Converging on a Cure

Highlights of the Melanoma Research Alliance Sixth Annual Scientific Retreat

FEBRUARY 26-28, 2014 WASHINGTON, DC

Melanoma Research Alliance

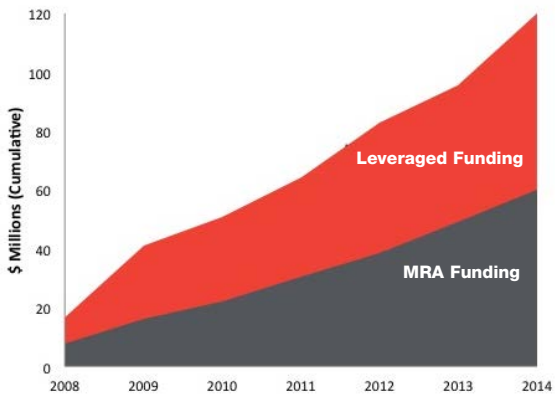
Contents

300 leaders · attendees representing 77 institutions · 29 companies · new models for advancing earlier stage therapies · cutting-edge breakthrough research results · convergence · development of many combination therapies · multi-disciplinary nature · optimism and potential for life-saving progress

Overview

Melanoma, a cancer of pigment-producing cells (melanocytes), most often arises in the skin, but may also originate in the eye, mucous membranes, brain, and spinal cord. Melanoma is the deadliest of all skin cancers because of its ability to spread widely to other parts of the body. Nearly 200,000 new cases are reported each year worldwide, and the incidence is growing. In the United States alone, melanoma incidence has tripled over the past three decades and melanoma is the fifth most common cancer. Alarmingly, melanoma is the second most frequently diagnosed cancer in U.S. young adults. If caught early, melanoma can be successfully treated by surgery, while those diagnosed with widespread metastatic disease (Stage IV) have a median survival of less than one year.

FIGURE 1: GROWTH OF MRA'S IMPACT ON MELANOMA RESEARCH FUNDING



Historically, options for patients with metastatic disease have been severely limited, but unprecedented progress for patients is showcasing melanoma as a case study for all of oncology. The U.S. Food and Drug Administration (FDA) has approved six new melanoma treatments since 2011, including the first immune checkpoint blocking drug (ipilimumab), the first molecularly targeted therapy (vemurafenib) and its companion diagnostic, and the first combination therapy (dabrafenib/trametinib). Agents in late stage clinical testing, notably the "next generation" immune checkpoint blocking drugs targeting PD-1 and PD-L1, are showing great promise in melanoma and other cancers as well.

The Melanoma Research Alliance (MRA), a unique foundation launched in 2007 by Debra and Leon Black under the auspices of the Milken Institute, 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. To date, MRA has awarded more than $60 million in funding to 144 innovative, translational research programs led by 204 Principal Investigators at 92 institutions in 14 countries. As a result of the data that has been generated with this investment, an additional $60 million has been applied to melanoma research, doubling MRA's impact. MRA's investments in

(From left to right) Wendy Selig, Paul Chapman, Debra Black, Jackie King, and Ross King

research with the potential to transform melanoma treatment in the near-term are yielding critical insights that will improve current therapies by identifying new biomarkers, combining treatments aimed at countering drug resistance, as well as discovering new and more effective drug targets. In addition, MRA is playing a key role in new prevention and early detection efforts on multiple fronts, including research and policy engagement.

A key component of MRA's unique research program emphasizes collaboration within and across sectors. The annual Scientific Retreat is an 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 Sixth Annual Scientific Retreat, held in Washington, DC, on February 26-28, 2014, was MRA's largest and most diverse meeting yet with approximately 300 thought leaders in attendance. Participants included academic scientists from nine countries and 77 institutions, almost 60 industry allies, more than 50 representatives of non-profit organizations, and 15 senior-level government colleagues.

At the meeting, MRA-funded investigators—including young investigators, established investigators, and interdisciplinary teams—reported on the progress of their research. In addition, several special sessions addressed key issues, such as opportunities and challenges in developing adjuvant and neo-adjuvant therapies, the role of scientists and other stakeholders in encouraging public support for research, and ways to foster collaboration between melanoma foundations. The meeting also provided an opportunity for interaction and engagement by MRA Young Investigators, a critical component of the MRA research program. Throughout the meeting, the participation of patients and their families underscored the sense of urgency in the attendees' shared mission of defeating melanoma. By promoting collaboration in the field and providing critical investments in innovative translational research, MRA is leading the field in converging on a cure.

(From left to right) James Allison, Wendy Selig, and Rusty Cline

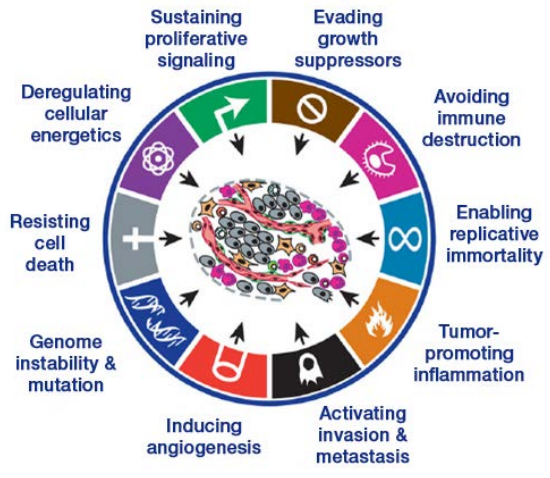
Combination Therapies for Melanoma

Developing rational combination therapies will be necessary to counter drug resistance and improve efficacy of single agent therapies. With immune checkpoint blocking drugs and kinase inhibitors now available to melanoma patients, much research is focused on how to improve upon them, including understanding how these two modalities should be combined. MRA-funded investigators are pursuing research that will inform how best to combine immuno-therapeutic agents, targeted therapies, and other approaches through pre-clinical and clinical studies. It is the hope that combinations will increase the response rate and the durability of response to single agents.

Testing checkpoint blockade combination therapy

Jedd Wolchok, Memorial Sloan Kettering Cancer Center, discussed his team's research aimed at understanding the mechanisms underlying clinical response to combination therapy with ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1). Supported by the Leveraged

FIGURE 2: HALLMARKS OF CANCER



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USED WITH PERMISSION

Finance Fights Melanoma-MRA Academic-Industry Team Science Partnership Award with Bristol-Myers Squibb, the team is working to identify predictive and pharmacodynamic biomarkers of response and toxicity that will allow for better patient selection and target discovery. A Phase 1 clinical trial was conducted treating patients with the combination of iplimumab and nivolumab on a sequenced schedule (ipilimumab followed by nivolumab on progression) or the concurrent combination of both medicines. In sequenced cohorts, even patients who had progressed on ipilimumab responded to nivolumab. Fifty-three percent of patients on the concurrent combination responded at the dose under assessment in Phase 2/3 trials. A biomarker program has been initiated to understand the distinct responses seen in this trial. A biomarker previously identified for single agent PD-1 blockade, tumor expression of PD-L1, was also associated with higher likelihood of response in the sequenced cohort but not in the concurrent combination therapy. This implies that the combination overcomes biomarker driven constraints to monotherapy. Analysis of peripheral blood showed a robust proliferative response (as measured by Ki67) in both CD4 and CD8 T cells in patients treated with the combination compared to patients who received the sequenced regimen. There is an early change in the phenotype of these Ki67 positive cells after combination therapy, and looking at these cells and other elements of tumor specimens will be a focus moving forward. Even though single agent checkpoint blocking antibodies have shown durable efficacy in a subset of patients, Wolchok concluded that, “combination therapy is going to be necessary for immunotherapy to achieve its full potential.”

“Combination therapy is going to be necessary for immunotherapy to achieve its full potential.”

JEDD WOLCHOK

(From left to right) Jedd Wolchok and Michael Atkins

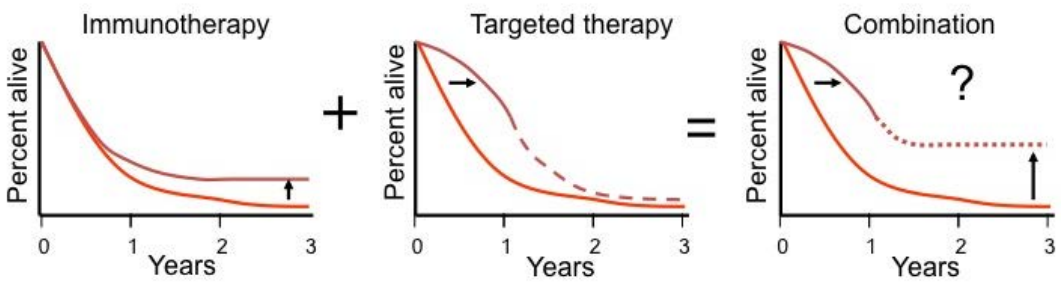
Elucidating drug resistance mechanisms and combinatorial approaches for mutant BRAF melanoma

MRA Established Investigator **Neal Rosen of Memorial Sloan Kettering Cancer Center** focuses his research on uncovering mechanisms behind resistance to BRAF inhibition to uncover additional drug targets and to develop combination therapies that have better effectiveness than single agents. ERK signaling drives most melanomas, and maximal inhibition is required for therapeutic benefit. However, this inhibition is limited by a) relief of ERK-dependent feedback inhibition of signaling, and b) toxicity. These problems can be overcome through the development of new MEK and ERK inhibitor combinations that block feedback reactivation and novel schedules that perhaps will reduce toxicity. Rosen's lab has described that, in contrast to wild-type BRAF that signals as a dimer, V600E mutant BRAF signals as a monomer. As a result, BRAF(V600E) produces increased ERK output, inducing the expression of feedback elements and severely attenuating signaling from other receptor tyrosine kinases. This creates a paradigm relevant to the mechanism of BRAF(V600E) melanoma transformation as well as drug sensitivity and resistance. To improve the treatment of RAS dependent tumors, Rosen's lab is working to identify feedback reactivated receptor tyrosine kinase pathways and develop combinations based on these. More work needs to be done to optimize drug schedules, which he said is "key" as some studies have shown alternative drug schedules mitigate the development of resistance. Working with Jedd Wolchok and others, Rosen is determining whether tumor death induced by targeted inhibitors can sensitize responsiveness to checkpoint therapy.

Studying effects of BRAF inhibition on immunity

Understanding the mechanisms behind the relationship between the immune system and melanoma cell signaling pathways will be necessary for designing combination regimens that target each system. Preliminary evidence from patient tumor biopsies has shown that blocking mutant BRAF with drugs leads to increased expression of tumor antigens and CD8 T cell infiltration. These data suggest that BRAF inhibitors may potentiate the effects of immunotherapy and have stimulated interest in these combinations as a way to enhance and to sustain the effects of molecularly targeted therapy. However, the role of CD8 T cell response in patients treated with BRAF inhibitors and to what extent these drugs contribute to the antitumor effects of BRAF inhibitors is unknown. To try to answer these questions, **Mary Jo Turk of Dartmouth College**, is looking at the effects of BRAF inhibition on immune responses in mouse models supported by an MRA Development

FIGURE 3: COMBINING IMMUNOTHERAPY AND TARGETED THERAPY HAS THE POTENTIAL TO "RAISE THE TAIL" OF OVERALL SURVIVAL IN MELANOMA



COURTESY OF ANTONI RIBAS

Award. Using the BRAF/PTEN inducible mouse model, Turk's lab treated mice with BRAF inhibitor (PLX4720) and found that it significantly increased CD8 T cells by proportion, but not by absolute number compared to pre-treatment. PLX4720 did not promote cross-priming of melanoma antigen-specific CD8 T cells in tumor-draining lymph nodes. Depletion of CD8 T cells did not impair the ability of PLX4720 to stably arrest melanoma growth. However, after BRAF inhibitor treatment, they did see a decrease in suppressive regulatory T cells (Tregs) and myeloid suppressor cells (MDSCs). Furthermore, the Tregs were undergoing apoptosis, but not the MDSCs. Based on these data, BRAF inhibition appears to modulate two main immunosuppressive mechanisms, Tregs and MDSCs, within the tumor. Turk said that a key question that needs to be answered is, "When is the best time to administer immunotherapy in conjunction with BRAF inhibitors?" This preliminary data suggests that perhaps it is late in the course of treatment, such that immune suppression may be reduced, but prior to the development of drug resistance.

MRA Established Investigator **Michael Atkins, Georgetown Lombardi Cancer Center**, is performing studies to define the impact of BRAF targeted therapy on immune function within melanoma metastases from patients. To address this, a clinical trial of vemurafenib is to be conducted at four sites in the U.S. to include multiple biopsies throughout the course of treatment as well as CT scans and peripheral blood mononuclear cell analyses. The study's primary objective is to determine the time course by which vemurafenib increases T cell infiltration. The investigators will also look at many other characteristics and functions of tumor infiltrating lymphocytes and at the immune microenvironment. Preliminary results suggest that immune infiltration peaks at two weeks and can include a mixture of immune cells, including CD8 cells and those associated with immune regulation. If confirmed, this suggests that immune infiltration could result from breakdown of cell-trafficking barriers rather than a specific tumor antigen driven process. An amendment is being pursued to add the MEK inhibitor cobimetinib to the protocol, which will allow investigation into whether it can restore immune infiltration in patients starting on vemurafenib alone as well determination of how starting with the combination of a BRAF inhibitor + MEK inhibitor affects the timing, character, and extent of immune changes in the tumor compared to a single-agent BRAF inhibitor.

Sensitizing immunotherapy with epigenetic therapy

Stephen B. Baylin, **Johns Hopkins University**, gave a special lecture on combining epigenetic therapy with immunotherapy. Baylin is the leader, with Peter Jones as the co-leader, of the Stand Up to Cancer Dream Team focused on bringing epigenetic therapy to the clinic. If one considers DNA the "hard drive" of cells, the concept of epigenetic therapy is to reverse abnormalities caused by problems in the "software," said Baylin. There are multiple mechanisms of epigenetic regulation of genes, including DNA methylation, and studies have linked aberrant methylation with melanoma. Their work on breast, colon, and non-small cell lung (NSCLC) cancers has revealed potential synergy between epigenetic therapy and immunotherapy, which has relevance to melanoma as well. A trial in NSCLC is ongoing to test a sequenced regimen of the epigenetic drug 5-azacitidine (5-AZA) either alone or in combination with the histone deacetylase inhibitor, entinostat, followed by anti-PD-1. To investigate mechanisms underlying this approach, Baylin's team looked at molecular responses to 5-AZA in NSCLC cell lines and found changes in molecules related to immune response pathways, including increased antigen presentation, pro-inflammatory chemokines, interferon pathway, and PD-L1 expression. In a subsequently published study, the group found such dynamics for breast, colon, and ovarian cancer as well. One hypothesis is that this gene signature, which they are calling the "AZA-inducible immune genes", defines a group of tumors that might benefit from epigenetic therapy sequenced with immunotherapy. The analysis of this panel of approximately 300 genes has been applied to breast, colon, and ovarian cell lines as

well, and findings have been similar. Looking at the melanoma TCGA dataset, the investigators see such a signature may be present in this tumor type as well. These findings should stimulate additional research avenues in melanoma on the potential for epigenetic therapies to be combined with immunotherapies.

Novel Listeria melanoma vaccine as platform for combination immunotherapy

Listeria based vaccines have shown promise in clinical trials in pancreatic cancer. With an MRA Academic-Industry Partnership Award with Aduro Biotech, **Charles Drake, Johns Hopkins University**, is testing this approach in murine models of melanoma with the goal of combining it with checkpoint blockade. Listeria monocytogenes is a bacterial species that, in humans, is typically transmitted through contaminated food. The specific Listeria based vaccine that Drake is testing is attenuated by knocking out two mechanisms that affect the way it: 1) is internalized into cells (through a receptor called internalin B) and 2) moves from cell to cell (a gene called ActA). In a B16 melanoma model, Drake and his team showed that the Listeria vaccine caused T cell division without PD-1 and LAG-3 upregulation. To investigate the underlying mechanism of this, microarray analyses of dendritic cells isolated from Listeria vaccinated mice compared with control mice revealed a unique gene program activated in the Listeria vaccinated mice. Next, a melanoma specific Listeria vaccine was created that has GP100 and Trp2 as melanoma antigens. Testing this vaccine in mice led to 30-50% in tumor growth inhibition. In mouse studies, Drake remarked that the Listeria vaccine is “superior when compared head-to-head with other vaccine constructs.” Going forward, the investigators will test this vaccine in combination with PD-1 checkpoint blockade and other therapies.

Combining radiation therapy with ipilimumab

Over the past few years, data has emerged suggesting that high-dose radiation can be a potent stimulator of an anti-tumor immune response through tumor antigen release. Case studies of patients treated with radiation therapy have shown tumor regression in lesions that were not directly radiated (the so-called abscopal effect). Supported by an MRA Pilot Award, **Ramesh Rengan, University of Washington**, is leading a Phase 1/2 clinical trial of ipilimumab in combination with hypofractionated high-dose radiation (SBRT) in patients with advanced melanoma. The idea is that SBRT might cooperate with anti-CTLA-4 to improve response rates both for irradiated and un-irradiated tumors. In addition to determining the safety of this approach, the trial is testing the central hypothesis that SBRT delivered to an index metastatic lesion will stimulate tumor antigen release and improve the anti-tumor immune response to anti-CTLA-4 in advanced melanoma. Preliminary data from 19 patients was presented. To date, no dose-limiting toxicities have been observed in the first set of patients enrolled on this trial. Regressions of irradiated as well as non-irradiated lesions have been observed. Despite encouraging results, resistance is still common. Immune assessments to understand the mechanisms behind response and resistance are underway. Additionally, a pre-clinical mouse model (B16) is being interrogated for potential mechanisms of resistance and to optimize dose and schedule of this combination strategy.

Ramesh Rengan

HIF-1 modulation in melanoma immunotherapy
Highly proliferating cells, such as tumor cells, require more oxygen than can be supplied by the circulation, which creates a hypoxic condition in the tumor microenvironment. MRA-Collaborative Donor Young Investigator **Fan Pan, Johns Hopkins University**, is studying how this hypoxia affects the immune response to melanoma tumors. Cellular adaptation to oxygen scarcity is primarily facilitated by the transcription factor Hypoxia-Inducible Factor 1 (HIF-1). HIF-1 in tumor cells contributes to cancer progression by enacting glycolytic metabolism. Additionally, HIF-1 may aid tumor progression by modulating the anti-tumor immune response. Pan's group and others have shown that HIF-1 shapes the T helper response by driving generation of Th17 cells—a source of IL-17, a cytokine thought to aid tumor development and progression. Knocking out HIF-1 in T cells resulted in slower B16 melanoma tumor growth. However, increased regulatory T cells (FoxP3+ cells) were seen, which may be expected to dampen the immune response. Therefore, next steps are to look at the combination of HIF-1 and FoxP3 inhibition as a therapeutic approach in pre-clinical models.

WHAT THIS MEANS FOR PATIENTS

Tumors are able to continually evolve strategies for survival, which hampers the long-term effectiveness of therapies that target just one specific driver of the cancer, such as mutant BRAF. Immunotherapies have shown longer-lasting responses, but fewer patients respond compared with molecularly targeted therapies. Researchers are working to understand the biology underlying drug resistance and to identify factors in the immune system that influence response to therapies. This work will set the stage for the development of the most effective drug combinations for melanoma patients, including combinations of immunotherapies, agents that target mutated proteins and abnormally expressed genes that drive the cancer, radiation therapy, and vaccines. A significant amount of research still needs to be done to understand how to give combination therapies to patients by determining the right doses and schedules of the drugs. Nevertheless, MRA-funded research is accelerating promising combinations that have the potential to significantly improve the outcomes for patients with metastatic melanoma.

Biomarkers: The Key to Melanoma Prognosis and Treatment Outcomes

Cancer drug development is increasingly linked to the molecular or immunologic subtype, and advances in biomarker research are making personalized medicine a reality. Predictive biomarkers give information about a therapeutic intervention and can be used to identify subsets of patients who are more or less likely to respond to a given therapeutic regimen. Prognostic biomarkers anticipate the likely clinical outcome. MRA researchers are pursuing both of these avenues with innovative clinical and pre-clinical approaches that hold promise for better risk stratification, improved patient selection for certain therapies as well as clinical decision-making throughout the course of treatment.

Discovering genetic drivers of melanoma development and progression

Little is known about the early stages in nevus and melanoma development, and how driver genes cooperate with co-drivers for malignant transformation. The melanoma field has already identified and studied the dominant high penetrance susceptibility genes, but there are many low to moderate penetrance genes yet to be studied. Supported by the MRA-L'Oréal Paris Team Science Award, **Meenhard Herlyn of the Wistar Institute** is developing a human skin model system to investigate the interaction between genes and UV in order to identify new genetic drivers in melanoma. Not all individuals that have been over-exposed to UV radiation develop melanoma because as Herlyn remarked, "these genes have to be in the right environment, in the right person" to promote melanoma. Because obtaining and working with melanocytes from high risk patients is difficult, the investigators are taking an indirect approach. Fibroblasts are taken from patients and reprogrammed to become embryonic stem-like cells, which can then be differentiated into melanocytes and keratinocytes. These cells are then used to regenerate human skin grafts on host animals, which are then exposed to UV irradiation,

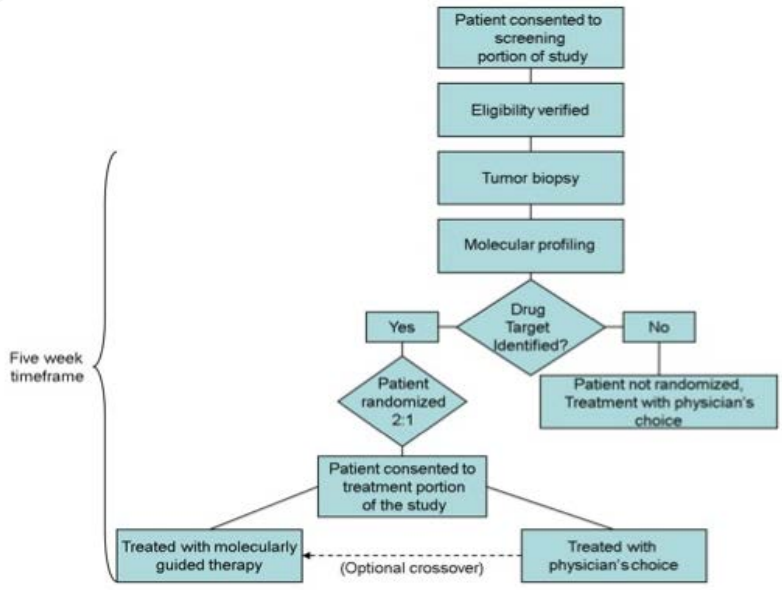
which is used along with various genetic manipulations, to promote tumor formation. Using this model, the team will work to identify genetic drivers that, in combination with UV exposure, promote the transformation from nevus to melanoma. The ultimate goal of this work is to determine new ways to prevent melanoma as well as possibly identify new drug targets.

Graeme Walker, Queensland Institute for Medical Research, summarized results from an MRA Pilot Award using an innovative mouse model system, called the collaborative cross, to discover melanoma modifier genes. These genes do not cause melanoma per se, but modify its time or severity of development, and they are difficult to discover in human populations due to the need for very large high-risk cohorts, and the potential skewing of results because of differences in individual treatments and precursor/early lesion removal. The advantage of the collaborative cross system is that it allows the study of melanoma on scores of genetic backgrounds, identification of strains that are protected from melanoma, and mapping of genes that are responsible for modifying melanoma development. Using a well-characterized mouse model of melanoma combined with the collaborative cross, Walker has begun to map genes for many aspects of melanoma development, including age of onset and multiplicity of nevi and melanomas. In terms of genes that modify whether or not the animals develop melanoma, the best candidate modifier gene identified so far is TGFbeta2, which has also been shown to be associated with survival and recurrence in high-risk patients. The information regarding the genes, and the biological pathways that they regulate, will be used to develop strategies to slow melanoma growth in patients.

Developing a personalized medicine approach for BRAF wild type melanoma

Jeffrey Trent, Translational Genomics Research Institute, co-leader of the MRA-Stand Up to Cancer Melanoma Dream Team provided an update on the Dream Team program, which is focused on developing an innovative biomarker-driven approach for patients with non-BRAFV600 mutant melanoma. The central module of the project is a clinical trial (called the GEMM trial) for patients who have failed or are ineligible for immunotherapy who will be randomized 2:1 to molecularly informed therapy versus physician's choice. The primary endpoint is best overall response rate. Their available FDA-approved and investigational drugs with recommended Phase 2 dosing currently consist of 24 agents, including a MEK inhibitor + AKT inhibitor combination. Additional agents, including a MEK inhibitor + CDK4/6 inhibitor combination, are awaiting finalization of a recommended Phase 2 dose. Two milestones have been completed: 1) a feasibility study to confirm a timeline of patient biopsy to return of information to the tumor board within three weeks; and 2) FDA clearance has

FIGURE 4: GEMM CLINICAL TRIAL SCHEMA



COURTESY OF JEFFREY TRENT FOR THE MRA-SU2C MELANOMA DREAM TEAM

been granted for the molecular profiling. In early May, the study opened up to patient accrual. The overarching goal of this ambitious program is, as Trent said, "Not just to test whether individual drugs are effective but rather test the concept of precision medicine with individual drugs in specific patients." To do this, the team will iteratively refine and standardize a set of statistical and informatics methodologies for matching treatments to a patient's tumor. If successful, this approach has the potential to transform research and care not just for melanoma patients but for other cancer patients as well.

Identifying markers of response and resistance to PD-1 pathway blockade

Supported through an MRA Team Science Award, **Suzanne Topalian, Johns Hopkins University**, reported on research to identify biomarkers for

Suzanne Topalian

WHAT THIS MEANS FOR PATIENTS

Identifying markers in blood or tumor samples that predict which patients will benefit from different treatments is a major area of research. For example, BRAF inhibitors have been approved for patients whose tumors express the BRAF(V600E) mutation—a biomarker that is detected by a diagnostic test. Given the dynamic nature of the immune system's response to cancer, immunotherapies, including both approved (ipilimumab) and investigational (e.g., PD-1 pathway inhibitors), have been typically more difficult for biomarker identification compared to molecular targets. MRA-funded research is accelerating the identification and development of biomarkers that will be important not only for better patient selection, but will also promote better understanding of how the drugs work or do not work in certain patients. An innovative personalized medicine trial jointly funded by MRA and Stand Up to Cancer is testing whether molecular information from individual patient tumors can inform the selection of therapies against these specific drivers. MRA-funded investigators are also identifying new melanoma risk genes and working to understand how these genes interact with UV radiation to promote melanoma formation.

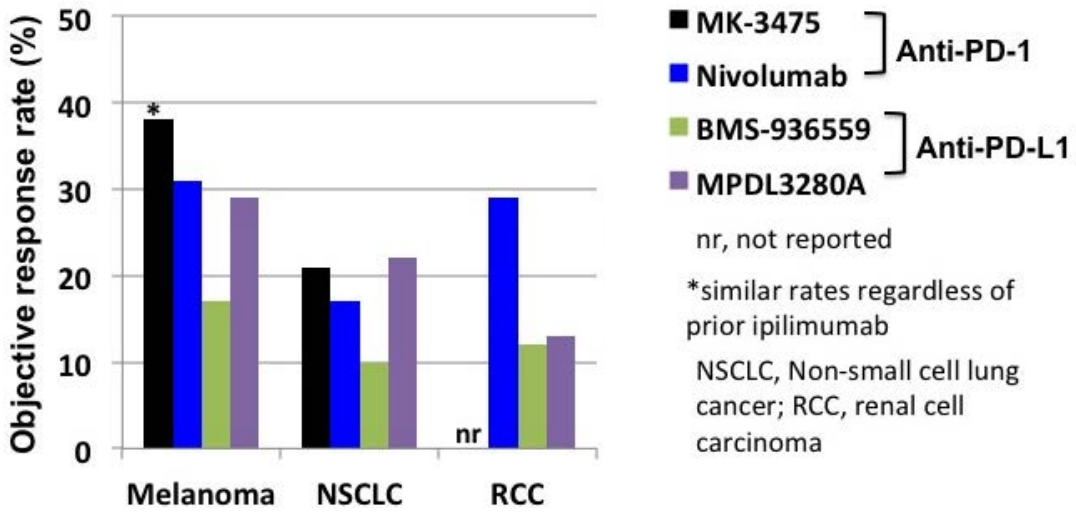
PD-1 pathway blockade. While responses to anti-PD-1 and anti-PD-L1 antibodies have been remarkable, there is still a large group of patients who do not respond to these agents. Understanding the biological basis for these varied responses can not only inform better patient selection, but help to determine the mechanism of action of these drugs and identify other drug targets. T cells from patients who have successful anti-tumor immune responses often recognize mutant tumor antigens and, therefore, the molecular diversity of individual patients may underlie these results. "Just as melanoma is molecularly diverse, melanoma is also immunologically diverse," said Topalian. This diversity is across space (anatomic sites of metastases) and also across time (primary to metastatic lesions). While the strongest predictor of clinical response identified to date is PD-L1 expression by the tumor, it is not absolute, meaning that there are responders in the marker negative population. Thus, much more work needs to be done to determine its utility as a treatment

"Just as melanoma is molecularly diverse, melanoma is also immunologically diverse."

SUZANNE TOPALIAN

biomarker. Examining other factors, Topalian's team found that interferon gamma was overexpressed in PD-L1 positive melanomas versus PD-L1 negative tumors. These findings support the model of adaptive melanoma immune resistance where T cells that recognize melanoma antigens presented on tumor cells migrate to sites of the tumor. Once there, if these activated T cells secrete interferon gamma, PD-L1 expression by tumor cells is promoted, and those T cells are turned off. In addition, the team found several other genes overexpressed in PD-L1 positive tumors, such as IL-10, LAG-3, and others that might contribute to local immune suppression. In fact, LAG-3 + PD-1 combination blockade is currently being testing in clinical trials.

FIGURE 5: CLINICAL ACTIVITY OF PD-1 AND PD-L1 BLOCKING ANTIBODIES IN MELANOMA AND OTHER CANCERS



COURTESY OF SUZANNE TOPALIAN

Theraputic Targeting of NRAS Mutant Melanoma

Mutations in the NRAS gene have been found to drive melanoma growth and survival in approximately 15 percent of cases and are typically mutually exclusive to the BRAF mutations that are found in about half of melanomas. NRAS tumors tend to carry a poorer prognosis, and it is a particularly challenging protein to target therapeutically. MRA researchers are aiming to overcome these obstacles through innovative approaches to develop new therapeutics for NRAS mutant melanomas including targeting downstream nodes on the pathway, enzymatic modulation of the protein, and exploring drug combinations through synthetic lethal screens and epigenetic factors.

PKC-delta inhibition as a therapeutic approach in melanomas with NRAS mutations

MRA Established Investigator **Douglas Faller, Boston University**, reported on the development of a new approach to treat NRAS mutant melanoma by inhibiting the enzyme protein kinase C delta (PKC-delta). His laboratory showed that the activity of this enzyme is required for the survival of melanoma cells and has shown in other cancer cell types that cells transformed by HRAS and KRAS mutations undergo apoptosis when PKC-delta is inhibited. PKC-delta has pro-apoptotic activity in certain normal cells but anti-apoptotic activity in cancer cells. PKC-delta knockout mice have no major phenotypic abnormalities, and inhibition of PKC-delta is not toxic to normal cells, suggesting that this is a suitable therapeutic approach. Novel small-molecule inhibitors of PKC-delta were designed as chimeric hybrids of two naturally occurring PKC-delta inhibitors, staurosporine, and rottlerin. One of the most active compounds, called B106, inhibited PKC-delta with nanomolar potency and is ~1000 times more specific for PKC-delta over PKC-alpha. In studies of 15 different NRAS mutant melanoma cell lines, B106 efficiently inhibited cell growth and decreased clonogenic capacity. Normal melanocytes were not significantly affected. The investigators also studied the downstream effectors following PKC-delta inhibition and observed that

the JNK pathway was activated, leading to the activation of downstream H2AX. In BRAF-mutant melanoma cell lines that had evolved resistance to a BRAF inhibitor, PKC-delta inhibition effectively induced cytotoxicity in these cells, suggesting the potential clinical utility of targeting PKC-delta in patients who have relapsed following treatment with BRAF inhibitors as well. These candidate drugs may represent a new therapeutic approach for these subgroups of melanoma patients, and Faller's team will continue to develop the molecules with properties more suitable for clinical application.

Targeting NRAS palmitoylation in melanoma

NRAS protein requires a lipid modification (called palmitoylation) for its membrane localization and tumorigenic functions. Stewart Rahr-MRA Young Investigator **Xu Wu, Massachusetts General Hospital**, is exploring whether inhibiting NRAS palmitoylation could efficiently block NRAS-driven melanoma. To do this, his group developed a novel "chemical strategy," as Wu calls it, to study the DHHC-family palmitoyl acyltransferases (PATs) that regulate NRAS palmitoylation and that may be therapeutic targets for NRAS driven melanoma. The compound 2-bromopalmitate is an irreversible PAT inhibitor. Wu showed that this inhibitor blocked NRAS localization to the cell membrane. His lab developed a chemical probe based on this compound, allowing them to profile the "elevated" PATs activity in melanoma cells using mass spectrometry. Knocking down the gene DHHC5 with shRNA resulted in NRAS trapped inside the cell, suggesting this is a specific gene that regulates palmitoylation of NRAS. His lab is in the process of fully validating the oncogenic activities of DHHC-PATs in melanoma using shRNAs targeting PATs and design and synthesis of compound libraries targeting PATs. In addition to application to NRAS mutant melanoma, Wu said that this approach could also be applied to other molecular subtypes of melanoma, including Rac1, GNAQ, and GNA11.

Mechanisms of resistance for constitutively-activated NRAS melanoma

Combined targeting of either MEK + PI3K/mTORC1,2,

Levi Garraway

or MEK + CDK4/6 has been shown to be effective at abolishing the growth of NRAS mutant melanoma, and clinical trials testing these combinations are in progress. However, the complete inhibition of NRAS oncogenic signaling is challenging due to existence of redundant feedback signals that activate MAPK and lead to heterogeneous mechanisms of resistance. Ellis Family-MRA Young Investigator **Susana Ortiz-Urda, University of California, San Francisco**, is pursuing laboratory studies to anticipate mechanisms of resistance to these drugs by comprehensively analyzing the diverse functions of the NRAS gene and the different mechanisms of resistance to inhibitors. Using NRAS mutant melanoma cell lines that were induced to become resistant to MEK inhibitor, she found expression of several so-called long noncoding RNAs (LNCs). LNCs are transcripts of >200 nucleotides that have diverse functions such as transcriptional and post-transcriptional regulation, translational repression, and epigenetic regulation. One in particular, called LNC8, is produced in MEK inhibitor resistance, and is the subject of additional studies. According to Ortiz-Urda, preliminary data indicate that "LNCs may be biomarkers present in some cells that are resistant to the drug." As the project continues, the lab will analyze patient samples from ongoing clinical trials to identify and validate biomarkers of resistance and response.

Development of rational therapeutic regimens for NRAS-mutant melanoma

Given that combinations will most likely be the best treatment approach for NRAS mutant melanomas, MRA Established Investigator **Levi Garraway, Dana-Farber Cancer Institute**, is addressing the question of what should be combined with MEK inhibition in NRAS mutant melanoma. His lab is using a synthetic ally ethal screening approach using a genome-wide shRNA library. To find possible targets, he is testing the library in NRAS mutant melanoma cell lines that are either given a MEK inhibitor or control and looking for genes, which when knocked down, synergistically kill cells with the MEK inhibitor. In this screen, top hits were BRAF and MAPK1 (which encodes ERK2), suggesting the consideration of ERK inhibitor in combination with a MEK inhibitor. Testing this preclinically, in fact, a synergistic effect (so called "excess over bliss") was observed using this combination in NRAS mutant cell lines. A pan-RAF inhibitor also showed synergy with MEK inhibitor in some cell lines. Similar screens with uveal melanoma cells revealed BRAF as the top synthetic lethal partner with a MEK inhibitor in a GNAQ cell line. A pan-RAF inhibitor was also synergistic with a MEK inhibitor in uveal melanoma cells. These studies suggest that a combination of a pan-RAF inhibitor and a MEK inhibitor could be worth pursuing clinically in both NRAS mutant and uveal melanoma. These data also support the current concept that most melanomas have a major MAPK dependence. More meaningful signals from synthetic lethal screens emerge when multiple cell lines are examined. As this project continues, Garraway's lab will continue to follow up on these leads as well as other hits that emerged from the screens. In discussing the future of melanoma treatment, Garraway said that what will be needed are "higher order therapeutic combinations—4, 5, even 6-drug combinations—that's really the only way to cure cancer."

> "Higher order therapeutic combinations—4, 5, even 6-drug combinations—that's really the only way to cure cancer."
>
> **LEVI GARRAWAY**

WHAT THIS MEANS FOR PATIENTS

Mutations in the NRAS gene have been found to drive melanoma growth and survival in approximately 15% of cases and are typically mutually exclusive to BRAF mutations that are found in about half of melanomas. NRAS mutant melanomas are particularly challenging to target therapeutically. However, MRA-funded researchers are developing innovative approaches to address this area of unmet need. Their work is revealing several novel therapeutic approaches, such as the development of inhibitors of a protein called PKC-delta, which is one of the proteins that NRAS affects. Another novel approach is manipulating how NRAS itself is attached to the cell membrane, which is where it needs to be to function. MRA-funded research is accelerating combination therapies for this subtype of melanoma, and early results have identified and supported the use of several drug targets for use with MEK inhibitors, which are already in clinical testing.

New Strategies for Target Discovery and Credentialing

New discoveries fueled by MRA-funded research are revealing a wide range of new potential therapeutic targets and candidate drugs, including those specific to certain tumor cell types, as well as novel molecular and immunologic approaches. MRA-supported investigators are developing therapeutic agents and have also revealed potential application in melanoma of drugs used for other cancers.

Targeting melanoma cell subpopulations

Tumors consist of a heterogeneous mass of cells with diverse genetic and molecular alterations that arise as the disease progresses. The changing tumor microenvironment may also influence which cancer cell subpopulations are able to survive, proliferate, spread, and resist therapy. MRA Established Investigator **Jonathan Cebon, Ludwig Institute for Cancer Research at Melbourne**, has observed that cellular plasticity in melanoma has many of the characteristics of the so-called "Epithelial-to-Mesenchymal transition" (EMT). As a result of EMT, cells that have more invasive characteristics emerge, and these are thought to significantly contribute to disease progression. Thus, blocking their emergence may prevent treatment failure. Through analysis of tumor cells derived from patients, his group identified a clear dichotomy of cells having either epithelial or mesenchymal characteristics. Cebon's group discovered that thrombospondin-1 (TSP-1), a major activator of TGF-beta, was expressed at high levels by the invasive cells. Knocking down TSP-1 restored sensitivity of BRAFi-resistant cells lines to a BRAF inhibitor, suggesting that this mechanism may play a role in drug resistance. High expression of another molecule, pregnancy-associated plasma protein A (PAPP-A), was also seen in a subset of mesenchymal-like melanomas. Knocking down PAPP-A affected cell invasion and migration. Anecdotal evidence suggests that melanoma in pregnancy is associated with increased relapse and poorer outcomes.

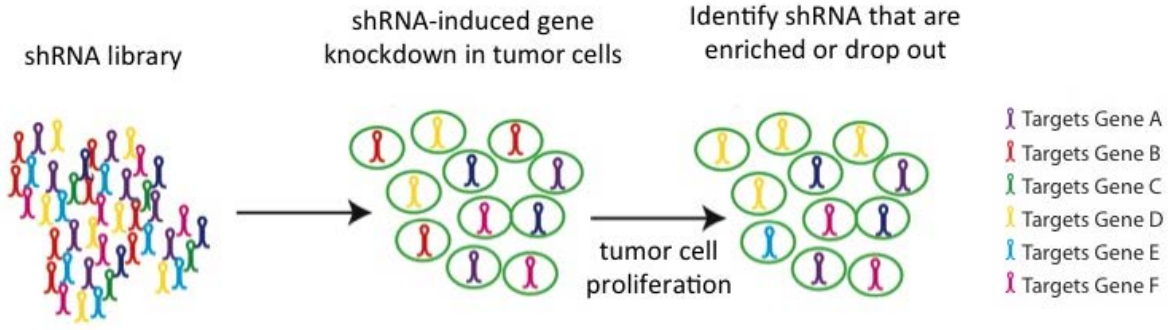
PAPP-A is a placental protein that increases the bioavailability of insulin-like growth factors (IGFs). Cebon's data suggest that activation of the IGF pathway by PAPP-A may contribute to melanoma progression in pregnancy. In total, these data suggest that TSP-1 and PAPP-A are potential targets for a subset of cells in melanoma that are more invasive and likely contribute to disease progression and treatment failure.

SkinCeuticals-MRA Young Investigator **Barbara Bedogni, Case Western Reserve University**, is elucidating the role of Notch and ERBB signaling in melanoma development and progression. Notch is very important during embryogenesis and in the renewal of adult tissue. It can regulate cell survival, proliferation, and migration and has been shown to have a role in different cancers. Notch and ERBB are evolutionarily conserved signaling molecules that play essential roles in melanocyte precursors, but are inappropriately re-activated in melanomas. Bedogni's lab has shown Notch1 directly promotes ERBB3 activation by regulating the expression of neuregulin1, the ligand for ERBB3 and 4; and that once activated, ERBB3 by co-opting ERBB2, promotes melanoma cell survival. Blockade of either the Notch or ERBB pathway alone triggered modest effects, however, the combination of a

Barbara Bedogni

gamma-secretase inhibitor (dibenzazepine) that blocks Notch activation and lapatinib, an ERBB2/EGFR inhibitor, elicited synergistic effects, leading to 90% loss of melanoma cell viability regardless of whether cells carried wild type or mutated BRAF. These studies suggest that Notch1 and ERBB3/ERBB2 are novel melanoma therapeutic targets with the potential to benefit patients across the spectrum of mutations that drive melanoma.

FIGURE 6: shRNA SCREENS TO IDENTIFY TARGETS THAT ARE IMPORTANT TO TUMOR CELLS



COURTESY OF CHRISTOPHER VAKOC

shRNA screening to identify new melanoma drug targets

Christopher Vakoc, Cold Spring Harbor Laboratory, described work to identify candidate drug targets in therapy-resistant melanoma by deploying sophisticated shRNA screening approaches that were supported by an MRA Team Science Award. Using shRNA libraries developed in team member Greg Hannon's lab, screenings of chromatin regulators in melanoma cell lines (mouse and human) were performed, and several candidate epigenetic vulnerabilities were identified. Bromodomain-containing 1 (BRD1) is their top candidate for further investigation. A related gene, BRD4, was also identified which has been shown to be relevant in melanoma by other groups. However, no published report has linked BRD1 to melanoma biology. BRD1 shRNAs applied to various melanoma cells of different genotypes showed complex sensitivity to BRD1 knock down. The findings suggest that BRD1 is relevant in a subset of melanoma cases, irrespective of BRAF mutation status. Since bromodomain proteins are potentially druggable, the team will continue to follow up on these results with mechanistic studies to explore the downstream pathways that are altered by BRD1 inhibition.

Identifying new targets through network models of signaling pathways

MRA Established Investigator **Chris Sander, Memorial Sloan Kettering Cancer Center**, reported on a combined experimental-computational effort to build predictive network models of melanoma cells' response to combination therapy. This systems biology approach is based on a large series of experiments using drug combinations in cell lines, and observation of protein levels on a high throughput antibody-based platform. Cell lines are treated with single drugs or drug combinations and phosphoprotein and protein levels are measured. Effect of the drug perturbations on cell viability is also examined. This information is used as input to build predictive mathematical models of cellular response to an untested drug or drug combination. Using this approach, Sander stated, "You can develop mathematical models of what happens in cells that go beyond the intuition that we typically draw on." This work has led to two hypotheses: 1) inhibition of polo-like kinase (PLK1) is effective in certain melanoma cell lines and may be a useful component of combination therapy in RAF inhibitor resistant melanoma and, 2) co-targeting of the two other signaling pathways currently being tested has a synergistic response that may potentially overcome RAF inhibitor resistance in melanoma cells.

> "You can develop mathematical models of what happens in cells that go beyond the intuition that we typically draw on."
>
> **CHRIS SANDER**

Improving agonistic anti-CD40 antibodies

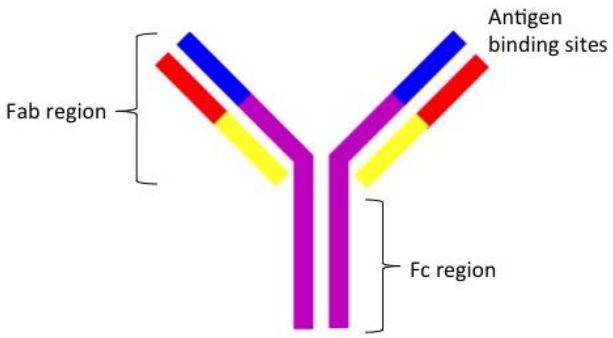
MRA Established Investigator **Jeffrey Ravetch, Rockefeller Universit**y, described his work to determine to what extent interactions of the antibody Fc region play a role in the in vivo activity of anti-CD40 antibodies for melanoma. Ravetch stressed that, "antibodies are more than V regions." The antibody Fc region is structurally and functionally diverse and can mediate a diverse array of functions. Work in other cancers has shown that the structure of the Fc makes a huge difference in the efficacy of therapeutic antibodies. CD40 agonistic antibodies work by mimicking the CD40 ligand, which activates the antigen-presenting cell, up-regulates co-stimulatory molecules, and drives T cell activation. Ravetch's lab discovered that agonistic, anti-CD40 immunotherapeutic antibodies

require binding to a specific type of Fc receptor—the IIB Fc receptor—to work optimally in vivo. Based on these studies, they developed a fully human agonistic anti-CD40 antibody optimized for enhanced Fc receptor IIB binding for the treatment of metastatic melanoma. Preclinical studies showed improved activity over other anti-CD40 antibodies, and Ravetch's team is now looking for collaborators to move this agent into clinical testing.

In vivo discovery of novel targets for melanoma immunotherapy

MRA Established Investigator **Kai Wucherpfennig, Dana-Farber Cancer Institute**, described the novel approach his lab developed for the discovery of immunotherapy targets in melanoma. Their hunt for targets is focused on key negative regulators of cytotoxic T cells as identified through an in vivo shRNA screen that enables simultaneous testing of many genes. CD8 T cells are infected with shRNAs, injected into B16 mouse melanoma models, and proliferation in response to tumor antigen is measured. The T cells are then isolated from the tumor and analyzed. Using this approach, a total of 43 candidate genes have been identified. One of these, called Ppp2r2d (a regulatory subunit of the protein phosphatase, PP2A), has been characterized in detail. This gene seems to inhibit T cell proliferation and promotes T cell apoptosis in tumors. When Ppp2r2d was silenced, the T cells secreted more cytokines, in particular gamma interferon, and there were higher levels of MHC class I on the tumors, which may make them better targets for T cell killing. The ultimate goal of this work is to improve upon T cell based therapies, such as adoptive cell transfer therapy.

FIGURE 7: DIAGRAM OF ANTIBODY STRUCTURE SHOWING ANTIGEN BINDING SITES, Fab, AND Fc REGIONS



"Bringing together basic and translational scientists can achieve far more than either discipline alone."

GLENN DRANOFF

Developing anti-MICA antibody immunotherapy

MRA Team Science Award leader **Glenn Dranoff, Dana-Farber Cancer Institute**, reported on work to develop novel antibodies for melanoma immunotherapy. Dranoff described this project as illustrative of how "bringing together basic and translational scientists can achieve far more than either discipline alone." Their work is based on the finding that some patients who respond well to ipilimumab developed antibodies to a protein called MHC class I chain-related protein A (MICA). MICA is up-regulated on the tumor cell surface after cell injury and is the ligand for NKG2D expressed on cytotoxic lymphocytes; their interaction results in cytolysis and inflammatory cytokine production. In collaboration with Kai Wucherpfennig, Dranoff isolated a panel of human anti-MICA monoclonal antibodies of which a subset showed broad reactivity. These antibodies inhibited MICA shedding from melanoma cells, antagonized the immunosuppressive effects of soluble MICA present in the sera of melanoma patients, promoted NKG2D-dependent killing of melanoma cells by human peripheral blood mononuclear cells, and inhibited tumor growth in model systems. The team plans to bring these antibodies into the clinic in the near future, and they have promising potential to be combined with other therapies, such as HDAC inhibitors or CTLA-4 blockade.

Jeffrey Weber and Iman Osman

WHAT THIS MEANS FOR PATIENTS

The development BRAF and MEK inhibitors as well as therapies targeting CTLA-4 and the PD-1 pathway represent major breakthroughs in the treatment of melanoma. Yet, a significant number of patients either do not respond to these agents or develop resistance and relapse. Thus, additional therapeutic targets need to be identified and developed. In recent years, MRA-funded researchers have made tremendous strides in the identification of new melanoma targets including factors on subsets of particularly aggressive melanoma cells and other molecules that are responsible for melanoma cell development and growth. Additionally, investigators are developing new leads for melanoma immunotherapy, such as proteins on melanoma cells that the immune system recognizes and mechanisms that regulate the immune cells themselves.

Selected Therapeutic Approaches: Unanswered Questions, Future Roles

The availability of new and effective melanoma treatments has drastically altered the melanoma landscape and expectations for the field. In addition to these molecularly targeted and checkpoint blockade approaches, other established and experimental therapeutic modalities are available to metastatic melanoma patients, including surgery, vaccines, and adoptive cell therapy. Leaders in these respective fields discussed their perspective on the role of these specific approaches in melanoma treatment and research.

Surgery

Daniel Coit, Memorial Sloan Kettering Cancer Center, focused on the role of surgery, including sentinel lymph node procedures as well as surgery involving visceral metastases, in the current era of systemic therapy options. Sentinel lymph node biopsy (SLNB) has a significant false-negative rate, but it is the most important prognostic indicator in melanoma—much more important than other characteristics of the primary tumor. It is associated with improved relapse-free survival, but the clinical significance of that has not been clearly defined, and it does not lead to improved overall survival. The role of SLNB may become more important as effective adjuvant therapies emerge for patients with positive nodes, unless comparable prognostic information can be derived from genetic characteristics of the primary tumor. When a positive sentinel node is identified, complete lymph node dissection (CLND) is usually recommended. In contrast to SLNB, complete node removal is associated with high morbidity, and it is unclear if it makes a difference in patient outcomes. Similar to SLNB, it provides useful prognostic information, particularly for stratifying patients in clinical trials. An ongoing prospective, international clinical trial will evaluate the role of CLND on melanoma specific survival. With regard to the role of surgery in metastatic disease, said Coit, “The paradigms are changing.

Integration of surgery with systemic therapy is how patients are going to be treated." As an example, he described a case study of a patient with brain metastases who had a complete response to ipilimumab but later developed a small bowel metastasis, which was successfully removed with surgery. Systemic therapy prior to surgery (neoadjuvant therapy) has many advantages for both clinical care and research, including improving tumor resectability, minimizing the operation, and sometimes avoiding surgery altogether. Scientists can learn an immense amount of information about response to therapies from the resected tumors in this setting. Coit emphasized that the course of clinical care for patients will need to be individualized with information from predictive biomarkers that will improve clinical decision-making.

Vaccines

Nina Bhardwaj, Icahn School of Medicine at Mount Sinai, discussed the role of therapeutic vaccines in melanoma. Despite much research in this area, there is currently only one FDA-approved cancer vaccine, sipuleucel-T, which is for patients with prostate cancer. While vaccines have been shown to slow tumor growth in clinical trials, complete durable anti-tumor responses in the metastatic setting have thus far been infrequent. In general, vaccines do not target inhibitory mechanism in the tumor microenvironment and use single or weak immunogenic antigens, often favoring immune escape. Given the efficacy of other available therapies, the question now is how vaccines might improve upon them. There are a number of combination therapies with vaccines now in clinical testing, such as NY-ESO-1 vaccination + ipilimumab and multi-peptide vaccine + anti-PD-1. In addition to combining vaccines with other therapies, the development of personalized vaccines is another evolving area. There is great opportunity for personalized vaccines in melanoma due to the large number of mutations in melanoma tumor cells that can give rise to numerous neo-antigens. Several research groups are integrating individual patient tumor sequencing data with sophisticated algorithms to identify neo-epitopes suitable for personalized vaccine development. Currently, this process is very expensive and in order to move it to clinical use, rapid, low-cost platforms will be required. Better vaccine adjuvants and booster schedules to maintain anti-tumor responses also need to be developed. While much of the clinical testing of vaccines is done in the metastatic setting, Bhardwaj posed the question, "Do we go much, much earlier than we've been doing right now to include testing in earlier stage disease and in the neo-adjuvant setting?" As other speakers had noted throughout the meeting, better predictive and prognostic biomarkers will improve patient selection for vaccines as well.

Steven Rosenberg

> "The paradigms are changing. Integration of surgery with systemic therapy is how patients are going to be treated."
> **DANIEL COIT**

Adoptive cell transfer

Steven Rosenberg, U.S. National Cancer Institute, reviewed the state-of-the-art adoptive cell therapy (ACT) in melanoma. Advantages of ACT include the ability to administer very large numbers of activated, tumor specific T cells to patients whose own immuno-suppressive immune cells have been abolished. ACT has been shown to elicit long term complete responses in approximately 20% of patients regardless of number of metastatic deposits, bulk of metastases, sites of disease, or prior therapy. These data suggest that, "A tumor infiltrating lymphocyte with anti-tumor activity has the ability to eliminate the last cancer cell in the patient's body," said Rosenberg. He hypothesizes that ACT, like other cancer immunotherapies, works when the immune system recognizes unique mutations that are expressed by the cancer. However, Rosenberg noted that, "Having a mutation is not enough." To have an effect, the mutation needs to encode a protein that can be processed and recognized by the patient's immune system. Rosenberg's lab developed several innovative methods for using tumor exome sequencing data to identify and predict mutations that T cells recognize. Another approach is to identify T cell receptors that target mutated antigens and transduce them into cells for ACT. More recently, a third method they developed involves transfecting mini-genes of the mutations into dendritic cells, which allows the patient's own immune system to select the mutations of importance. Through this work, they have not identified any shared melanoma mutations (e.g., BRAF, RAS) that are recognized by tumor infiltrating lymphocytes that are capable of mediating tumor regression. Thus, it appears that every patient is unique. In more recent work, Rosenberg's group isolated T cells from fresh tumors that express immune inhibitory markers, such as PD-1 (presumably cells that been stimulated by the tumor), and found that there are subtypes that express T cell receptors that recognize mutations that they identified using other techniques. Potentially, this method could be used to select for subsets of T cells for use in cell therapy. While such personalized ACT approaches hold promise, immunotherapies based on shared melanoma antigens have had mixed results. However, results from a small clinical trial of ACT using lymphocytes expressing the T cell receptor for the cancer testes antigen NY-ESO-1 have shown 53% response (RECIST criteria) with 21% having complete regressions in melanoma patients. While ACT has already demonstrated durable regressions in patients with metastatic cancer refractory to other treatments, several new technologies are being developed to improve upon it and create the "ultimate personalized therapy," said Rosenberg.

"A tumor infiltrating lymphocyte with anti-tumor activity has the ability to eliminate the last cancer cell in the patient's body."

STEVEN ROSENBERG

Development of Adjuvant and Neo-Adjuvant Treatments

Over the last several years, there has been remarkable clinical progress in melanoma, providing new options and hope for metastatic melanoma patients. Yet, clinical testing of agents in the adjuvant (systemic therapy after surgery) and neo-adjuvant (systemic therapy prior to surgery) settings has lagged behind despite the need for more options for these patients. More than twice as many melanoma patients are diagnosed with regional metastases versus distant metastases. Some of these patients with high risk for progression might be better managed with systemic therapies in conjunction with surgery. Leaders from industry, academia, NIH, and FDA participated in a small roundtable discussion of challenges and solutions in the development of therapies for high-risk early stage melanoma patients. The session was moderated by **John Kirkwood from University of Pittsburgh Hillman Cancer Center**. Several themes arose during the discussion, including:

John Kirkwood and Louise Perkins at the Industry Roundtable Breakfast

Criteria for high-risk patient selection for adjuvant trials: In an era of personalized medicine, more tools are needed to identify the most appropriate treatments for each patient. This individualized approach is particularly important in the adjuvant and neo-adjuvant settings to help identify patients at high risk of progression and to weigh the potential therapeutic benefits versus the risk of side effects. One way to address this need is to develop evidence-based biomarkers to differentiate between high and low-risk patients. Additionally, the development of predictive markers to tailor adjuvant and neo-adjuvant therapy is important.

Dose and duration of treatment: Several therapies have been approved for adjuvant therapy of melanoma including high-dose interferon alpha-2b and pegylated interferon alpha-2b. More recently approved agents (ipilimumab, vemurafenib, dabrafenib, and trametinib) for patients with unresectable or metastatic disease are now being tested in clinical trials as adjuvant therapy in patients at high risk for relapse after surgical resection of tumor. In addition, anti-PD1/PDL1 agents, radiotherapy, and various therapeutic vaccines are also being pursued. Given the availability of newly approved and investigational agents, key questions remain regarding combinations, doses, and/or sequences of these therapies in the adjuvant setting. More clinical data is needed to determine the most safe and effective adjuvant and neoadjuvant treatment approaches.

Optimal endpoints: The cost of conducting trials with larger numbers of patients and longer timeframes to measure clinical efficacy is a prominent challenge to developing adjuvant therapies. Thus, one current area of emphasis includes developing criteria for surrogate endpoints in adjuvant trials that facilitate early decision-making in clinical development. Recent data on small-molecule therapy suggest that surrogate endpoints such as progression-free survival (PFS) may be used in future adjuvant trials in melanoma, leading to reductions in trial time and cost. While PFS has been used as an endpoint in adjuvant trials in breast cancer, it is unclear if immune therapy approaches will yield similar or different results.Thus, the difference in endpoints based on therapeutic modality should also be examined.

Michael Giordano at the Industry Roundtable Breakfast

Role of Scientists and Stakeholders in Encouraging Public Support for Cancer Research

MRA Board Member Michael Milken moderated a lively discussion featuring Former U.S. Senator Connie Mack, an MRA board member, and award-winning journalist Cokie Roberts that focused on their personal encounters with melanoma including how it impacted their families and how it helped define their efforts to advance the cause of biomedical research. Mack traced his efforts to advance the commitment of federal funds into medical research through the National Institutes of Health (NIH) and National Cancer Institute (NCI), while Roberts spoke of the importance of engaging the public in the process, including working with the news media to energize the cause. Milken emphasized the necessity of collaboration among all stakeholder groups—from patients and academics to industry, government and the media—to bring forward new treatments and ultimately cures for melanoma and other serious diseases. Ellen Davis, an MRA Board Member and melanoma survivor, introduced the panel by noting that "Melanoma does not discriminate—it can strike any person, any family, at any time. And when it does, it changes everything—not just for the patient, but for their loved ones and friends. It can have a profound impact on the choices people make for the rest of their lives."

"Melanoma does not discriminate—it can strike any person, any family, at any time. And when it does, it changes everything—not just for the patient, but for their loved ones and friends. It can have a profound impact on the choices people make for the rest of their lives."

ELLEN DAVIS

(From left to right) Connie Mack, Cokie Roberts, and Michael Milken

Conclusion

Transformative research results from MRA-funded programs have been leading the way in this extraordinary era of progress against melanoma. These findings were highlighted at the 2014 MRA Scientific Retreat in a forum that allowed stakeholders across sectors to share, discuss, and plan ways to accelerate the pace of discovery. The overarching theme of the meeting was convergence in the science as well as in the disciplines and sectors working together toward a cure for melanoma. On the scientific front, there is increasing activity and interest in the development of combinatorial approaches for metastatic melanoma, including combining molecular targeted therapies and immunotherapies. Indeed, research and clinical experience indicates that combination therapy will be required for long-term control and cure of most patients. Success in research and clinical development in this area will require scientists from different disciplines and companies to work together. This year's Retreat showcased scientists with expertise in a variety of clinical fields (oncology, dermatology, surgery) and scientific disciplines (e.g., molecular biology, cell biology, immunology, chemistry, systems biology, informatics), reflecting increasing interest in melanoma research by the scientific community at large, catalyzed by MRAs unique model of growing the field. The interactions, discussions, and presentations held at the Scientific Retreat highlight the importance of continued robust cross-sector and cross-disciplinary effort toward a common mission of eliminating melanoma as a cause of death and suffering.

"If ever you are thinking, 'Am I making a difference?' Please think of me and the thousands of others who have sat in an exam room and been told, 'There is no cure,' and then proved the doctors wrong."

RUSTY CLINE

Acknowledgements

MRA is grateful to Lisa Simms, *FasterCures* external affairs and operations director, for coordinating the many details of the MRA Retreat. MRA thanks Paul Bliese and Brendan O'Hara for photography and Birds Nest Foundation for videography. Laura Brockway-Lunardi, MRA scientific program director wrote this report. Wendy Selig, MRA president and chief executive officer; Louise Perkins, MRA chief science officer; Alex Carney, MRA scientific program manager; and Marissa Maybee, MRA communications and outreach manager; made editorial contributions.

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.

MRA is grateful to its allies for their generous financial and in-kind support of the retreat: Aduro Biotech, AdvaMedDx, Amgen, BASF, Biotechnology Industry Organization, Birds Nest Foundation, Bristol-Myers Squibb, Caris Life Sciences, Celldex Therapeutics, Celgene, Cynthia Hazen Polsky, Daiichi-Sankyo, Eli Lilly, EntroGen, Foundation Medicine, Genentech, Gregory Simon, Holland & Knight, MedImmune, Merck, National Pharmaceutical Council, Novartis, OncoSec, Pfizer Oncology, PhRMA, Poliwogg, Provectus Biopharmaceuticals, Royalty Pharma, and Sanofi.

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.

MRA-sponsored Young Investigators at the MRA Young Investigator Breakfast

Melanoma Research Alliance

Sixth Annual Scientific Retreat

February 26-28, 2014 Washington, DC

AGENDA

Mayflower Renaissance Hotel, 1127 Connecticut Avenue NW

Wednesday, February 26th

4:00-8:00 pm	*Registration open*.....Grand Ballroom Promenade
6:30-8:30 pm	**Welcome Reception:** "A Celebration of Progress for Patients".....**State Room**

Thursday, February 27th

7:00 am-5:00 pm	*Registration open*.....*Grand Ballroom Promenade*
7:00-8:15 am	General Breakfast.....State Room
7:00-8:15 am	Young Investigators Breakfast (by invitation only).....Senate Room "The successful mid-career transition: a conversation"
8:30-8:45 am	**Opening Remarks**.....**Grand Ballroom** Wendy Selig, MRA President and Chief Executive Officer Louise Perkins, MRA Chief Science Officer
8:45-10:05 am	**Intersection of Immunotherapeutics and Kinase Inhibitors:** Current Treatments and Emerging Paradigms Chair: Michael Atkins
8:45-9:10 am	Jedd Wolchok, Memorial Sloan-Kettering Cancer Center: Checkpoint blockade combination therapy
9:10-9:30 am	Neal Rosen, Memorial Sloan-Kettering Cancer Center: Combinatorial approaches to treating mutant BRAF melanomas
9:30-9:50 am	Mary Jo Turk, Dartmouth College: BRAF-inhibition and tumor immune-suppression: lessons from a mouse model
9:50-10:05 am	Michael Atkins, Georgetown Lombardi Cancer Center: Kinetics and effects of BRAF inhibitors on intratumoral immunity
10:05-10:20 am	*BREAK*
10:20-11:45 am	**Biomarkers: The Key to Melanoma Prognosis and Treatment Outcomes** Chair: Suzanne Topalian
10:20-10:45 am	Meenhard Herlyn, Wistar Institute: Drivers in melanoma development and progression
10:45-11:05 am	Graeme Walker, Queensland Institute for Medical Research: Discovery of genes for melanoma development using the Collaborative Cross approach
11:05-11:25 am	Jeffrey Trent, Translational Genomics Research Institute (TGen): Personalized medicine for BRAF wild type melanoma
11:25-11:45 am	Suzanne Topalian, Johns Hopkins University: PD-1 pathway blockade: markers of response and mechanisms of resistance

Melanoma Research Alliance

Sixth Annual Scientific Retreat

February 26-28, 2014 Washington, DC

AGENDA

Mayflower Renaissance Hotel, 1127 Connecticut Avenue NW

Thursday, February 27th (cont.)

11:45 am-12:15 pm — **Special Lecture:** Stephen Baylin, Johns Hopkins University.....**Grand Ballroom**
Can Epigenetic Therapy Sensitize to Checkpoint Immunotherapy?

12:30-1:45 pm — **Lunch and Discussion**.....**State Room**

- Connie Mack, Senior Policy Advisor, Liberty Partners Group LLC; Former U.S. Senator; and MRA Board Member
- Michael Milken, Chairman, the Milken Institute and MRA Board Member
- Cokie Roberts, Political commentator, NPR and ABC

2:00-3:20 pm — **Therapeutic Targeting of NRAS Mutant Melanoma**.....**Grand Ballroom**
Chair: Levi Garraway

2:00-2:20 pm — Douglas Faller, Boston University: Targeting NRAS as a therapeutic approach for melanoma

2:20-2:40 pm — Xu Wu, Massachusetts General Hospital: Targeting NRAS palmitoylation in melanoma

2:40-3:00 pm — Susana Ortiz-Urda, University of California, San Francisco: Mechanisms of resistance for constitutively-activated NRAS melanoma

3:00-3:20 pm — Levi Garraway, Dana-Farber Cancer Institute: The development of rational therapeutic regimens for NRAS-mutant melanoma

3:20-3:35 pm — *BREAK*

3:35-4:55 pm — **Combination Therapies for Melanoma**
Chair: Charles Drake

3:35-3:55 pm — Kai Wucherpfennig, Dana-Farber Cancer Institute: Synergistic targeting of inhibitory T cell pathways in melanoma

3:55-4:15 pm — Ramesh Rengan, Fred Hutchinson Cancer Research Center: RADVAX: Stereotactic body radiation therapy with ipilimumab in melanoma

4:15-4:35 pm — Fan Pan, Johns Hopkins University: Targeting HIF-1 inhibitors in combination with Treg depleting drugs (cyclophosphamide) and targeted anti-melanoma therapy

4:35-4:55 pm — Charles Drake, Johns Hopkins University: Combination therapy to augment anti-PD-1 in melanoma

4:55 pm — **Closing Remarks:** Laura Brockway-Lunardi, MRA Scientific Program Director

6:30-10:00 pm — **Reception and Dinner**.....**Hill Country Barbecue**
Dress: Casual
410 7th Street NW, (202) 556-2050
6:15-7:15 pm, Transportation provided to restaurant, Pick up at Desales Street entrance of hotel
6:30-7:30 Reception; 7:30 Dinner; 8:30 Line Dancing

Melanoma Research Alliance

Sixth Annual Scientific Retreat

February 26-28, 2014 Washington, DC

AGENDA

Mayflower Renaissance Hotel, 1127 Connecticut Avenue NW

Friday, February 28th

7:00-10:00 am	*Registration open.....Grand Ballroom Promenade*
7:00-8:30 am	General Breakfast.....State Room
7:00-8:30 am	Industry Roundtable Breakfast (by invitation only).....Colonial Room "Development of adjuvant and neo-adjuvant therapies for melanoma and other cancers"
8:40-8:45 am	**Opening Remarks Day 2:** Louise Perkins, MRA Chief Science Officer
8:45-11:10 am	**New Strategies for Target Discovery and Credentialing.....Grand Ballroom** Chair: Glenn Dranoff
8:45-9:05 am	Jonathan Cebon, Ludwig Institute for Cancer Research, Melbourne-Austin Branch: Targeting inducible invasive cells in melanoma
9:05-9:25 am	Barbara Bedogni, Case Western Reserve University: Targeting melanocyte precursor pathways for melanoma therapy
9:25-9:50 am	Christopher Vakoc, Cold Spring Harbor Laboratory: A functional approach to targeted melanoma therapy
9:50-10:10 am	Chris Sander, Memorial Sloan-Kettering Cancer Center: Network models of signaling pathways and combinatorial therapy in melanoma
10:10-10:25 am	*BREAK*
10:25-10:45 am	Jeffrey Ravetch, Rockefeller University: Enhancing immunotherapeutic activity of agonistic anti-CD-40 antibodies
10:45-11:10 am	Glenn Dranoff, Dana Farber Cancer Institute: Human anti-MICA monoclonal antibodies for melanoma immunotherapy
11:10 am-12:10 pm	**Selected Therapeutic Approaches: Unanswered Questions, Future Roles** Chair: Paul Chapman, Memorial Sloan-Kettering Cancer Center
11:10-11:30 am	Surgery: Daniel Coit, Memorial Sloan-Kettering Cancer Center
11:30-11:50 am	Vaccines: Nina Bhardwaj, Icahn School of Medicine at Mount Sinai
11:50 am-12:10 pm	Adoptive cell therapy: Steven Rosenberg, U.S. National Cancer Institute
12:10 pm	**Closing Remarks:** Louise Perkins
12:15-1:30 pm	General Lunch.....State Room

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