advent of immunotherapy, one of the most exciting developments in melanoma and oncology more broadly over the past decade is the ability to collect enormous troves of data about tumors, their surrounding cells – what researchers call the microenvironment – and potential new drugs that might stop tumor growth dead in its tracks. But how can researchers make sense of this massive 'treasure trove' of data to actually help patients? One answer artificial intelligence (AI) to sift through the data to detect patterns unrecognizable to humans to inform cancer diagnosis, drug design, and treatment selection.

At the 2019 Scientific Retreat, scientists at the frontlines of applying AI to medicine, and melanoma in particular, participated in a stimulating panel discussion that addressed the promise of AI and outlined challenges to overcome to leverage this approach to improve patient care. Jonathan Simons, MRA Board Member, President and CEO of the Prostate Cancer Foundation, moderated the discussion.

Representatives from both the Defense Advanced Research Projects Agency (DARPA) and the Food and Drug Administration (FDA) talked about their AI-focused programs aimed at showing the benefits of adopting the technology so that the drug industry and other commercial ventures are more willing to invest in and apply the technology to their work. Although AI technologies are expected to have big payoffs, they are also relatively expensive and are considered high-risk for companies to adopt. "Industry is risk averse, so we are de-risking big-data," Sean Khozin of the FDA stressed.

DARPA's AMD Program

DARPA's Accelerated Molecular Discovery program (AMD), explores the intersection of AI and chemistry as applied to disease and other issues that affect soldiers, according to Anne Fischer, its program manager. Specifically, AMD is investigating the ability of AI to predict how drugs interact with molecules of interest in diseases, such as melanoma. She noted her program doesn't generate any new data, but relies on other scientists to bring their research projects to the agency, which will work with them to apply and test AI techniques.

Unlike previous AI systems, which rely on a rigid set of rules or big datasets to make predictions, the "third wave" AI technologies AMD is testing will have more reasoning and fewer scripted responses. This should allow these programs to make predictions on complex and changing features they haven't encountered before, such as predicting whether a potential drug will bind with its target based on its three-dimensional structure, as well as predicting what toxic reactions it might cause.

Harnessing Existing Capabilities to Do Good

Allan Halpern of Memorial Sloan Kettering Cancer Center stressed that researchers should not only develop next-generation AI systems, but also focus on what can be done with current AI. "If we could just harness the kind of AI we take for granted on our iPhones, we could diagnose skin diseases better." He noted that the road map already exists with computerized image processing technology, but what is missing is a pipeline of skin images on which to train AI systems. This is because many dermatologists do not routinely use imaging in their daily practices. Halpern is part of the International Skin Imaging Collaboration. This group is trying to standardize skin imaging technologies and techniques as well as develop an imaging archive that can be used to advance AI-based computer programs capable of distinguishing between malignant and non-malignant moles. An initial study on one of these melanoma detection systems had 500 expert physicians compete against the AI system. This study found that "97% of the time the computer outperformed the clinician," Halpern said. If this technology is validated as anticipated, it could provide valuable tools to help physicians in their daily work separating nevi from melanoma.

The FDA is also trying to apply AI to imaging, for instance to mine facial images for reliable features that can be used for more precise and less subjective pain assessment of patients, Khozin reported. FDA has a new program called INFORMED (Information Exchange and Data Transformation), that among other things, is feeding the massive amounts of data FDA has in-house into AI programs with the aim of discerning factors that can predict the effectiveness and safety of drugs and other drug development tools. FDA's devices center is also piloting a pre-certification program that will enable a regulatory pathway to approve AI software and other digital devices. "We're developing the criteria that could be used to approve AI-based health solutions so they are available to patients and physicians," stressed Khozin. "AI is by nature multidisciplinary, so we have a multidisciplinary approach across the agency," he added.

Allan Halpern

Lynda Chin

In 2019, MRA issued three awards that are focused on using artificial intelligence to better detect melanoma. Researchers hope that artificial intelligence will allow physicians to identify melanomas earlier when they are more easily treated.

With the International Skin Imaging Collaboration archive of 23,000 images in hand, Dr. Veronica Rotemberg, a researcher at Memorial Sloan Kettering and recent awardee of the Michael and Jacqueline Ferro Family Foundation – MRA Young Investigator Award for Artificial Intelligence Applied to Melanoma, is trying to identify patient factors that can help improve the accuracy of artificial intelligence-based diagnosis. By giving artificial intelligence more information – it will be better able to imitate dermatologists.

In addition to Dr. Rotemberg's work, MRA also funded two Established Investigator Awards. Drs. Wei and Elmore are both working to improve the accuracy and reliability of the computer algorithms used to detect melanoma.

Overcoming Infrastructure Barriers

A major barrier to implementing AI – and other digital medicine technologies – that Lynda Chin from the University of Texas pointed out, is a lack of a coordinated infrastructure to support them. Many AI systems depend on access to large amounts of data, both to develop the systems and to assess their accuracy and effectiveness. Although a lot of that real-world data is routinely collected by healthcare systems, many of these systems aren't integrated in a way that allows them to share their data. "It's like there are railroad tracks from one company that are not meeting up with the others. We need a common digital highway, a common infrastructure that supports technology," said Chin. She added, "We talk about bright and shiny objects—AI apps, implantable sensors, etc., but they're not sufficient because we need the infrastructure to integrate them." Chin claimed that progress has been made on the integration front over the last five years, but in addition to connecting healthcare systems, we still have to connect the data collected by health systems to patient data from the home, work, or even at the beach, where, for example, sun exposure relevant to developing melanoma can be assessed. "It's not effective for every big hospital to extend its big tentacles all the way to the beach, but instead we should leverage technology already on the beach. We have to think of it as an ecosystem," Chin said.

Machines Replacing People?

When discussing AI technologies, such as those that enable the detection of malignant moles, the question that often arises is whether AI might someday replace physicians. "Are dermatologists like Wiley Coyote already over the edge of the cliff and they just haven't looked down yet, in terms of AI technology?" Halpern mused. He suggested that though diagnostic dermatologists may not be needed as much as treating dermatologists, with the advent of the new AI technologies, the treating dermatologists are likely to be busier than ever. "Doctors do more than just diagnose," Chin stressed and pointed out that physicians will need to be trained in how to apply AI technologies in their practices. Khozin agreed and noted that a number of medical schools are "changing training so they can leverage AI to empower themselves." For example, Harvard and MIT just started offering fellowship programs in AI and machine learning.

All these new initiatives should soon bear fruit, because, as the moderator Simons noted, quoting Margaret Mead, "Never doubt that a small group of thoughtful and committed citizens can change the world; indeed it's the only thing that ever has."

Allan Halpern and Anne Fischer

Sean Khozin

IMAGING THE IMMUNE RESPONSE IN MELANOMA

We are fortunate to now have effective immune therapies for many melanoma patients. But unfortunately, we also now know that these treatments can often cause serious side effects, like diabetes and colitis, among other reactions. Consequently, there has been a push to develop a way to detect early on if these drugs are working and worth the risk of the side effects they can cause, let alone their high expense. MRI's and other traditional means of predicting whether a cancer treatment is working cannot be depended on because these rely on seeing if there is tumor shrinkage. But often in patients responding to immunotherapies can take months to detect and in some cases, tumors initially expand, falsely indicating progression (pseudoprogression) due to the infiltration of immune cells into the tumors.

Janis Taube

There may soon be a way out of this conundrum, several presenters suggested at the 2019 MRA Research Retreat. These researchers are working on the frontlines of imaging the immune response to tumors so as to better predict if immunotherapies are working. The novel hybrid techniques they use to image key immune cells and how they interact with tumors include genetically engineered llama antibodies in PET scans, mass spectrometers combined with single-cell imaging, and dozens of stains for different immune cells combined with analytical techniques used by astronomers to make sense of the massive amounts of imaging data on the cosmos.

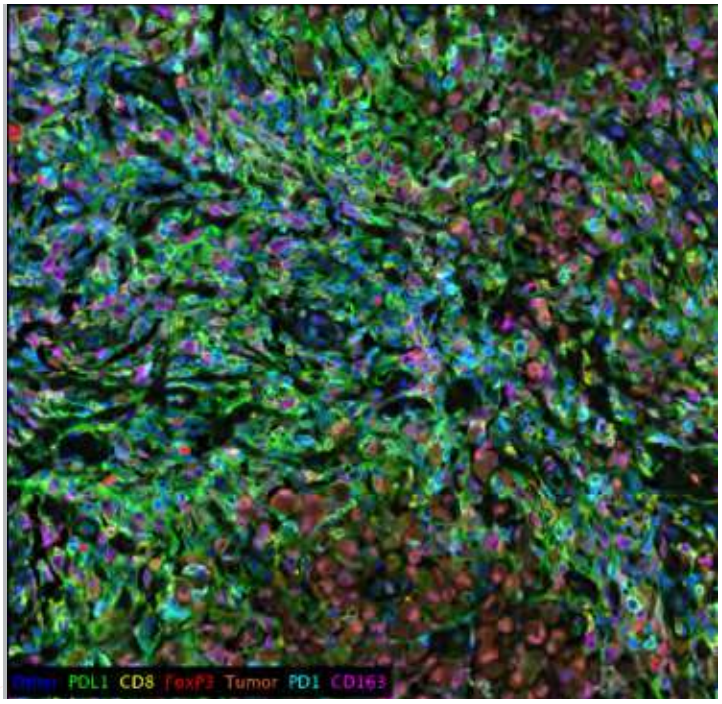
Hidde Ploegh

Immune responses to tumors change over time so to understand their dynamic nature better, you need live animals in which you can image their immune cells and how they interact with tumors over long periods, stressed Hidde Ploegh of Boston Children's Hospital. To do that imaging, he enlisted the help of llamas, who have unusually small antibodies that can be easily modified and attached to an imaging agent for PET (positive electron tomography) such that they seek out and light up specific key components of the immune system in tumors. By using such "nanobodies" in mice with melanoma, he has been able to distinguish a true response to cancer immunotherapy from a pseudoprogression of the tumor. He has also shown that one of the earliest responses to these treatments is killer T cells distributed throughout the tumor, whereas non-responders show a more varied distribution, much of which occurs in peripheral regions of the tumor. "In responder animals, the tumor is penetrated to the core by CD8 [killer T] cells, but in nonresponders there isn't that full penetration," Ploegh stressed. He also found in responders massive increases in a molecule that attracts immune cells and can help them home in on tumors.

Ploegh has developed human versions of his mouse nanobodies that are ready to be tested in the clinical setting and can be used to image key immune cells in both the tumor and lymph nodes with good sensitivity, he said. He also developed a nanobody that can be used to detect melanoma metastases. "Our approach is ready for translation to the clinic. We just need an industrial partner to make it good to go," Ploegh concluded.

Sean Bendall of Stanford University reported on his work imaging an immune response to breast cancer from preserved slices of tumors that he is currently applying to melanoma. He combined the mass spectrometer's ability to detect minute quantities of specific substances with single-cell imaging to reveal patterns in the types and quantities of immune cells that infiltrate breast tumors in biopsy samples. He found two distinct patterns: tumors that were diffusely infiltrated by immune cells, and tumors that had more compartmentalized infiltration. "In one, the immune cells looked like grains of sand in the tumor, while within the compartmentalized ones, it was more like islands of immune cells in the tumor," he said, stressing, "Not all immune infiltration is equal—it's not just a matter of getting immune cells into tumors, but how they are infiltrated."

Bendall found those patients whose tumors showed the compartmentalized pattern of infiltration were more likely to survive. He also found this compartmentalized pattern of response was conserved throughout an entire tumor, regardless of from what region the sample was taken. He next plans to apply his imaging technique to see whether there are distinct differences in immune infiltration in melanoma tumors between responders to immune therapies versus non-responders. "We expect our data will help us understand why we get responses in some patients and not in others," Bendall said.



In this image, captured by Janis Taube, tumor tissue and multiple other parameters can be imaged together.

Sean Bendall

That's also the ultimate goal of Janis Taube, who reported on her efforts to use traditional fluorescent staining of tumor slices, but in an innovative way. Instead of staining for just a few cell types, Taube uses multiple stains "for the basic roll call of immune cells present and also lymphoid structures, tumor cells, and new vasculature," she said. That staining combined with an innovative stacking technique enables her to simultaneously view dozens of parameters. Because of the large data sets generated by this technique, she then uses sophisticated tools and processes borrowed from astronomers to analyze her results so she can superimpose and make sense of one set of findings on top of another.

"We have used the astronomy experience to generate high-quality, three-dimensional maps of the local interactions between melanoma and immune cells that will provide critical insights," Taube said.

Because each tumor slide is linked to patient information such as survival and response to immunotherapy, researchers can use this information to help determine what features in pre-treatment biopsies predict response to therapy. "We've taken what we've learned in terms of imaging the whole sky to image whole tissue sections and are starting to drill down to individual cells and subcellular structures and patterns in data that can resolve even more structures. Our goal is to have perfect prediction to match patients to appropriate therapy," Taube concluded.

NOVEL ANIMAL MODELS FOR TESTING CANCER DRUGS AND VACCINES

Nikhil Joshi

Before experimental drugs and vaccines can ever be tested in people, they must first be studied in animal models of the disease. Such models allow researchers to investigate scientific questions that they cannot answer using people due to unknown risks. These models help researchers to better understand how melanoma forms and progresses, and what happens during treatment response and resistance. Fortunately, melanoma researchers have several experimental animal models from which to choose, each with its own advantages and disadvantages. Because these models are still far from perfect, some investigators have opted to tinker with them so that they more closely mimic certain melanoma subtypes or so they enable a better understanding of how the immune system interacts with tumor cells and tumor vaccines. A few of these novel animal models and what they can reveal were highlighted at the 2019 MRA Scientific Retreat.

NINJA mice reveal anti-tumor immunity

Nikhil Joshi of Yale University reported on his NINJA mice that he and his colleagues genetically engineered to activate production of novel tumor-specific proteins, called neoantigens. He aims to use the mice to better understand the balance between tolerance (T cell non-response to tumors) and the anti-cancer immune response over time and in different tissues. In melanoma and other cancers, tumor neoantigens play an important role in driving T cell killing of tumors in patients taking immunotherapy. NINJA mice will help reveal to researchers why some cancers, such as melanoma, tend to respond to immunotherapies, while others don't, and why some tumors, depending on their surroundings, are seemingly better tolerated by the immune system than others.

Joshi suspects that an immune response to tumors might depend on where in the body it occurs. Other studies have found some parts of the body tolerate novel proteins, meaning they are less likely to prompt an immune response to them. For example, liver transplants are less likely to provoke an immune response than other types of tissue transplants. Joshi verified this with his NINJA mice. "In the liver, when we turn on the production of a tumor neoantigen, we don't get much of an immune response and a lot of the T cells [needed to destroy tumor cells] we see there look exhausted and nonfunctional, unlike those we see in the skin when we turn on the neoantigen," Joshi said. This suggests that T cells in the skin are more primed to "see" neoantigens, and that may explain, at least in part, why melanoma is more likely to respond to cancer immunotherapies than cancers arising in other sites of the body, he added.

Joshi also wants to use the NINJA mice to explore what regulates the natural immune response to melanoma tumors, that is, the killing of tumor cells by T cells that happens in the absence of treatment and can keep small numbers of cancer cells from growing into a larger tumor at the primary site or prevents micrometastases from growing into larger tumor masses. "We want to understand why immune cells ultimately stop functioning, which we think leads to metastatic disease," Joshi stressed.

What's a Model?
Models are powerful tools that help make things easier to understand. In medical research, models help researchers to advance science without subjecting people to possible therapies without reasonable expectation that the benefit of the treatment will outweigh the risks. Specifically in melanoma, researchers use a variety of models, including cell lines, computer simulations, mouse models, zebrafish, and other techniques to determine what agents make sense to advance forward.

Mouse models for cancer vaccines

To better predict an immune response to personalized melanoma vaccines, Nina Bhardwaj of the Icahn School of Medicine at Mount Sinai has modified mice so that they have all the major components of a human immune system. This will allow the researchers to study tumor cells taken from patients in mice with an intact immune system – something that isn't possible in normal mice because the mouse immune system rejects any human cells it sees, similar to organ rejection.

Elizabeth Patton and Mark Gorman

The researchers 'humanize' the mice by destroying these animals' own immune systems with radiation, and then injecting human stem cells derived from patient blood samples into their bone marrow. These stem cells can then generate all the key components of the human immune system. Bhardwaj next plans to make humanized mice using stem cells taken from melanoma patients and then inject the fragments of the patient's tumor into these mice. Using these mice, Bhardwaj plans to study the effectiveness of tumor vaccines and tease apart the immune responses they generate. By first testing personalized tumor vaccines in these mouse 'patient avatars,' Bhardwaj and her colleagues hope to one day be able to select the specific components of the vaccine that elicit the strongest immune response and then use that to fine tune personalized vaccines for cancer patients.

A. Thomas Look

Zebrafish reveal promising compounds for difficult-to-treat melanoma subtype

Researchers are also developing novel animal models to better predict effective drug combinations in subtypes of melanoma that traditionally do not respond to current therapies. To better understand how to treat melanomas that have a mutation in the gene NF-1, a particularly aggressive and treatment-resistant genetic subtype, A. Thomas Look of Dana-Farber Cancer Institute and his colleagues created zebrafish with this subtype of melanoma. Zebrafish, which are smaller than a nickel in size, are a favored model for some cancer researchers because they have translucent skin, so the growth or shrinkage of tumors is easily visible. They also have a short lifecycle compared to mice, making rapid genetic manipulation feasible.

Thomas is using the NF-1 mutant zebrafish to understand and predict molecular pathways that cause resistance to drugs. Better understanding this could suggest combination therapies that are more likely to cause a durable response to treatment. For example,

Thomas' studies found the need to simultaneously inhibit two proteins (MCL-1, BCL-2) that work together to promote the survival of melanoma cells. When these two inhibitors were combined with another drug (rapamyacin) that slowed the growth of tumors, they dramatically prolonged survival of the NF-1 zebrafish by killing off melanoma cells. This three-pronged attack also killed NF-1 human melanoma cells grown in culture. "This subtype of melanoma is likely to respond to this treatment strategy," Thomas said, as well as perhaps other molecular melanoma subtypes. He suggested the three-agent treatment be tested in mouse melanoma models to better understand its clinical potential.

Together, these studies demonstrate the importance of model optimization to discover new treatments and understand the complex dynamics of tumor-immune cell interaction.

Thorsten Memphel and Lynn Schuchter

Nina Bhardwaj

Brent Hanks

Melanoma > Exchange Advocate Forum

No one understands the life-long mark that melanoma can leave on a person – or family – like people who've experienced it firsthand. That's why the **Melanoma > Exchange Advocate Forum** is such a charged and powerful experience for all those who attend. The forum brought together patients, survivors, and loved ones with world-renowned melanoma clinicians and researchers to learn about cutting-edge advances in melanoma treatment and how emerging research can benefit everyone.

Participants walked away with practical tips and strategies to get the most out of their care while navigating melanoma diagnosis, treatment, or beyond.

Jennifer McQuade

TAKING CONTROL AFTER A MELANOMA DIAGNOSIS

You are used to giving the marching orders to your own body, but when cancer steers it in the wrong direction, it can feel like you are no longer in control. Yet this is when it's most important to take control, stressed melanoma physicians, patients, and advocates at the 2019 Melanoma > Exchange Advocate Forum. "You really have to be the CEO of your own health," said melanoma survivor and patient advocate T. J. Sharpe.

Melanoma physician Sapna Patel agreed. Patel, an Associate Professor in the Department of Melanoma Medical Oncology at The University of Texas MD Anderson Cancer Center, noted that although there are things you can't control, such as treatment side effects, there is a lot you can and should be proactive about, including finding the information you need, identifying a clinical trial if appropriate, expressing your wishes and values in regards to your treatment, and managing your supportive team of caregivers and family members.

Finding the Right Information About Melanoma

"What you don't know can hurt you," said Patel. Sharpe added, "Be informed. Do research to understand what the doctor has given you, and what your questions are ahead of time." However, he recognized how overwhelming all the information can be, especially when it is surrounded by so much misinformation that can show up in a Google search. "The hardest thing is finding the right information," Sharpe stressed, and noted a number of good sources for information about melanoma, including the MRA website CureMelanoma.org. He also suggested reaching out to fellow patients who have a unique perspective. Patel pointed out that just like for print media, when scouring the internet, make sure resources are reliable and cite credible sources for their information. "You have to be careful about the information out there," she said. "Although patient blogs can be helpful, they can suggest treatments or tests that worked for them, but may not work or even be appropriate for you."

Get Copies of Your Test Results

Sharpe suggested that patients work to understand their own diagnosis and treatment options, and melanoma survivor and advocate Mark Gorman suggested patients acquire printed copies of all their scan and test results. He noted terrible outcomes he has seen happen because a scan wasn't communicated to the patient and proper physician. Sharpe agreed, noting he once received a scan report from the emergency room that recommended further follow up that the staff at the emergency room never communicated to him or his regular care team. Patel added that this is why it is important to get scans done before patients see their oncologists so the doctor can review and interpret them together and avoid miscommunication about what those results mean.

Getting a Second Opinion for Melanoma

Part of gathering the right information about your condition is to seek out second opinions or even third or fourth opinions. "It's natural to want to believe in your doctor, but that doesn't mean that he or she knows everything. It's okay to tell your doctor that you want another opinion, and good doctors will encourage you to get one about your diagnosis or treatment plan, especially if you are being seen at a small facility that doesn't have clinical trials or all the treatment options," Sharpe said. Patel agreed, noting that "Second opinions are a must when you are dealing with life and death like we are with cancer."

Join the Online Community

MRA's **Melanoma > Exchange** is a free online melanoma treatment and research focused discussion group and support community.

The community is led by patients and survivors who have been personally touched by melanoma – including T.J. Sharpe.

Join the Melanoma > Exchange at
CureMelanoma.org/Community

But Patel cautioned about seeking out so many opinions that it causes delays, which can hamper treatment. "If it gets to be like Baskin Robbins and hard to decide what flavor of treatment to have, and that decision takes three months, the delay can be harmful. I tell patients to act sooner rather than get more opinions, and encourage patients I work with to set a treatment decision deadline so they are not forever searching for opinions," she said. Maura Flynn, a participant in the forum, also pointed out the importance of having an accurate diagnosis and seeking out a pathologist who specializes in identifying skin conditions (dermatopathologist) to provide a second opinion on your skin biopsy, if it was initially examined by a non-specialist.

See a Doctor Who Treats Many Melanoma Patients

Gorman noted that it is also important to see physicians who are experts in the type of cancer you have, especially for rarer cancers like melanoma. “The less common the cancer, the more effort is needed to find a team that sees more of it,” he said adding, “You are best served by finding someone for whom melanoma is more common than not.” This is especially true when facing rarer melanoma subtypes, including uveal, acral, and mucosal melanoma. Patel agreed, saying “General oncologists have to be abreast of all types of cancer and can’t keep up with everything. You are looking out for yourself, whereas the doctor is looking out for a cadre of patients.”

Seek out Information About Clinical Trials

Before you start to make treatment decisions, you should get up to speed on all of your options – including clinical trials. This is particularly important for patients with advanced stages of melanoma. Patel noted that patients on clinical trials tend to get better care because they are so closely monitored. “Clinical trials add to the standard of care,” she stressed. Sharpe agreed, pointing out that clinical trialists apply the most up-to-date science in their care of patients. “It’s likely you won’t get worse treatment, and often you get better care when you are part of a clinical trial,” he said.

Make Your Needs and Wishes Known

Patel noted that although it is the doctor’s job to educate the patient about their condition, he or she also has to respect how much a patient wants to know. She suggested patients convey this to their practitioners, family, and caregivers. For example, not all patients want to know their prognosis, and many just want to know what the next step is ahead of them. Often family members want to know the prognosis and the patient doesn’t, she said. “Family and caregivers all have to be on the same page as the patient about this,” Patel stressed. They also have to be on the same page about what treatment the patient wants, Sharpe added. A younger patient may want aggressive treatment no matter how low the odds of success, while an older patient might want supportive care that minimizes side effects. “Express your wishes and values to your caregivers, family, and doctors,” Sharpe emphasized.

Bring Someone to Your Appointments

It is also important to have family and caregivers at meetings with your doctors. “They need to be there to support, listen, and write down the information because it may be hard for you to comprehend and remember what is said when you are so worried about your future,” he said. Patel agreed, noting that when family or caregivers come to an appointment, “they are a second set of eyes, ears, or even a voice,” for the patient and they can also help patients determine and write down their questions before meeting with their healthcare providers.

Lisa Simms Booth, Sapna Patel, and T.J. Sharpe

Keep Everyone on the Same Page

But taking control of your health also requires you to take control of your support team, Sharpe pointed out. “I was the quarterback of my caregiving team and had family members doing different things to help, while the head coach was the doctor and medical team. When everyone functions well together, it works well,” Sharpe said. Patel suggested that patients indicate a point person on their caregiving/family team to communicate with the doctor. “I want everyone who cares about the patient to come and be involved, but I don’t have the bandwidth to handle five different phone calls about the same patient,” she said.

Cut Things Out that Don’t Bring You Joy

Taking control may also involve limiting your social circle and saying no to lunch dates, family gatherings, or other social interactions that may be more energy draining than gaining. “You need to cut out the things in life that aren’t bringing you joy,” Patel said. “It’s your life not theirs, so take control of it!” Sharpe added.

Grace Wenzel

Missy Rand

WHAT COMES NEXT? THE NEW NORMAL AFTER MELANOMA

Rachel Vogel, Tracy Callahan, Lauren Miller, and Dan Engel

Although many patients and their loved ones would like to put melanoma behind them, it tends to be a lifetime journey, pointed outDr. Rachel Vogel, of the University of Minnesota, who lost a brother to cancer, and now devotes her research to better understanding the needs of cancer survivors. “A cancer diagnosis is life changing,” she stressed when moderating a panel discussion at the MRA Melanoma > Exchange Patient Forum. The panel brought together Tracy Callahan, a four time early-stage survivor, Dan Engel, a 20-year stage 4 survivor, and Lauren Miller, who’s twin sister died from the cancer in 2014, to discuss the impact of melanoma on patients and their loved ones. From life-long prevention concerns, fear of recurrence, feelings of isolation, and survivor’s guilt – the panel and the audience shared candidly about the ‘new normal’ after melanoma.

Life-Long Vigilance

“I thought once they cut out my melanoma, I would be done. But I quickly found out it is not one and done,” said Tracy Callahan, who was first diagnosed with early-stage melanoma at the age of 38. Since then, she’s had countless biopsies and has been diagnosed with melanoma an additional three times. “I thought if you cut it out, you could be done, but I have to meet my doctor every three months,” she said.

Vogel stressed that once you have melanoma, the risk for being diagnosed with another melanoma is nine times greater than that for the average person. Melanoma patients have to be vigilant about regular checkups, body scans, and sun safety.

Managing Anxiety

The panel also discussed the anxiety of ‘living scan to scan’ and not knowing what the results would suggest. Callahan mentioned that each and every biopsy plagues her and her children with anxiety. “I’ve found that humor is the best way for me to deal with it. I either laugh about it – or I cry,” says Callahan. She wears superhero underwear for all her doctor visits. “Humor is great medicine,” she said.

Lauren Miller, shared how her sister Tara demanded humor and positivity of everyone. “She was just hilarious on her blog, and made a point of having fun and making the best of it – and that really set the tone for our family as we handled her illness.” For example, “she had a post-brain-surgery party,” she said.

Dan Engel, a long-term melanoma survivor who was first diagnosed with Stage 4 melanoma in 1999, suggested one way to help counter the anxiety of a melanoma diagnosis is to “never let the odds dictate anything. You are the only statistic that matters.” This sentiment is particularly important as more information becomes available online. Statistics don’t lie, but they aren’t always presented in a useful or non-biased way. For all of the ‘miracle stories’ that are told about modern medicine there are still people who aren’t benefiting. On the flip side, sometimes patients respond to something that can’t be fully explained by the data we have available. “Statistics are important, but they shouldn’t dictate you,” says Engel.

Engel also suggested expressing gratitude more often. “The fastest way to reduce blood pressure is to say ‘thank you.’ I’m thankful I’m alive every day,” he said.

Speaking from the audience, Mark Gorman, suggested patients undergoing active treatment make a point of taking the weekends off or giving themselves (and their loved ones) opportunities to take a break from thinking about their cancer to spend it enjoying family and friends. “Whatever you are worrying about Friday afternoon will keep until Monday. If you’re trying to think about what comes next, don’t lose sight that one of the reasons you are being treated is to spend time doing things that don’t have anything to do with cancer,” he stressed.

Heather Davis and Jamie Goldfarb

Finding Your Tribe

A cancer diagnosis can be isolating. Even when you are surrounded by loving friends and family – it's almost impossible for them to fully understand what you are going through, several participants noted. "Those you think will always be there disappear, and sometimes the people you didn't expect - just 'get it' and intuitively know how to help you," Engel noted.

Callahan agreed that she had incredible friends, but they didn't fully understand what she was going through, unlike other melanoma patients and their caregivers who she called her "melahomies." She suggested after a melanoma diagnosis, that you "find your tribe, your support. It's amazing how many of us are out there and need to talk about it, and it's so great when we find each other and can talk openly." Miller added that she found the melanoma community of patients and family members to be more understanding of what she was going through than her good friends. "They understand that sometimes you just need to have a melt down and accept it," she said.

"The Melanoma > Exchange online community, hosted by MRA, is a great example of a virtual resource where people affected by melanoma can get support and share experiences," offered Vogel. "Sometimes, it's even easier to let your guard down with a screen separating you."

Engel also stressed the importance of steering clear of people that add stress to your life. "Cancer is the perfect trump card. When someone asks you if you want to come over for dinner, you can say no because you have cancer," he said. He added, "If there's any time to be selfish, it's when you are dealing with cancer because it's your life that is in danger." Callahan added that it is important to "be kind to yourself and remember you don't have to be the strongest person in the room always." One melanoma patient in the audience noted that insisting cancer patients be positive and strong can place a huge burden of guilt on the patient if he or she doesn't feel so heroic. "There are a lot of us who don't feel that way, and it's not our fault," he said, to a loud round of applause.

"This is a particularly important in an era where cancer is frequently described using war or battle metaphors," said Vogel. "Today, despite every research advance or the heroic efforts by patients, doctors, and scientists alike some people still die from melanoma. It's not because they didn't try – and that's important to keep in mind."

Mary Colette Coyne

Overcoming Survivors' Guilt

Several participants spoke of the survivors' guilt they experience, and how they try to alleviate it by giving back to support other patients, advance research, or raise awareness. "Survivors' guilt is difficult, but being able to give back to the melanoma community helps me overcome those feelings," said Callahan.

"I'd like to figure out a way that science can learn from me," Engel said, noting that survivors could contribute their blood and tissue specimens to research aimed at understanding who responds to immune and other innovative treatments and why. Gorman noted that the National Cancer Institute has just started collecting data on long-term survivors of cancer, which is "an opportunity not to be missed," he said.

Another way to support melanoma research is by participating in or raising awareness about the importance of clinical trials. MRA's recently launched *Fight Back Give Back* campaign offers free resources to help patients and their loved ones understand how clinical trials work and the importance they play in patient care and the research process. In addition to accessing experimental treatments, there are also many studies that need healthy volunteers as a control population.

Miller said that every passing birthday she doesn't share with her sister has been difficult for her, and she has questioned why her sister, with whom she did everything, died from melanoma, while she lives on. Her way of dealing with that guilt is to help her family carry on her sister's legacy – the Tara Miller Melanoma Foundation – to support and help advance melanoma research. "My sister dreamed of a cure for melanoma that would make sure the next person in her shoes didn't have to go through what she did," she said. To date, the foundation has donated more than $2.4 million to support research, including 4 MRA Young Investigators. "Her marching orders were to focus on her foundation and find some silver lining."

Wayne Conners

Lauren Miller and Jeff Rowbottom

AGENDAS

ELEVENTH ANNUAL SCIENTIFIC RETREAT

February 25 – February 27, 2019, Washington, DC

Monday, February 25

7:30am-5:00pm	Grant Review Committee Meeting (by invitation only)……Plaza Ballroom
12:30-5:00pm	Melanoma Advocates & Foundations Forum (by invitation only)……Salon I
4:00-8:00pm	*Registration Open……Outside of Salon Ballroom*
6:00-7:30pm	**Opening Reception……Salon III**

Tuesday, February 26

6:30am-6:00pm	*Registration……Foyer of Salon III*
7:00-8:15am	General Breakfast……Salon III
7:00-8:15am	Young Investigators Breakfast (by invitation only)……Plaza Ballroom
8:30-8:45am	**Opening Remarks Day 1……Salon I & II** Michael Kaplan, MRA President & CEO Heather Davis, Patient Advocate Louise Perkins, MRA Chief Science Officer Emerita Marc Hurlbert, MRA Chief Science Officer
8:45-9:15am	**Lecture:** **Antoni Ribas, University of California, Los Angeles:** Novel combination therapies for melanoma
9:15-11:00am	**Session I: Overcoming resistance to targeted and immunotherapy** ***Chair: Caroline Robert, Institut Gustave Roussy***
9:15-9:35	**Willy Hugo, University of California, Los Angeles:** Immune evasion mechanisms in MAPKi and anti-PD1-treated melanoma
9:35-9:55	**Vashisht Yennu Nanda, MD Anderson Cancer Center:** Targeting mitochondrial activities to overcome melanoma resistance to standard of care treatments
9:55-10:15	*Break*
10:15-10:35	**Poulikos Poulikakos, Icahn School of Medicine at Mt. Sinai:** Next generation strategies to target oncogenic RAS/ERK signaling
10:35-11:00	**Caroline Robert:** Translation inhibitors to overcome therapeutic resistance
11:00-11:20am	**Marlana Orloff, Thomas Jefferson University:** Unique geographic accumulations of uveal melanoma: A Special Update
11:20-11:50am	**Lecture: Ugur Sahin, Johannes Gutenberg-Universität Mainz:** RNA vaccines for melanoma
11:50 am-12:00 pm	*Transition to lunch*
12:00-1:05pm	**Lunch: Focused roundtable discussions/Networking……Salon III**

1:05-1:20pm	*Transition to room*
1:20-2:50pm	**Session 2: The melanoma tumor microenvironment**
	Chair: Ashani Weeraratna, The Wistar Institute
1:20-1:45	**Yardena Samuels, Weizmann Institute of Science:** Towards deciphering the neo-antigenic and microbial landscapes in melanoma
1:45-2:05	**Ping-Chih Ho, University of Lausanne:** What you eat makes you strong and vulnerable: Metabolic targeting of intratumoral Tregs for cancer treatment
2:05-2:25	**Nikhil Joshi, Yale University:** Developing NINJA mice for studying anti-tumor immunity
2:25-2:50	**Ashani Weeraratna:** The Matrix Reloaded: How the aging extracellular matrix affects metastasis, angiogenesis, and therapy response
2:50-3:10pm	*Break*
3:10-4:00pm	**Session 3: Novel models for studying melanoma**
	Chair: Nina Bhardwaj, Icahn School of Medicine at Mount Sinai
3:10-3:35	**A. Thomas Look, Dana-Farber Cancer Institute:** Zebrafish models to optimize melanoma cell death during therapy
3:35-4:00	**Nina Bhardwaj:** Melanoma models for translational assessment of neoantigen-based vaccines
4:00-4:30pm	**Lecture: Sancy Leachman, Oregon Health and Science University:** Oregon's War on Melanoma: A Public health early detection experiment
4:30-4:35pm	**Closing Remarks Day 1** Kristen Mueller, MRA Scientific Program Director
4:45-6:15pm	**Young Investigator and Pilot Awardee Poster Session…..……..……Salon III** *Open to all retreat attendees*
6:30-9:00pm	**Reception and Dinner…….……Zaytinya** Dress: Casual 701 9th St NW Reception: 6:30-7:15pm; Dinner 7:15pm

Wednesday, February 27

6:30-10:00 am	*Registration open……Foyer of Salon III*
7:00-8:30 am	General Breakfast……Salon III
7:00-8:30 am	Industry Roundtable Breakfast (by invitation only)……Plaza Ballroom
8:40-8:45 am	**Opening Remarks Day 2 ……Salon I & II**
	Marc Hurlbert and Kristen Mueller
8:45-9:15am	**Lecture: Kim Margolin, City of Hope:** Melanoma: From skin to brain, laboratory to clinic
9:15-11:45am	**Session 4: Next generation technologies for melanoma treatment and detection**
	Chair: Janis Taube, Johns Hopkins University
9:15-9:35	**Sidi Chen, Yale University:** Genome scale identification of genes regulating melanoma metastasis
9:35-10:00	**Hidde Ploegh, Boston Children's Hospital:** Non-invasive imaging of the response to checkpoint blockade in melanoma as a prognostic tool
10:00-10:20	**Alan Hunter Shain, University of California, San Francisco:** Single cell genotyping to reveal melanoma's origins
10:20-10:50am	*Break*
10:50-11:15	**Sean Bendall, Stanford University:** Composition and structure of the human immune system to predict and control pathobiology
11:15-11:40	**Janis Taube:** Astronomy accelerates pathology: Multiplex immunofluorescence imaging of the melanoma tumor microenvironment
11:40am-12:20pm	**Panel Discussion:** Employing novel technologies to advance melanoma diagnosis, prognosis and treatment *Moderator: Jonathan Simons, Prostate Cancer Foundation* *Panelists: Lynda Chin, University of Texas System* *Anne Fischer, Defense Advanced Research Projects Agency* *Allan Halpern, Memorial Sloan Kettering Cancer Center* *Sean Khozin, Food and Drug Administration*
12:20-12:30pm	**Closing Remarks** Michael Kaplan and Marc Hurlbert
12:30-1:30 pm	**Lunch and Departures……Salon III**

MELANOMA > EXCHANGE ADVOCATE FORUM

February 25, 2019, Washington, DC

12:30 pm- 1:10 pm	**Lunch & Networking**
1:10 pm – 1:15 pm	**Welcome Remarks** Michael Kaplan – President & CEO, Melanoma Research Alliance
1:15 pm – 1:30 pm	**Introductions: Who We Are. Why We Are Here.**
1:30 pm – 2:20 pm	**On Giants' Shoulders** Learn where we are, where we've been, and where research is taking us. Brent Hanks, M.D., Ph.D. – Duke Cancer Institute, Duke University Medical Center
2:20 pm – 2:30 pm	*Break*
2:30 pm – 3:20 pm	**Panel Discussion: Be Your Own Best Advocate** From asking questions, getting a second opinion, and doing your homework – get tips and insight into how you can be an advocate for yourself or those you love! T.J. Sharpe – Melanoma Advocate Sapna Patel, M.D. – University of Texas, MD Anderson Cancer Center Moderator: Lisa Simms Booth – Biden Cancer Initiative
3:20 pm – 3:45 pm	**Ask the Expert: The Microbiome** What does your gut have to do with immunotherapy? Jennifer McQuade, M.D. – University of Texas, MD Anderson Cancer Center
3:45 pm – 3:55 pm	*Break*
3:55 pm – 4:20 pm	**Ask the Expert: Understanding the Evolution of Melanoma** This MRA-funded investigator is studying the genetic changes needed for melanoma to form. Alan Hunter Shain, Ph.D. – University of California, San Francisco
4:20 pm – 5:10 pm	**What Comes Next? The New Normal After Melanoma** Hear from survivors and families honoring their loved one. Tracy Callahan – Founder & CEO, Polka Dot Mama Foundation Dan Engel – Founder, Patient True Talk Lauren Miller – Tara Miller Melanoma Foundation Moderator: Rachel Vogel, Ph.D. – University of Minnesota
5:10 pm – 5:30 pm	**Closing & Wrap Up**
6:00 pm – 7:30 pm	**MRA Advocate & Researcher Reception**

Keep the conversation flowing on the Melanoma > Exchange online discussion community.
CureMelanoma.org/Community

Kim Margolin

Michael Kaplan

MRA Young Investigator Awardees

Eva Hernando

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