

**THE NEXT FRONTIER IN
MELANOMA RESEARCH**

Melanoma
Research Alliance

Highlights of the Melanoma Research Alliance Eighth Annual Scientific Retreat

FEBRUARY 24-26, 2016 WASHINGTON, DC



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INTRODUCTION

The last few years have seen incredible progress for melanoma patients with 11 treatments approved since the founding of the **Melanoma Research Alliance (MRA)**, a public charity launched in 2007 by Debra and Leon Black under the auspices of the Milken Institute that aims to end suffering and death due to melanoma by collaborating with all stakeholders to accelerate powerful research, advance cures for all patients, and prevent more melanomas. As the largest non-profit funder, MRA has now awarded **more than \$79 million** to 198 innovative, translational research programs being conducted in 15 countries. Through our unique collaborative approach, MRA has leveraged an additional \$81 million, infusing a total of more than \$160 million toward melanoma research. Despite the amazing clinical progress against the disease, not all patients benefit even from current therapies. There is a continued need for research to advance the next generation of tools and treatment for patients and those at risk.

“We want to work with you to advance this field.”

As part of its mission to accelerate the field, MRA promotes collaboration within and across sectors, and the annual Scientific Retreat is one important forum for this engagement, providing an invitation-only, think-tank setting to share the latest findings and forge new partnerships in pursuit of better outcomes for patients. This year’s **Eighth Annual Scientific Retreat**, held in Washington, DC on February 24-26, 2016, included almost 300 thought leaders. Attendees comprised academic scientists and representatives from pharmaceuti-

cal and biotechnology companies, government, and philanthropy as well as patients and their families. The program featured leading scientists who reported on the progress of their research as well as several special sessions covering key clinical, scientific, and regulatory issues that need to be addressed to continue to accelerate progress for patients.

There were several underlying themes in the research presented at the Scientific Retreat all building on the inspiring advances in developing effective melanoma treatments over the past five years. Additional themes were the need to:

- further refine melanoma therapy by combining treatments so they are active for more patients and less toxic;



Michael Milken, Louise Perkins, Margaret Anderson, Robert Califf

- define biomarkers that indicate the right treatment for the right patient at the right time; and,
- uncover new targets for additional treatments.

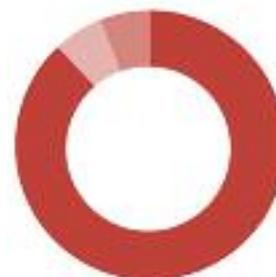
Many presenters highlighted the growing appreciation of the importance of the local tissue that surrounds melanoma tumors - the tumor microenvironment. Researchers recognize that the potential of immunotherapies is just being tapped, with many checkpoint inhibitors and tumor vaccines on the horizon, and that these treatments are likely to be especially effective when used in combination therapy regimens. New targets continue to emerge from laboratory studies moving beyond the genomic alterations in tumors that result in mutated proteins to include changes in microRNAs that regulate genes and the proteins that are ultimately produced. Studies on how melanoma evolves as the disease progresses and in response to treatment also provide new potential drug targets for metastases as they reveal genetic alterations in metastases not present in the primary tumor. Given the potential opportunity to prevent advanced metastatic disease via early detection, speakers discussed the latest activities and tools to catch melanoma before it spreads.

The pace of change in melanoma is truly dramatic and with new kinds of treatments and biomarkers comes the need for new ways to assess them earlier and better. After having just been sworn in as the **Commissioner of the U.S. Food and Drug Administration (FDA), Dr. Robert Califf** noted the increasing importance of better interlinking of drugs, biologics and devices that may be used concomitantly. “We will have to think how to regulate that differently than we did in the past as there needs to be more integration,” he said. He added that FDA is currently considering ways to continue to break down silos and work with all stakeholders to advance innovation. “We

Distribution of MRA funding

Total:

\$79.1 M



\$3.8 M

Diagnosis/Staging

\$3.7 M

Prevention

\$71.6 M

Treatment

want to work with you to advance this field,” he said. Other recent initiatives at the federal level, notably the National Cancer Moonshot, will also focus on enhancing collaboration between scientists and sectors and developing systems that encourage data sharing. At the center of all of these efforts are the patients and those at risk. Increasing participation in clinical trials and research, with patients as partners, is vital to continue to develop better prevention, diagnostic, and treatment approaches for melanoma and push forth the next frontier in melanoma research.

11

New therapies approved by the FDA to treat melanoma since MRA's founding.

NEW THERAPEUTIC TARGETS

Reaping what they discovered from their investigations into what furthers the growth of melanoma tumors and metastases, researchers reported a number of new potential targets for melanoma drugs. These targets include components of the PI3K/AKT/mTOR oncogenic pathway that appear to be especially important in fostering brain metastases – a particularly vexing problem in the management of melanoma. Also apparently crucial for such metastases are immune-regulating cytokines released by certain brain cells, while an enzyme that fosters lipid uptake by tumors appears to feed melanoma metastasis in general. Investigators also reported new potential targets for immunotherapy such as TGF-beta and gamma interferon signaling, novel checkpoint inhibitors as well as the excess of intracellular potassium that can hamper the functioning of tumor infiltrating lymphocytes (TILs) that act to fight melanoma growth.

NOVEL IMMUNE CHECKPOINTS

Dr. Gal Markel of Sheba Medical Center began his presentation by noting that despite the remarkable successes of current immunotherapies for melanoma, a lack of response or emergent resistance to these therapies by some patients underlies the need to identify new mechanisms and targets for this type of treatment. His research, funded by the Saban Family Foundation-MRA Team Science Award, focuses on the interaction between melanoma tumor cells and TILs because that is the crucial physiological frontline in the immune system's killing of tumor cells, he said. Using biopsy tissue and serum specimens from 40 melanoma patients who have undergone adoptive T cell therapy (ACT), he and his team analyzed the microRNA of their TILs in the tumors, as well as did proteomic analyses of tumor and plasma specimens to try to learn from the differences between responders and non-responders.

These analyses revealed that many proteins whose production is altered in tumors also regulate the immune

system, including those that govern TGF-beta and gamma interferon signaling. Two of these proteins may be ligands for activating receptors on TILs, as their expression correlates with TIL function in vitro, and response to ACT in patients. These proteins are regulated by microRNAs in the tumor, he discovered. Other proteins differentially expressed in responders versus non-responders were related to the regulation of the mitochondria, the powerhouses of cells. "Perhaps tumor cells, which are highly active metabolically, depend on mitochondria and it is an Achilles heel of the tumor," he said, adding that this remains to be proven and will be investigated in future studies. Dr. Markel also reported that his lab had previously identified CEACAM1 as a novel immune checkpoint that is induced by interferon. He developed a blocking antibody to it, which is being tested on melanoma patients in a Phase 1 study.

ICOS SIGNALING

Dr. Padmanee Sharma of MD Anderson Cancer Center reported on her findings that indicate the signaling pathway for inducible T-cell costimulator (ICOS), a novel checkpoint immune system regulator, could be an important potential drug target for melanoma and other cancers. Her studies in bladder cancer and melanoma patients undergoing anti-CTLA-4 treatment found increased ICOS signaling correlated with the treatment, leading to the hypothesis that ICOS would be an effective pathway to target and develop for combination therapy with anti-CTLA-4 drugs or other immunotherapies. This hypothesis was supported by work in mice (funded through a MRA Young Investigator Award) that revealed ICOS stimulation combined with anti-CTLA-4 cured 80 percent of mice with melanoma. She noted that ICOS-targeting treatments are currently being evaluated in several ways, including studies on a tumor cell vaccine that increases expression of the ICOS ligand and two different proteins that turn on ICOS signaling. Dr. Sharma's lab also discovered increased VISTA expression in two

different immune system cells—T cells and macrophages—after patients were treated with anti-CTLA-4. These data suggest VISTA as another target for combination approaches.

A key question for cancer immunotherapy is why do some patients respond and others do not? Dr. Sharma noted that tumors with a higher mutational load are more likely to respond to immunotherapy due to high mutational load enabling higher T cell infiltration into tumors but added that tumors with lower mutational load may be treated in order to drive T cell infiltration into tumor tissues. However, Dr. Sharma noted, “if we drive T cells to the tumor without turning off immune inhibitory pathways, it’s likely the T cells won’t do their job well.” Immune inhibitory pathways can be blocked by already available checkpoint inhibitors, such as anti-CTLA-4 or anti-PD-1/PD-L1, as well as potentially by other checkpoint inhibitors such as anti-VISTA. She suggested targeted and other therapies that boost T cell infiltration into tumors by killing tumor cells and creating an inflammatory tumor microenvironment could be given in combination with immunotherapy. To enable research and development of combination immunotherapy strategies, Dr. Sharma advocated for biomarker-based studies, such as pre-surgical and tissue-based clinical trials, which provide a platform to study biologic effects within tumor tissues and provide insights into mechanisms as well.

ENGINEERED T CELLS

The effectiveness of TILs in the tumor microenvironment appears to be affected by levels of potassium there, **Dr. Nicholas Restifo of the U.S. National Cancer Institute** reported. Potassium ions are present in all animal cells but are rare in extracellular fluid. When tumor cells die, however, they release potassium, which appears to shut off T cell immunity, Dr. Restifo’s findings suggest. He found that elevated potassium inhibited tumor-fighting CD8 T cells as measured by



Padmanee Sharma

“If we drive T cells to the tumor without turning off immune inhibitory pathways, it’s likely the T cells won’t do their job well.”

the amounts of interleukin 2 and gamma interferon they released, and also inhibited TIL responses directed at new antigens made by tumor cells. “CD8 cells don’t die but stop being effective,” Dr. Restifo said, adding that excess potassium “shuts down a lot of genes and alters production of some of the most important molecules T cells produce.” Notably, he found that excess potassium affected AKT-mTOR signaling, specifically through the activity of the enzyme protein phosphatase 2 (PP2A). By genetically engineering T cells to over-express a potassium ion transporter that decreased intracellular potassium levels, he was able to restore their production of cytokines and functioning and improve their ability to destroy melanoma cells in vitro as well as in vivo in an animal model. The next step will be to figure out if such genetically engineered T cells can influence anti-tumor function in human clinical trials.

“We can see single metastatic cells arrive at new locations with this model.”

ADIPOCYTES

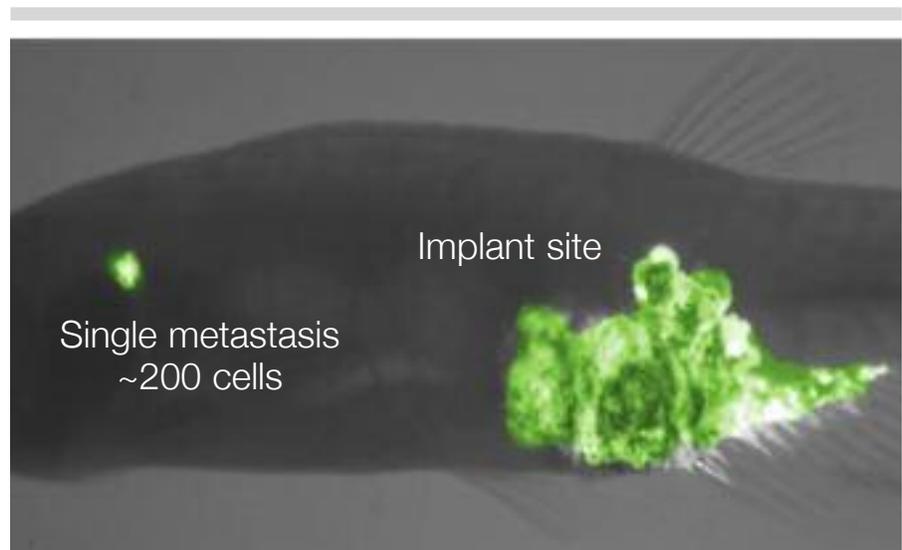
MRA Young Investigator **Dr. Richard White of Memorial Sloan Kettering Cancer Center** used a transparent zebrafish called Casper along with glow-in-the-dark fluorescent melanoma cells to try to uncover what key steps are involved in melanoma metastatic spread in a living organism. He injected this fish with fluorescent melanoma cells and then detected and sampled glowing metastases as they developed over time. “We can see single metastatic cells arrive at new locations with this model,” Dr. White noted. Dr. White analyzed gene expression using state-of-the-art RNA sequencing from the fish metastases. He found signaling pathways governing lipid synthesis and transport were altered, suggesting that metastatic tumor cells increase lipid uptake from extracellular sites rather than synthesize fats themselves. This led to an emerging hypothesis that lipid-laden fat cells (adipocytes) increase the growth of melanoma cells, which Dr. White later confirmed with in vitro studies using human melanoma cell lines. He then discovered a class of lipid transporters increased when adipocytes were co-cultured with melanoma cells, and that blockade of these transporters markedly impairs

melanoma growth. Dr. White concluded that fat transporters may be a promising new tumor microenvironment target in melanoma treatment.

MOLECULAR DRIVERS OF BRAIN METASTASES

Treatments for melanoma brain metastases are increasingly important as newer therapies effectively control tumors in all other parts of the body for many patients. Brain metastases may be resistant to treatment due to inadequate penetration of the treatment into brain tissue, or because there is a different complement of genetic drivers of melanoma in brain metastases compared to disease that spreads to other parts of the body. To help explore the latter, MRA Young Investigator **Dr. Priscilla Brastianos of Massachusetts General Hospital** compared the genomes of brain metastases to those of primary tumors in melanomas and other cancer types. She found that brain metastases harbored distinct clinically actionable genetic alterations compared to biopsies of primary tumors. In addition, different brain metastases

Visualizing Melanoma Metastasis Using Zebrafish



Courtesy of Richard White

from the same patients harbored many of the same mutations and were more closely related genetically to each other than to the primary tumor, even when they were sampled at different times. In about 53 percent of the cases, Dr. Brastianos found genetic changes in brain metastases that were not detected in the clinical samples of the primary tumors and some of these are known drug targets. The most common changes affected sensitivity to cyclin-dependent kinase (CDK) inhibitors that are currently being tested in melanoma patients. Mutations affecting the PI3K/AKT/mTOR pathway were also prevalent. Dr. Brastianos stressed that “extracranial metastases are not a reliable surrogate for brain metastases,” and noted that a molecularly-guided brain metastasis trial is currently underway in which patients will be given appropriate inhibitors based on the genomics of

“We are using nanomedicine to catch tumor cells while they are still circulating.”

their brain metastases. She was not able to discern from her data if the common mutations in brain metastases were driving the growth of these tumors, but hopes that targeting lesions in the brain might be able to improve survival of melanoma patients.

A key cell type needed for melanoma metastases to invade and thrive in the brain appears to be astrocytes, mouse and in vitro studies done by **Dr. Ronit Satchi-**



MRA Young Investigators



Ronit Satchi-Fainaro

Fainaro of Tel Aviv University suggest. These studies performed together with Neta Erez of Tel Aviv University and Zvi Ram and Rachel Grossman of Tel Aviv Medical Center, are supported by a Saban Family Foundation-MRA Team Award. Activated astrocytes can be observed surrounding melanoma metastases in both mouse models and in melanoma brain metastases tumor samples from patients. These cells overexpress inflammatory cytokines, and receptors for these cytokines are overexpressed in melanoma brain metastases, Dr. Satchi-Fainaro discovered. She also found that when she added astrocytes to melanoma cell culture medium, the tumor cells migrated faster through a membrane towards the astrocytes. Moreover, both in vitro and in vivo studies found leaky blood vessels (hyperpermeability) were linked to the presence of astrocytes. These findings led to the conclusion that when melanoma cells leave the primary site and circulate into the brain, they secrete cytokines that cause activation of astrocytes. These brain cells then secrete their own set of inflammatory cytokines that cause blood vessels to be more permeable, enabling more melanoma cells to migrate from the blood towards activated astrocytes in the brain, where they establish metastases. To counter the metastases-promoting effects of astrocyte cytokines, a polyplex nanocarrier was developed that silences key cytokines secreted

from activated astrocytes or silences the receptors on melanoma cells for those cytokines. A similar nanocarrier for both the BRAF inhibitor dabrafenib and the MEK inhibitor selumetinib inhibited melanoma cell migration as well as reduced the proliferation of melanoma tumors and brain metastases, in in vitro studies, Dr. Satchi-Fainaro reported. "We are using nanomedicine to catch tumor cells while they are still circulating," she explained.

DRUG TARGETS FOR ACRAL AND UVEAL MELANOMAS

Uveal melanomas, which develop in the eye, and acral melanomas which arise on nail beds, palms, and soles, are rare melanomas that tend not to respond well to current therapies that work for more common cutaneous melanomas. Several studies presented at the meeting suggest that acral and uveal melanomas genetic drivers are both similar and different from those of cutaneous melanomas, spurring the search for new drug targets for these aggressive diseases.

Dr. Nicholas Mitsiades of Baylor College of Medicine noted that microphthalmia-associated transcription factor (MITF) is well-known for driving the proliferation, survival and metastasis of uveal melanomas. But MITF is not a druggable target so Dr. Mitsiades explored ways to indirectly target this driver gene in melanomas of the eye through research supported by a Stewart Rahr-MRA Young Investigator Award. When he molecularly characterized uveal melanoma cells, he found that a protein called bromodomain 4 (BRD4) is closely associated with genes that are under the influence of MITF. A known inhibitor of BRD4, called JQ1, was used to explore whether interfering with BRD4 might also interfere with MITF function and therefore melanoma growth. The research revealed that, similarly to what is seen with genetic silencing of MITF, JQ1 could also decrease the transcription of MITF-regulated

genes. And while early in the treatment, MITF levels in the melanoma cells are not changed, with longer treatment or in the presence of more drug, MITF itself starts to be lost in cells. This is noteworthy since targeting transcription factors like MITF with drugs has been particularly problematic and yet such targets are known to be very important in tumor cell growth. Dr. Mitsiades showed that JQ1 had anti-cancer activity in uveal melanoma cell lines and mouse xenografts. His results with JQ1 suggest that BRD4 inhibitors, which are already in clinical development for other types of cancer, might be able to modulate MITF levels and activity and thus slow or kill melanoma cells in a different way from other treatments used today. “BRD4 inhibitors promise for the treatment of uveal melanoma,” he concluded.

A pair of studies supported by Hidary Foundation-MRA Team Science Awards was reported on at the retreat by research teams aimed at understanding the genetic drivers of acral melanomas. Each team used similar approaches to study genetic changes in acral melanoma tumor samples. This information was previously available for only a handful of acral melanoma patient samples. **Dr. Maryam Asgari of Massachusetts General Hospital and Dr. Iwei Yeh of University of California, San Francisco** pointed out that the genetic drivers were not known for more than half of acral melanomas, in part because it is hard to acquire tumor samples given that it is a rare subtype of melanoma. The research team relied on the large and rich clinical and tumor data from 121 acral melanoma patients in the database of the health insurer Kaiser Permanente, as well as 58 acral melanoma specimens acquired from the University of California in San Francisco. Targeted sequencing of these patient samples identified genetic drivers in over 70% of acral melanomas. Many mutations the researchers detected in the acral melanoma samples have also been found in cutaneous melanomas. These genetic alterations

“We detected known and novel mutations in the tumor samples that suggest new potential targets for treatment.”

include BRAF-activating mutations in 20 percent of tumors and KIT mutations in 11 percent. RAS mutations were identified in 27 percent of cases and included an increased frequency of exon 2 mutations (codons G12 and G13) as compared to cutaneous melanoma. Six percent of cases harbored a kinase fusion in a mutually exclusive pattern with RAF and RAS activating mutations. The research team also found telomerase reverse transcriptase (TERT) mutations occurred at a lower rate (27 percent) in the acral melanoma samples compared to cutaneous melanoma with a corresponding increase in TERT amplifications. “We detected known and novel mutations in the tumor samples that suggest new potential targets for treatment,” Dr. Asgari concluded.

Dr. Jeffrey Sosman of Vanderbilt University Medical Center and Dr. Jeffrey Trent of Translational Genomics Research Institute (TGen) conducted a comprehensive genomic and transcriptome analysis of 37 acral melanoma tumor specimens obtained from 34 patients, all with extensive clinical annotation. As expected from the study of cutaneous melanoma, they found commonly altered genetic pathways, including the MAPK pathway critical to cell proliferation and survival, the CDK4/CDKN2A pathway that governs cell cycle progression, the MDM2/TP53 pathway that controls aging and death of cells, and TERT, which maintains telomeres. However, in contrast to sun-exposed melanomas, Dr. Trent stressed that the

genetic changes “activating” the MAPK pathway and TERT were more frequently activated by alternate genetic changes. For example, MAPK activation through focal amplification (an amplification that does not encompass the neighboring Cyclin D1 gene) and over-expression of the PAK1 gene occurred in 12 percent of patients, suggesting PAK1 may be a unique target for acral melanoma. Additionally, the team found that TERT was transcriptionally altered in nearly half of the cases and was commonly highly expressed. Dr. Trent showed early evidence that a pharmacological chaperone targeting TERT transcriptional control may offer a novel strategy for molecularly targeting acral melanomas. A G-Quadruplex inhibitor thought to work through TERT promoter lockdown significantly reduced TERT activity in an acral melanoma cell line.

The researchers saw several other novel mutations in a small number of samples. Only 3 of the 34 (<10%) patients had the genetic signature that is associated with UV-induced DNA damage in these acral melanoma tumors and the genomes of acral melanoma patients are generally quiet compared to the tumor genomes of sun-exposed melanoma. The results of the Sosman and Asgari teams revealed that the relatively infrequent mutations in most acral melanoma almost always include ones that converge on MAPK signaling – the most frequently activated pathway in cutaneous melanoma, too.

What this Means for Patients

Researchers continue to find genetic and protein differences in melanoma tumor cells compared to normal cells that suggest new drug targets. In addition, similarities and differences across melanoma subtypes suggest that pathology results and the location of tumors may not be the gold standards for diagnosing and treating cancer patients, noted **Dr. Boris Bastian of the University of California, San Francisco**. “Even within melanoma, genetic alterations that originate from different types of pigment cells can have different clinical features. We need objective definitions of melanomas – a taxonomy with multiple dimensions—which would allow a more accurate clinical assessment,” said Dr. Bastian. “This would require a group effort to develop,” he added.

Studies are revealing molecular drivers for the growth of melanoma subtypes including rare but aggressive forms of melanoma that afflict the eye, and acral melanomas that arise in the nail beds, palms, and soles of the feet. Some drugs for these targets have already been developed and are undergoing testing in melanoma patients. In addition, the findings of investigators using tumor samples to study the interface between the immune system and melanoma tumors suggest a number of new therapeutic approaches to enhance immune response to cancers that differ from those already on the market. Investigators are also exploring key factors needed to foster melanoma metastases, uncovering drug targets unique to the metastatic arena that might help melanoma patients whose extracranial disease is well controlled by current treatments, but whose brain metastases continue to grow.

MEASURING TREATMENT EFFECTIVENESS



Paul Chapman

Dr. Paul Chapman of Memorial Sloan Kettering Cancer Center provided a perspective on how melanoma treatment has changed over the past five years with the advent of targeted treatments and immunotherapies, and how the paradigm for measuring treatment effectiveness in the future

needs to change in order to move the field forward. He noted that the long-term survival rate for patients with Stage IV melanoma at the end of the last century was only 10 percent, when the main forms of treatment were chemotherapies, IL-2 and interferon. Even though certain combinations of chemotherapies provided high response rates in some patients, they did not improve overall survival. Some patients benefitted, but most did not, Dr. Chapman said. In contrast, there have been 11 new FDA-approved treatments for melanoma since 2011. These new treatments have more than doubled the long-term survival rate for advanced melanomas.

But he stressed that there is still more work to be done because even with the best treatment, about half of advanced melanoma patients do not benefit. To aid in the development of new therapies for melanoma, Dr. Chapman suggested a new framework for assessing treatment efficacy. Traditionally, cancer treatment effectiveness is based on Response Evaluation Criteria in Solid Tumors (RECIST), which grew out of observations in 1977 of the accuracy of oncologists trying to measure spheres under a layer of foam rubber. In 1981, the World Health Organization (WHO) established that a partial response rate was a 50-percent decrease in the size of tumors based on these observations in 1977 and, somewhat arbitrarily, that tumor progression is revealed by an increase of 25 percent in size. “RECIST was never intended to correlate with anything medically or biologi-

“RECIST was never intended to correlate with anything medically or biologically relevant, but a way for us all to speak the same language.”

cally relevant, but a way for us all to speak the same language,” Dr. Chapman stressed and suggested that oncologists must develop better measures and markers that correlate with overall survival.

Using data from the Phase 2 and 3 trials of vemurafenib or dacarbazine (BRIM2 and BRIM3), Dr. Chapman reported that the measurement in the first 12 weeks that correlated the most with survival was not response, no matter what degree of tumor shrinkage was used to define a response. Rather, time to progression had the strongest correlation with disease progression when progression was defined as greater than 50 percent increase in the sum of tumor diameters or the early appearance of new tumors. Thus, time to progression or progression-free survival may be better surrogates that tumor response rate, he said.

With immune therapy, patients occasionally experience late responses and have pseudo progression early in their treatment. Dr. Chapman noted that pseudo progression only happens about 10 percent of the time for immunotherapies. He suggested a different metric for these treatments—time to treatment failure, with failure being defined as insufficient response such that a new treatment must be started. He noted that often patients treated with immunotherapy remain stable for long periods of time during which they do not need a new treatment.

BIOMARKERS OF TREATMENT RESPONSE

The development of biomarkers for melanoma continues at a rapid pace despite its challenges and the complexities involved. Biomarkers of treatment response will become increasingly important to best triage therapy now that there are several effective treatment options for melanoma. Several speakers stressed that pre-treatment biopsies are not sufficient to study potential biomarkers of response, especially for immunotherapies, which instigate a dynamic response in the tumor microenvironment that varies substantially over time. Rather, on-treatment or post-treatment tumor tissue and not pre-treatment tumor tissues are giving the most information on treatment response. Researchers reported on their efforts to find biomarkers that predict response to targeted therapies, such as BRAF inhibitors, or immune therapies, such as checkpoint inhibitors or adoptive T cell therapy. Potential biomarkers for response to checkpoint inhibitors and other immunotherapies that were discussed included tumor mutation status and load, levels of tumor infiltrating T cells, and interferon gene signatures.

RESPONSE AND RESISTANCE TO BRAF INHIBITOR THERAPY

Danny Fund-MRA Young Investigator **Dr. Michael Berger of Memorial Sloan Kettering Cancer Center (MSK)** used targeted next-generation DNA sequencing to analyze tumors from more than 75 metastatic melanoma patients obtained prior to treatment with BRAF inhibitors vemurafenib or dabrafenib used singly or in combination. Responses were graded to take into account both the duration and magnitude of response. Patients were classified into three response groups: excellent responders (>50% tumor shrinkage for 7 months or any shrinkage for 12 months), intermediate responders, and poor responders (tumor growth, new lesions, or <50% tumor shrinkage for <4 months). They found that the rate of mutation was not linked to response; poor responders had an equally high burden of mutations as the excellent responders. They exam-

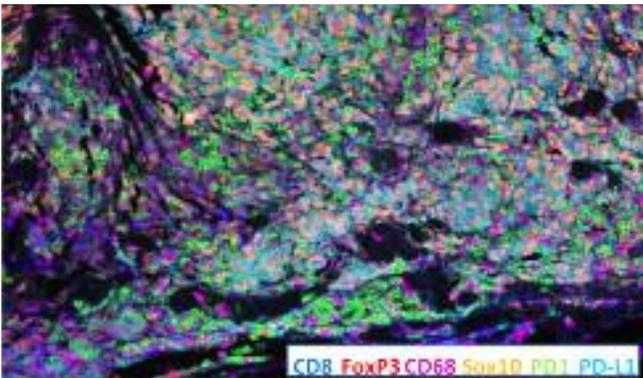
ined each gene of a 300 gene panel for a correlation between genomic alterations and clinical response and found that response to therapy was linked to PTEN mutations and the levels of BRAF mutant allele.

In the years since this study, the team has been able to optimize their methodologies in the lab, as well as the bioinformatics associated with the analysis, which allowed them to significantly scale up their efforts. As a result, a large-scale clinical sequencing initiative has been initiated using the MSK platform to run the assay for patients with recurrent/metastatic cancer across all solid tumors. Currently, this work is being conducted to provide improved diagnosis and prognosis data for patients. Through this initiative, oncologists aim to select targeted therapies based on the molecular profiles of their patient's tumors. Researchers can now build a large database of patients and their mutations to facilitate the screening of patients for eligibility of existing and future clinical trials as well.

RESPONSE TO PD1 THERAPY

MRA Young Investigator **Dr. Janis Taube of Johns Hopkins University** noted that several studies of melanoma patients treated with anti-PD-1 or anti-PD-L1 therapy have consistently shown that responders are more likely to have increased PD-L1 expression on their tumors, even when different assays are used for PD-L1 expression. Since each assay uses different antibodies and scoring systems, it is possible that the different assays could return different results even on the same patient's sample. Frequently, there is only one assay to predict a drug's response on a drug's label at the time of its first approval by the FDA, so such differences among tests could be problematic. The agency has convened a team of researchers from industry and academia who are currently conducting a clinical study of the comparative analytical performance of the PD-L1 immunohistochemistry assays in pathology specimens.

Multiplex Immunofluorescence Panel for Melanoma



Courtesy of Janis Taube

In the meantime, pathologists are challenged as to what tests they should use for PD-L1 expression, according to Dr. Taube. “It’s untenable for most labs to be able to host all four versions of a PD-L1 assay, and some may try to develop their own lab-derived tests,” she said. Researchers are also trying to define other biomarkers for response to anti-PD-L1/PD-1 therapy. The density of tumoral CD-8 cells discriminates between responders and those that progress, but it is not obvious what the cutoff point should be for responders. Patients who respond also tend to have high mutational loads. One analysis found that using global measurements of three indicators—CD-8 gene expression, PD-L1 gene expression and mutational load—CD-8 expression was the most informative predictor of prognosis in patients with melanoma, though it is important to note that PD-L1 protein was not measured in this analysis. Dr. Taube suggested that multiplex immunofluorescence panel technologies may be useful in spatially resolving protein expression of multiple factors such as CD8 and PD-L1, amongst others, to help prioritize their importance and improve patient selection algorithms for anti-PD-1/PD-L1 therapy.

Despite the progress that anti-PD-1 immunotherapy has engendered, not every melanoma patient experiences

or sustains a response to treatment. **Dr. Suzanne Topalian of Johns Hopkins University** noted that PD-L1 expression is not uniform in all melanoma tumors from an individual patient, and over time, which she claimed was a pitfall for using this biomarker to select patients for anti-PD-1 therapy. She and her team, supported by the Johns Hopkins Kimmel Cancer Center-Memorial Sloan Kettering-MRA Team Science Award with generous support from Judy and Russ Carson, conducted a series of rapid autopsies (within 6 hours of death) on melanoma patients that had anti-PD-1 treatment or other systemic therapies, to search for biomarkers associated with response or resistance. Establishing such a collection of multiple tumors from individual patients is important to be able to understand why some tumors respond to treatment while others worsen. So far she has obtained samples from six patients and collected 137 tumor specimens for pathologic and mutational analyses and gene expression profiling. In one patient having a mixed response to anti-PD-L1/PD-1 treatment in different tumors, no significant differences in mutational profiles or expression of candidate immune genes were found.

However, an unbiased gene expression profiling found clear separation of regressing from progressing metastases, providing several candidate genes that might serve as potential response/resistance biomarkers. Surprisingly, in this analysis, the most highly differentially expressed genes in progressing lesions were not known as melanoma-specific genes. Dr. Topalian and her collaborating Principal Investigator at Memorial Sloan Kettering Cancer Center, Dr. Christine Iacobuzio-Donahue, plan to further explore these findings by evaluating related transcription factors and predicted immunopeptide profiles in these metastases. These investigations have the potential to reveal biomarkers for response and resistance; and to better inform the development of more effective therapies for patients with melanoma.

ADOPTIVE CELL THERAPY

Dr. Navin Varadarajan of the University of Houston

used a single cell method to find functional and transcriptional differences between complete responders and non-responders to adoptive T cell therapy by co-cultivating melanoma patient T cells with their tumor cells in worked funded by the Stewart Rahr-MRA Young Investigator Award. After separating out the TILs, he then compared their transcriptional profiles at the single cell level. While there were no obvious differences in genes related to T cell activation, and function, subsets of cells with unique transcriptional profiles were identified. But because there was a high degree of genetic variability in T cells seen within samples from the same patients, Dr. Varadarajan then used trapped individual cells in petri dishes of exceedingly small volume (nanowell arrays) to analyze the functioning of single T cells in a highly efficient manner. This analysis revealed

that the majority of killer T cells from non-responders undergo apoptosis and die, whereas the killer T cells from complete responders tended to survive and have higher motility. He noted that the ability of T cells to persist in patients is key to their long-term response. Finally, complete transcriptional profiling of the T cells indicated that T cells from responders had superior metabolic properties. "Killing is important, but only with the right survival skills and metabolic programming," he said and suggested that motility might be a biomarker for functional T cells. He also found that T cells from non-responders tended to generate more gamma interferon than those from complete responders. After his presentation, one participant asked if T cell motility might be related to the ability of T cells to track into the tumor microenvironment. Dr. Varadarajan responded that he is currently trying to answer that question with testing in a mouse model of melanoma.

What this Means for Patients

Now that there are many treatment options for melanoma patients, it is crucial to develop tests that can predict the right drug for the right patient at the right time. Researchers are exploring biomarkers-factors that differ in the tumor or blood samples of patients that respond to a specific treatment compared to those that do not. Investigators reported the discovery of a number of new biomarkers for response to therapies. There is also a need to better identify earlier stage patients who are at a high risk for recurrence after surgery and for whom systemic therapy might be appropriate now that there are two FDA approved adjuvant treatments for Stage III patients. As Dr. Lynn Schuchter of the University of Pennsylvania pointed out, there is not consensus among clinicians that every such patient should receive such treatment. She added, "Our current ability to prognosticate isn't where it needs to be."

Researchers stressed the need to have patient tumor samples in order to discern biomarkers of response as well as learn about how the drugs work. Tumor samples taken before treatment provide a baseline for comparison but have not yet provided information that predicts response to immunotherapies. It appears that tumor samples taken during treatment may provide important information about patient response. One thing is quite clear: data from a large number of patients are needed to develop biomarker tests. This necessitates the sharing of samples and data. But often such information or samples are held by the entities that first collected them, and sharing is constrained due to technical or legal hurdles. Mr. Michael Milken, Chairman of the Milken Institute and MRA Board Member suggested applying 21st century technologies to solve these problems. "We need to think about technology and what patients would be willing to do," he stressed.

COMBINATION THERAPY

Now that there are multiple treatment options approved for melanoma, several presenters stressed the need to rationally combine immuno- and targeted therapies so as to achieve the most effective and durable responses. But what is the optimal order to give treatments? For example, should drugs A and B be given at the same time, A before B or B before A? Considering investigational therapies as well, there are so many potential combinations of all types of melanoma therapies that it is not feasible to do studies on all possible combinations and instead combination therapy clinical studies should be based on basic biology and animal findings that can help prioritize which treatment combinations are likely to have synergistic effects.

PI3K SIGNALING

Preclinical studies were conducted by **Dr. Martin McMahon, formerly of University of California, San Francisco and now of the Huntsman Cancer Institute**, to explore the role of the PI3-kinase (PI3K) pathway in melanoma initiation, progression, and maintenance. Previous observations piqued McMahon's interest regarding the precise combination of activating BRAF mutations in conjunction with PTEN silencing which are fairly common. In contrast, mutational activation of BRAF combined with point mutations in the catalytic subunit of PI3-kinase alpha (PIK3CA) are comparatively rare and only recently observed. He was intrigued as to why this difference was observed in melanoma, especially since PI3K mutations are common in many other malignancies. They hypothesized that PTEN silencing in melanoma might be indicative of activities of PTEN that are non-canonical despite the fact that the role of PTEN as a PI3'-lipid phosphatase is well-established.

His studies employed genetically-engineered mouse melanoma models of BRAF(V600E)-driven melanoma that were developed in collaboration with Marcus Bosenberg (Yale University). Silencing of PTEN or muta-

tional activation of PIK3CA was achieved using mice generated by Pier Paolo Pandolfi or Wayne Phillips, respectively. One observation is that the 'tone' of PI3'-lipid signaling could account for differences in melanoma-genesis observed when BRAF(V600E) was combined with either PTEN silencing versus gain-of-function PIK3CA. Dr. McMahon found that a PI3K alpha inhibitor significantly blocked PIK3CA-driven melanoma but was less active on PTEN-driven melanoma. Moreover, a PI3K beta inhibitor had no effect in these PTEN-silenced melanoma cells, either alone or in combination with the PI3K-alpha inhibitor. In PIK3CA mutated cells co-expressing BRAF(V600E), the PI3K alpha inhibitor forestalled the onset of drug resistance to the MEK inhibitor, cobimetinib, whereas the PI3K inhibitor alone was insufficient to elicit substantial tumor regression. Hence, these findings suggest that adding a PI3K inhibitor may not be likely to be clinically useful in enhancing the shrinkage of tumors in response to BRAF(V600E) pathway inhibition. "Although the PI3K inhibitor did not significantly augment the response of BRAF mutated melanoma to MEK inhibition, a compelling reason to use a BRAF inhibitor and a PI3K inhibitor up front may be to forestall the emergence of treatment resistance," he said.

ANTI-PD1 AND BRAF INHIBITION

Dr. Omid Hamid of The Angeles Clinic and Research Institute in Los Angeles, California pointed out that BRAF inhibitors have been shown to increase T cell infiltration into tumors as well as increase expression of tumor antigens. Recent data presented relates a poor prognosis for these patients with high risk features (high LDH, multiple sites of disease) despite the benefits of initial dual kinase inhibition. "Recent data has shown that BRAF inhibitors can make a 'cold' tumor a 'hot' immune environment so we should combine it with immunotherapy," he said. He noted using BRAF inhibitors with or without MEK inhibitors as frontline therapy followed by immunotherapy could harness and per-

“A compelling reason to use a BRAF inhibitor and a PI3K inhibitor up front may be to forestall the emergence of treatment resistance”

petuate the rapid enhanced anti-tumor response from the targeted therapies and may lead to a more durable response that prolongs survival.

Initial clinical findings seem to support this since a study in melanoma patients given a BRAF inhibitor for 56 or 28 days followed by the addition of a PD-L1 antibody had response rates of 76 and 100 percent respectively.

Triple therapy with inhibitors to BRAF, MEK and PD-L1 may boost effectiveness even further, Dr. Hamid noted. A clinical study of patients with advanced BRAF-mutant melanoma found that when a BRAF inhibitor is combined with a MEK inhibitor, progression-free survival increases from 7 months to 12 months, on average, and the overall response rate increases from 50 percent to 70 percent, Dr. Hamid reported. This study is currently giving melanoma patients a BRAF inhibitor combined with a MEK inhibitor and followed by a PD-L1 inhibitor. “With most metastatic melanoma patients in the community only getting single-drug therapy, we need to get the data out on combination therapy effectiveness,” Dr. Hamid said. While initial studies of BRAF inhibitor (vemurafenib) in combination with anti-CTLA-4 (ipilimumab) were stopped owing to hepatotoxicity, it seems that the PD-1/PD-L1 inhibitors may not exhibit the toxicity seen with that combination.

ONCOLYTIC VIRUS IMMUNOTHERAPY

Tumor oncolytic viruses may also elicit stronger and more durable responses when combined with checkpoint inhibitors. **Dr. Howard Kaufman of Rutgers University** reported on virus T-VEC, which is a genetically engineered herpes virus designed to selectively target and destroy cancer cells as well as stimulate the immune response with its release of the cytokine GM-CSF. The virus is injected directly into tumors. A Phase 3 study showed the treatment was



Boris Bastian, Lynn Schuchter, Michael Milken, Suzanne Topalian, Levi Garraway

well tolerated with an overall response rate of 26 percent and a durable response rate of 16 percent. These data led to its approval by the FDA for use in melanoma patients with inoperable tumors in October of 2015.

“There were good local responses but the immune response didn’t ramp up to destroy untreated lesions, so we need to add other agents,” Dr. Kaufman noted.

He also reported encouraging results when T-VEC was combined with anti-CTLA-4 or anti-PD-1 treatments. Initial findings of a Phase 1b trial of T-VEC followed 3 weeks later by ipilimumab in 18 patients with advanced melanoma found a 50 percent response rate, with 22 percent of the patients having a complete response – a relatively uncommon event in patients treated with ipilimumab alone. A Phase 2 study of this combination was recently completed. The patients that responded seem to have durable responses with a progression-free survival rate of 60 percent seen at 26 months. A phase 3 study just opened for T-VEC given in combination with the anti-PD1 inhibitor pembrolizumab.

The T-VEC approval has encouraged clinical testing of other oncolytic viruses, including coxsackievirus A21, which causes the common cold. Only 15 percent of patients have pre-existing antibodies to the virus, but given that the virus is injected directly into tumor lesions rather than into the bloodstream, these antibodies are not likely to limit the vaccine’s effectiveness, Dr. Kaufman noted. A Phase 2 study on this intra-tumoral therapy found similar response rates as seen with T-VEC. Biopsied tumor sites before and after injection revealed an influx of T cells and upregulation of PD-L1 after treatment, suggesting the treatment might be more effective when used in combination with an inhibitor of PD-L1, Dr. Kaufman said. A study of such an inhibitor combined with the coxsackievirus A21 tumor vaccine found synergistic effects in a mouse model leading to a Phase 1b clinical study of the virus combined with pembrolizumab.



Antoni Ribas, Craig Slingluff

VACCINES

Dr. Craig Slingluff of the University of Virginia

reported on his efforts to improve tumor vaccines so they are more likely to induce strong immune response at tumor sites rather than at injection sites – research supported by an MRA Team Science Award. He noted that the problem with many current tumor vaccines and adjuvants is that they have suboptimal antigen formulations, include weak adjuvants, and fail to incite circulating T cells to go beyond the injection site and traffic to the tumor. His solutions to these shortcomings are to make vaccines with compounds that activate toll-like receptors (TLRs), a relatively recently discovered component of the immune system that can provoke strong immune responses, and to lodge the antigenic portion of the vaccine on long peptides. Long peptides are more likely to stimulate CD4 “helper” T cells than the short peptide antigens typically used in vaccines. Long peptides also require processing by dendritic cells before inducing T cell activation. Because, dendritic cells migrate to the lymph nodes after TLR activation, they are absent from the vaccine site so theoretically long peptide vaccines would avoid the problem of killer T cells mainly homing to the injection site rather than to the tumor.

Dr. Slingluff reported that Stage IV melanoma patients given an intermediate-length peptide vaccine experienced a 74 percent 5-year survival rate and had enhanced CD4 T cell and antibody responses that were linked to clinical response. Encouraged by these findings, Dr. Slingluff is currently testing a vaccine in melanoma patients that has a mixture of long peptides and adjuvants including TLR agonists or incomplete Freund's adjuvant (IFA), a more traditionally used adjuvant. So far this multi-armed adaptive trial has found that all seven combinations of long peptides and various adjuvants tested were safe on the first 40 patients that have received them, and that those patients have

had durable and functional T cell and antibody responses induced most effectively when the TLR agonists polyI:CLC and resiquimod are combined with IFA in the vaccine. "It is encouraging that the antibody and T cell response magnitudes are quite large especially when all three of these adjuvants are used," Dr. Slingluff said. He currently is further delineating the immune responses seen to these vaccines, including assessing the effects of each adjuvant combination on the vaccine site microenvironment, and whether these vaccine formulations support T cell homing to melanoma metastases and tumor control.

What this Means for Patients

Promising findings in both animal studies and patients are revealing that combinations of melanoma treatments work better than when treatments are used singly. Two combination targeted therapies are already available as is a combination immunotherapy and others are in clinical testing. Early data suggests another effective approach is a regimen in which patients are first treated with a targeted therapy or tumor vaccine that destroys most cancer cells, followed by an immunotherapy which kills any remaining tumor cells. Animal studies reported at the retreat found this strategy to be remarkably effective. Similar high response rates are seen in the initial studies of these combination therapies in patients, but how reproducible or durable these responses are remains to be seen.

While they may work better, combination therapies tend to also increase the rate of adverse reactions, some of which can be life-threatening. Some of the toxicities linked to immunotherapy can be deadly, especially when immunotherapies are combined, **Dr. Lynn Schuchter of the University of Pennsylvania** pointed out, but added that blunting those side effects might also reduce the effectiveness of the immunotherapy. Such side effects initially discouraged researchers and led to the assumption by some that combination therapy would not work. Clinical investigations reported at the retreat reveal that when targeted therapy is followed by immunotherapy, rather than used simultaneously, the treatment is well tolerated by most patients. More studies are needed to find the best order and duration of combination treatment that leads to optimal safety and efficacy. Research is also investigating intermittent dosing schedules (not taking drugs continuously) as a way to reduce toxicity. As **Dr. Levi Garraway, Dana-Farber Cancer Institute**, pointed out, today it is difficult to give drugs in a way that maximizes their effectiveness because of the toxicity. "We need a serious effort to investigate drug dose and schedule in melanoma and other solid tumors like what has been done in leukemia and lymphoma with chemotherapy," he said.

SCREENING FOR MELANOMA

Because melanoma can be such a deadly form of skin cancer, several have suggested implementing a routine screening program for it, while others are concerned that the risks of such a program, such as excessive mole excisions and visits to dermatologists, may exceed the benefits. The latest findings in this regard based on the few studies done on existing melanoma screening programs were discussed, followed by a presentation describing a new app for measuring mole nevi that might aid melanoma prevention as well as melanoma research.

Dr. Martin Weinstock of Rhode Island Hospital noted that currently the United States Preventive Services Task Force (USPSTF) does not recommend routine screening for melanoma. This influential task

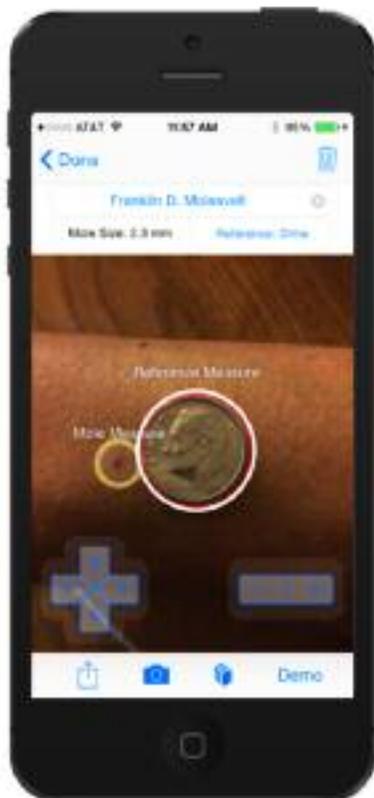
“This study suggests that the harms of such screening will be relatively minor.”

force bases its recommendations on randomized trials and systematic reviews of them, but as Dr. Weinstock pointed out, there are no randomized trials on screening for melanoma that have been completed, and because of the large expense of such a trial, none is likely to be done in the future. The evidence is insufficient to recommend for or against screening, concluded the USPSTF in its last review of it in 2009.



MRA Scientific Retreat

Screenshot of Mole Mapper App



Courtesy of Sancy Leachman

That said, Dr. Weinstock reported that there has been substantial new evidence on how screening can reduce melanoma mortality from non-randomized studies. But the harms of such screening were not documented in the medical literature, and he noted that screening could cause unnecessary surgery and patient distress. One study, in part funded by the MRA Team Science Award with matching support from the Rhode Island Hospital, University of Pittsburgh Cancer Institute and Brown University, attempted to assess both the risks and benefits of screening for melanoma was recently conducted in Pennsylvania. This large-scale effort

screened for melanoma in patients 35 years of age or older using an online training program for primary care physicians called INFORMED, which was also developed with support from an MRA Team Science Award. When researchers compared the results of screening to retrospective data, they found that compared to one year earlier, 8 months after the screening program started, screening exams were more frequent among patients seen by INFORMED-trained physicians and there were no differences in the rate of skin surgeries. The number of dermatology visits did not significantly increase, and the group with the most INFORMED-trained physicians experienced a large increase in melanoma diagnoses, unlike those treated by physicians without this training. Although this study found a substantial increase in melanoma diagnoses in the screening program effort, these may not have been screen-detected melanomas, Dr. Weinstock noted. "This study suggests that, at least as implemented in the Pennsylvania study, the harms of such screening will be relatively minor," Dr. Weinstock said.

As for the benefits of melanoma screening, there is currently controversy over whether it can reduce mortality, he said. A study of a screening program conducted of the employees of Lawrence Livermore National Laboratory found the screening was linked to a significant decrease in mortality. Another study in Germany found that after 10 years of implementing a melanoma screening program, the melanoma mortality rate was lower where it had been implemented compared to neighboring regions without the program. But after those findings inspired implementation of a national melanoma screening program in Germany in 2008, nationwide melanoma mortality has not decreased so far, Dr. Weinstock noted, and more recent data revealed that melanoma mortality increased in the area in Germany that initially implemented the screening

program. The reasons for these observations are controversial and more data is needed, he said.

Dr. Sancy Leachman of Oregon Health and Science University discussed Mole Mapper, a new iPhone app to measure moles. Mole Mapper is a free app developed by Oregon Health and Science University in collaboration with Sage Bionetworks and Dan Webster with the hope of facilitating mole tracking and collaboration worldwide. The app measures and tracks moles monthly based on pictures provided by users. The app cannot diagnose melanoma nor make recommendations for care. It currently isn't known what percent increase in mole size should trigger a doctor's visit, but Dr. Leachman said the data collected from use of the app should reveal this over time. While providing a free, quantitative mole-tracking tool for people that could facilitate productive clinic visits, the app is also enabling a large-scale, crowd-sourced research study, Dr. Leachman reported. People who use the

app can choose to keep their data on their phones or can consent to share their data, which is stripped of patient identifiers to preserve patient privacy while retaining risk data, demographics, and other personal health information for the use of researchers.

The app has been in operation for four months and has had 32,000 views, 8,000 downloads, and 2,000 registrants, who have submitted almost 3,000 photos. Thirteen percent of users of the app are melanoma patients and 27 percent have a family history of the cancer. "We want to reduce unnecessary patient visits and detect melanoma earlier when it is more treatable," Dr. Leachman said. Data gathered from the app is open-source, available to qualified researchers worldwide and could be used as a patient source for accrual to melanoma prevention clinical trials, she noted. "We think such team science will move things forward and we need the whole melanoma community's help to succeed," she added.

What this Means for Patients

When caught in its earliest stage, melanoma is almost always curable with surgery. However, once it spreads, or metastasizes, to organs (Stage IV), it is often fatal. Thus, early detection has great potential to reduce melanoma mortality. But for the general population, regardless of risk factors for the disease, there is not enough information to know if a routine screening program for it should be implemented. The concerns around such a program include excessive removal of benign moles, visits to dermatologists and unfounded anxiety that may exceed the benefits. The limited studies that have been done on melanoma screening programs to date suggest that the harms of such screening are minor and that screening programs do increase melanoma diagnoses. But findings on melanoma screening are contradictory and implementing a population-based screening program remains controversial. An alternative approach or as a complement to such screening that encourages early diagnosis may be technologies that allow patients to keep track of their own skin, such as a newly developed app for measuring the size of moles so patients can detect when moles are increasing in size and might be worthy of being checked by a physician.

ACCELERATING MELANOMA CLINICAL DEVELOPMENT



Scot Ebbinghaus and Grant McArthur at Industry Roundtable Breakfast

Since 2011, new melanoma treatments and diagnostics continue to emerge at a blazing pace with 11 therapies approved in just 5 years. Targeted therapy, immunotherapy, novel combinations, and diagnostics have sparked revolutionary change in the field and for melanoma patients. Regulatory approaches, such as breakthrough therapy designation, accelerated approval and expanded access programs have provided a beneficial framework to speed new treatments to melanoma patients. Unfortunately, not all melanoma patients are fully benefiting and new therapies are required. What is needed to spur further development of new melanoma therapies and their proper use in the clinic? Key questions include how to ensure that accelerated approvals remains a useful regulatory strategy; are there new ways to identify patients who are progressing; and, what can be done to acquire and/or share patient samples and clinical information to propel research. To address these questions, 50 leaders from industry, academia, and the FDA participated in a roundtable discussion of challenges and opportunities to accelerate clinical development and approval of new melanoma drugs and combinations. The session was moderated by **Dr. Paul Chapman, Memorial Sloan Kettering Cancer Center, Dr. Louise Perkins of MRA, and Dr. Lynn Schuchter of the University of Pennsylvania.**

KEEPING THE DOOR OPEN ON ACCELERATED APPROVAL

The FDA's accelerated approval mechanism helps to rapidly bring treatments forward for patients with serious and life-threatening diseases who have no satisfactory available therapy or where there is a significant advance over available therapy. Traditionally, accelerated approvals are based on endpoints such as duration of response (DOR) and an important component of such endpoints is that they are reasonably likely to predict clinical benefit. In the era of immuno- and targeted therapy, how does the field continue to pursue accelerated approval toward patient benefit. Much discussion focused on patients with BRAF mutant melanoma (half of melanoma patients) in the event such a patient progresses on immunotherapy since these patients do have a therapy available to them. What should come next—a clinical trial that stands the chance to offer enduring benefit or approved targeted therapy? There seemed consensus that since immunotherapy treatment decreases the 'cadence' of BRAF mutant melanoma progression and that there is room for improvement in the duration of response to targeted therapy, then it is feasible to consider a clinical trial for such patients and reserve targeted therapy for later use. One recommendation arising from the discussion is that the community of academic thought leaders should publish a position paper on this subject to aid regulators as they evaluate new treatments and trials.

EARLIER IDENTIFICATION OF PATIENTS WHO ARE PROGRESSING

Beyond current means to assess disease progression, a number of other techniques are under investigation that could enhance the ability of doctors to detect earlier when a patient's melanoma is worsening thereby opening the door to treatment of more limited disease or to measure currently undetectable remaining melanoma (minimal residual disease). Among the techniques are the use genetic signatures from tumor samples as well as detecting tumor

cells or DNA in so-called liquid biopsies that rely on blood samples. Liquid biopsies may be the next frontier of biomarker diagnostics. Nonetheless, in order to understand the biology underlying progression and how to optimize the use of current therapies, tumor samples will be required for some time to come and will also be needed in the study of new biomarkers that are developed.

MOBILIZING PATIENTS, THEIR DATA AND CLINICAL SAMPLES A long-standing challenge in cancer research and development relates to the acquisition and sharing of patient samples and clinical data associated with them. Major investments of money and time are required for the collection and storage of both samples and data hence it is understandable that their use is constrained by the pharmaceutical companies and academic institutions that fund and execute data and sam-

ple collection. More financial resources, global standards, larger studies, partnerships and consortiums would improve and support the systematic donating, collecting, and analyzing of patient samples and the sharing of the data linked to those specimens. Engaging patients with state-of-the-art digital tools as participants and drivers is another approach that may mobilize samples and data for research. There is a widespread sense that existing tissue and data can fuel needed research, yet it was noted by several that neither the quality of the clinical data nor of the samples may be sufficient for every study. Instead, there is a need to mobilize resources and patients along with the establishment of standardized approaches that could provide large, robust and useful resources fit for the purpose of specific research objectives. This will enable researchers to move closer to learning from every patient.



MRA Scientific Retreat

NEW FRONTIERS IN MELANOMA RESEARCH

Researchers need to share their information across institutions, and clinicians need to encourage more patients to donate their samples.

MRA Young Investigators gathered to discuss the most exciting opportunities and difficult challenges in melanoma research today from their perspective. The MRA Young Investigator program aims to attract to melanoma research early career faculty with novel ideas, thereby encouraging and supporting the next generation of melanoma research leaders. Among the scientific themes that emerged from this discussion were the following:

PLASTICITY AND TUMOR MICROENVIRONMENT

Better understanding of the mechanisms of tumor plasticity, which fosters drug resistance and metastasis, will be critical to effectively administering therapies, including combination therapies. Mechanisms of adaptive resistance by both tumor and immune cells are also important to understand and counter so the immune system can be reactivated, especially when there is a low tumor load. The tumor microenvironment seems key to assessing the dynamic responses of tumors to drugs and the immune system to tumors.

BIOMARKERS

Opportunities for discovery of biomarkers include genetic and immunologic, and promising recent avenues include mutational density, antigen presentation, T cell clonality, and circulating markers. PD-L1 status remains an area of intense interest. There is

also a need to better understand how and when metastases occur. Important questions include where (in the tumor itself, other cells in the microenvironment, or in the blood) and when to identify and assess biomarkers to provide the most accurate information for diagnostic purposes.

PRECISION MEDICINE

Exciting efforts are underway to develop enhanced personalized treatment approaches based on information at the single cell level, including exome sequencing and based on cellular and genetic mosaicism in tumors as well as at the patient-level, including somatic genome and microbiome.

IMPROVING T CELL RESPONSE

Once anti-tumor T cells are generated with vaccines or adoptive T cell therapy, they need to be guided towards the tumor and enabled to survive and function in the tumor microenvironment. Targeting coordinately expressed checkpoints might help in this regard, as well as giving a treatment that digests tumor cells to make their antigens more accessible to T cells. This is another important area of active investigation.

What is needed to accelerate these and other exciting areas forward? Technologies that allow higher resolution would better enable researchers to interrogate immune cell function, identify neo-antigens, and measure other tumor microenvironment changes. Better tools for prognostication, including detection of minimal residual disease and early detection of disease progression, are areas of clinical need. Precision medicine requires the development of multiple drug targets and response biomarkers for them, but sample sizes for each tumor subtype are limited. Researchers need to share their information across institutions, and clinicians need to encourage more patients to donate their samples and participate in clinical research.

PARTNERING WITH PATIENTS

Before the opening of the Scientific Retreat, more than 50 patients, family members, advocates, and foundation partners gathered to discuss how patients are influencing research and the regulatory process and offer unique input and ideas on how to move the field forward. The forum included a presentation by **Dr. Rajan Kulkarni of the University of California, Los Angeles** who reviewed currently approved melanoma treatments and what is on the horizon. He also discussed his research focused on developing technology for the detection of circulating tumor cells as a melanoma liquid biopsy, which is funded by the SkinCeuticals-MRA Young Investigator Award.

Ms. Kim McCleary of *FasterCures* discussed the history and current initiatives to better engage patients as partners in research and the drug discovery and development process. A major milestone occurred in 1973 with adoption of the Patient's Bill of Rights by the American Hospital Association that required practitioners to provide patients with information about their diagnoses and treatment options. About that time, medicine began to be increasingly specialized such that patients were no longer treated by the same and sole provider during their lifetime but needed to see several different medical specialists to receive the medical care they required. This shift has increasingly necessitated patients navigating their own healthcare. In the 1980s and 1990s, the AIDS crisis led to a new model of effective and powerful patient advocacy to become knowledgeable about the science as well as their own care options. Patients have been empowered further with the advent of new communications technologies.

Pharmaceutical companies and federal agencies are responding to such patient demand, and several new federal initiatives have accelerated patient input and involvement in medical research, including the Patient Centered Outcomes Research Institute (PCORI), Patient-Focused Drug Development initiative by FDA, and the 21st Century Cures Initiative that aims to incorporate patient perspectives into the regulatory process.

A brainstorming session followed focused on melanoma patient needs, and what symptoms and aspects of melanoma impact patients' lives the most. Among the issues that were surfaced include access to quality care and financial burden of treatment. Impediments to participation in clinical trials were also discussed, such as finding information about available trials, geographical proximity to trials, and criteria for trials that exclude certain populations from participation. Participants also shared their experiences regarding the physical and emotional pain associated with a melanoma diagnosis. Understanding diagnosis, treatment options, patient support, and changes in lifestyle that should be made, if any, were raised as important needs for patients and caregivers.



Debra Black, Louise Perkins, Vicki Goodman, Eric Rubin

CONCLUSION



Leon Black

“I’m gratified in the advancements that have occurred in melanoma, but also painfully aware that more progress needs to be made.”

While the past several years have been one of extraordinary medical advances in the treatment of metastatic melanoma, the fact remains that in the U.S. alone over 76,000 individuals are afflicted by melanoma each year and nearly 10,000 die. Even with new immunotherapies, molecularly targeted drugs, and combination regimens on the market, a large proportion of patients with metastatic melanoma will not benefit from them. As **Dr. Suzanne Topalian, Johns Hopkins University**, stressed, “We still have a lot of work to do. This depends on discovery in research laboratories and clinical development, and we need the resources to do this.”

With the support of MRA’s generous donors and founders, innovative MRA-funded research programs have been pushing towards this next frontier in melanoma. Key research findings were highlighted at

the 2016 MRA Scientific Retreat in a forum that allowed stakeholders across sectors to share, discuss, and plan ways to further accelerate the pace of discovery. The progress in melanoma has also had a notable impact on the oncology community as a whole with drugs approved in melanoma now being tested in more than 30 different cancer types. As **Mr. Michael Milken, Chairman of the Milken Institute and MRA Board Member**, pointed out, “Melanoma has moved from the back of the line to the front.” **Dr. Levi Garraway, Dana-Farber Cancer Institute** agreed, saying “Melanoma is a bellwether for cancer as a whole.” But, he added, “The next challenge facing our field is to lead the way once again against the next set of barriers between where we are now and our goal of making melanoma a disease that is no longer life-threatening.”

Mr. Leon Black, MRA Co-founder, closed the meeting noting the incredible progress in melanoma treatment that has been made during the eight years that MRA has been operational. At MRA’s first annual retreat “there was a feeling of dedicated scientific and clinical researchers that had been laboring in the wilderness with no real progress having been made over a long period of time. But now we’re in a different universe—there’s a palpable buzz here, a feeling of momentum and excitement,” he said, noting that the immunotherapy championed by MRA-funded researchers has become a poster child for progress in cancer research. Scientists who were given MRA Young Investigator Awards years ago are now leading worldwide programs in melanoma. “We have a lot to be proud of,” he said. “I’m gratified in the advancements that have occurred in melanoma, but also painfully aware that more progress needs to be made,” he said. Then noting the teamwork and collaboration among researchers, clinicians, donors, companies, and regulators, Mr. Black stressed, “My goal for MRA is to be out of business. We are well on our way.”

ACKNOWLEDGEMENTS



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MRA would like to thank the scientists who presented their work at the retreat and the participants whose support is facilitating melanoma prevention, diagnosis, and treatment. Finally, MRA would like to thank its Board of Directors, Scientific Advisory Panel, Medical Advisory Panel, and Grant Review Committee for their guidance, counsel, and ongoing vision.

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Adaptive Biotechnologies
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Bristol-Myers Squibb
Castle Bioscience
Celldex Therapeutics
CheckMate Pharmaceuticals
Cynthia Polsky
Daiichi Sankyo
Eli Lilly Oncology
EMD Serono
Foundation Medicine
Genentech
Immunocore
Incyte
Johnson & Johnson Consumer Companies
MedImmune
Merck & Co.
Myriad Genetics
Novartis
Pfizer Oncology
Provectus Biopharmaceuticals
Spectral Molecular Imaging

For more information, visit the MRA website at **www.curemelanoma.org**. The website contains additional information about the MRA research program and past MRA retreats.

AGENDA

Wednesday, February 24th

4:00-8:00 pm Registration open.....Outside Grand Ballroom

4:30-6:00 pm Melanoma Forum: “Patients: From Passengers to Co-Pilots” (by invitation only).....Senate Room (Ground)

6:00-8:00 pm Opening Reception.....State Room (Ground)

- Debra Black, MRA Co-founder and Chair
- Louise Perkins, MRA Chief Science Officer
- Vicki Goodman, Bristol-Myers Squibb
- Eric Rubin, Merck & Co., Inc

Thursday, February 25th

6:30 am-6:00 pm Registration open.....Outside Grand Ballroom

7:00-8:15 am General Breakfast.....State & East Rooms (Ground)

7:00-8:15 am Young Investigators Breakfast: “New Frontiers in Melanoma Research” (by invitation only).....Chinese Room (Ground)

8:30-8:45 am Opening Remarks.....Grand Ballroom

- Margaret Anderson, Acting MRA President and CEO and Executive Director, *FasterCures*
- Louise Perkins, MRA Chief Science Officer

8:45-9:30 am Lecture: Paul Chapman, Memorial Sloan Kettering Cancer Center: How will we measure the efficacy of new drugs in clinical trials in the era of checkpoint and RAF inhibitors?

9:30-11:25 am Session: New Therapeutic Targets

Chair: Ronit Satchi-Fainaro

9:30-9:55 Gal Markel, Sheba Medical Center: Discovery of novel immune checkpoints in melanoma

9:55-10:15 Richard White, Memorial Sloan Kettering Cancer Center: Adipocytes in the melanoma microenvironment

10:15-10:35 Break

10:35-10:55 Nicholas Mitsiades, Baylor College of Medicine: Novel targeted therapies for uveal melanoma

10:55-11:20 Ronit Satchi-Fainaro, Tel Aviv University: Nanomedicine co-targeting of neuroinflammation in melanoma brain metastasis

11:20-11:50 am Lecture: Nicholas Restifo, U.S. National Cancer Institute: Qualities of highly effective anti-melanoma T cells

Thursday, February 25th (continued)**11:50 am- Session: Skin Screening for Melanoma****12:40 pm** Chair: Martin Weinstock

11:50-12:15 Martin Weinstock, Rhode Island Hospital: Melanoma screening consequences

12:15-12:40 Sancy Leachman, Oregon Health and Science University: Mole Mapper: An iPhone app to measure moles

12:40-2:15 pm Lunch.....State & East Rooms (Ground)

"Melanoma: What's on the Horizon": Discussion with Michael Milken, Chairman, Milken Institute and MRA Board Member

- Boris Bastian, University of California, San Francisco
- Levi Garraway, Dana-Farber Cancer Institute
- Lynn Schuchter, University of Pennsylvania
- Suzanne Topalian, Johns Hopkins University

2:25-3:35 pm Session: Genomic Characterization of Melanoma

Chair: Jeffrey Trent

2:25-2:45 Priscilla Brastianos, Massachusetts General Hospital: Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets

2:45-3:10 Maryam Asgari, Massachusetts General Hospital and Iwei Yeh, University of California San Francisco: Using genomic technologies to comprehensively characterize acral melanomas

3:10-3:35 Jeffrey Sosman, Vanderbilt University and Jeffrey Trent, TGen: Comprehensive genomic and transcriptomic analysis of acral melanoma

3:35-3:50 pm *Break***3:50-4:55 pm Session: Biomarkers of Therapeutic Response**

Chair: Janis Taube

3:50-4:10 Michael Berger, Memorial Sloan Kettering Cancer Center: Delineating the heterogeneity of response to BRAF inhibition in melanoma

4:10-4:30 Navin Varadarajan, University of Houston: Quantitative single-cell biomarkers of melanoma immunotherapy

4:30-4:55 Janis Taube, Johns Hopkins University: Measuring PD-L1 in melanoma: Update and next steps

5:00 pm Closing Remarks Day 1: Laura Brockway-Lunardi, MRA Scientific Program Director**6:30-9:00 pm Reception and Dinner.....National Museum of Women in the Arts**

1250 New York Ave NW, (202) 783-5000

Dress: Casual

6:15-7:15 pm: Transportation provided to museum; Pick up at Desales Street entrance of hotel

6:30-7:30: Reception and Art Viewing; 7:30: Dinner

Friday, February 26th

- 6:30-10:00 am Registration open.....Outside Grand Ballroom
- 7:00-8:30 am General Breakfast.....State Room (Ground)
- 7:00-8:30 am Industry Roundtable Breakfast (by invitation only).....Palm Court Ballroom (Ground)
"Building on the Momentum of Melanoma Clinical Development for 2016 and Beyond"
- 8:45-8:50 am Opening Remarks Day 2:** Louise Perkins.....**Grand Ballroom**
- 8:50-9:20 am Lecture:** Padmanee Sharma, MD Anderson Cancer Center,
From the clinic to the lab: Investigating immune responses to immune checkpoint therapies
- 9:20-11:20 am Session: Combination Therapies**
Chair: Martin McMahon
- 9:20-9:45 Howard Kaufman, Rutgers University: Oncolytic virus immunotherapy: Current combination regimens and future directions
- 9:45-10:10 Craig Slingluff, University of Virginia: Combined immunotherapy of melanoma with long peptides and TLR agonists
- 10:10-10:30 *Break*
- 10:30-10:55 Omid Hamid, The Angeles Clinic and Research Institute: Combination anti-PD-L1 and BRAF inhibition
- 10:55-11:20 Martin McMahon, Huntsman Cancer Institute: The role of PI3'-kinase signaling in melanoma progression and maintenance
- 11:20-11:50 Lecture:** Suzanne Topalian, Johns Hopkins University: Genetic and immunological heterogeneity of melanoma
- 11:50-12:00 pm Closing Remarks:** Leon Black, MRA Co-Founder
- 12:00-1:00 pm Lunch available and departures.....State Room (Ground)

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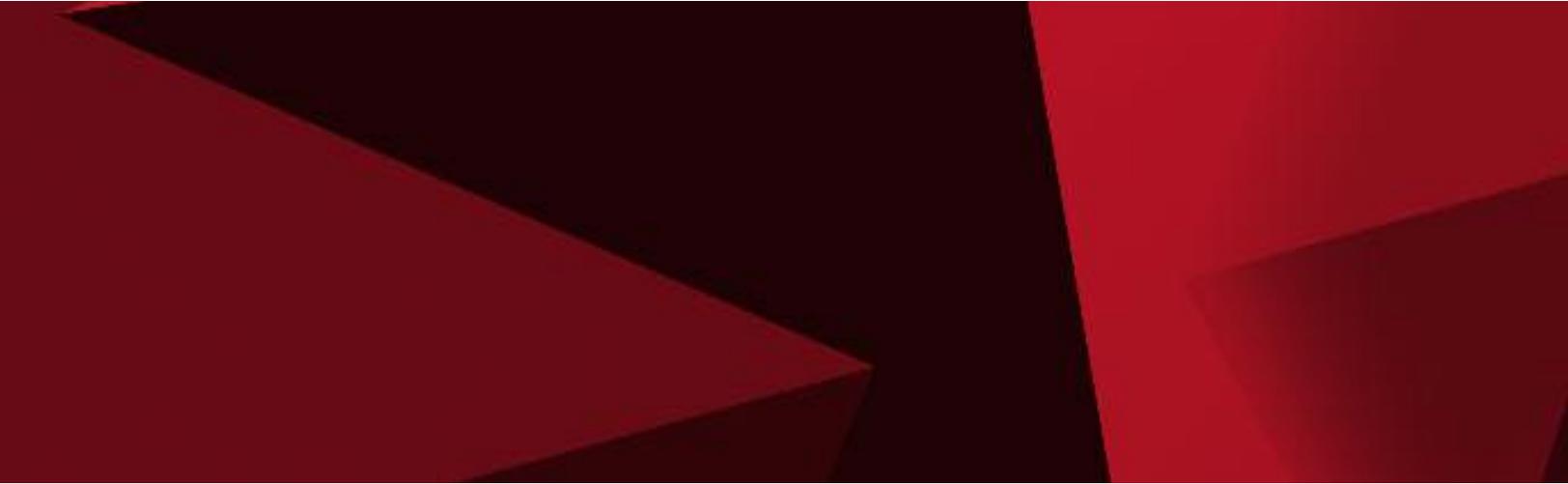


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