



Melanoma  
Research Alliance

# Investing In Innovation

Highlights of the Melanoma Research Alliance Fifth Annual Scientific Retreat

February 27-28, 2013 | Washington, DC



# Contents

Overview	<b>1</b>
New Melanoma Molecular Targets	<b>5</b>
Building Three-Dimensional Human Skin Models	<b>13</b>
Melanoma Immunotherapies	<b>14</b>
Drug Resistance and Combination Therapies	<b>21</b>
Clinical Care Decision-Making for Today's Melanoma Patients	<b>27</b>
New Models for Drug Testing and Approval	<b>31</b>
The Role of Government in Melanoma Prevention, Diagnosis, and Treatment	<b>34</b>
Conclusion	<b>38</b>
Acknowledgements	<b>39</b>
Appendix	<b>41</b>
Sponsors	<b>55</b>



## Overview

This is a time of great opportunity and progress in the field of melanoma research. Recent clinical advances offer better options for patients and those at risk, and scientists are pushing forth the next generation of innovative tools and treatments.

Exciting collaborations are integrating multiple research programs with critical investments and leadership by the Melanoma Research Alliance (MRA), a unique foundation launched by Debra and Leon Black under the auspices of the Milken Institute. MRA's mission is to accelerate scientific discovery to eliminate death and suffering due to melanoma. Discussions of cutting-edge melanoma research results and clinical care strategies took place on February 27-28, 2013, in Washington, DC, at the MRA's Fifth Annual Scientific Retreat.

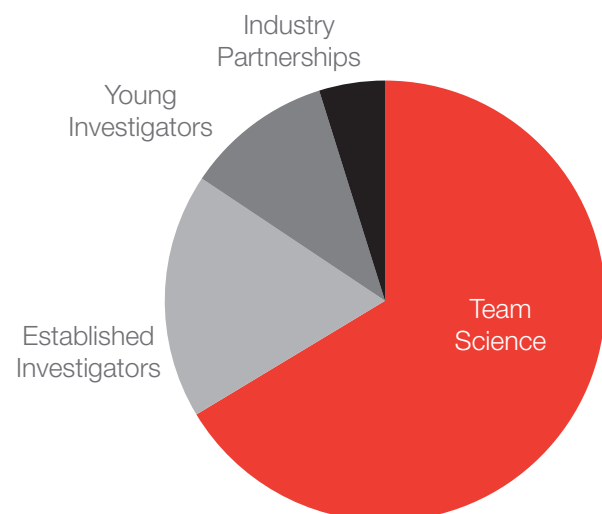
To date, MRA has awarded more than \$48 million in funding to 116 innovative, translational research programs led by 169 Principal Investigators at 80 institutions in 14 countries. As a result of these investments, an additional \$46 million in melanoma research funding has been leveraged from other sources, almost doubling MRA's impact.

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, bringing together more than 220 thought leaders from academia, industry, government, business, and philanthropy (including other melanoma non-profit organizations) in an invitation-only, "think tank" setting to share the latest findings and forge new partnerships in pursuit of better outcomes for patients. MRA-funded investigators, including young investigators, established investigators, and

interdisciplinary teams, reported on the progress of their work. In addition, several special sessions provided an opportunity to discuss and debate issues of mutual interest to academia, industry, and government, including regulatory approval pathways, research needs to guide clinical decision-making, and ways to foster collaboration among various sectors for better melanoma prevention and therapeutic avenues. The meeting also provided an opportunity for interaction and engagement by MRA Young Investigators, a critical component of the MRA research program. [This report summarizes the highlights of this unique meeting.](#)

Melanoma, a cancer of pigment-producing 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

Distribution of MRA research funding by award type (total = \$48.1 million)



of the body. More than 132,000 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 it now represents the fifth most common cancer in men and the seventh most common in women. More than 76,690 new cases and more than 9,480 deaths are expected in the United States in 2013. Alarming, melanoma is the second most frequently diagnosed cancer among young adults in the U.S.

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. Historically, options for patients with metastatic disease have been severely limited, but the approval of two new treatments in 2011 considerably changed the landscape.

The melanoma landscape is evolving quickly. As this goes to press, two additional drugs were approved by the FDA, bringing the



MRA Co-founder and Chair of the Board Debra Black addresses retreat attendees at the Embassy of Australia



MRA-sponsored Young Investigators at the first-ever MRA Young Investigator Session

total to four new treatments in the last two years. Along with a new adjuvant therapy and tools for prevention and diagnosis, patients and those at risk have considerably better options.

While these drugs alone will not cure most patients, they have laid the foundation for new, more successful approaches. As a result, there is unprecedented opportunity for transformational progress on behalf of patients, and all who are at risk, with more than 100 new melanoma compounds in the pipeline and nearly 300 clinical trials underway.

MRA-funded researchers are working to improve the success of the current therapies by identifying new biomarkers, combining treatments aimed at countering drug resistance, as well as discovering new and more effective drug targets for melanoma. In addition, MRA is playing a key role in new prevention and early detection efforts. By promoting collaboration in the field and providing critical investments in innovative translational research, MRA is at the forefront of these advances.

“ There is unprecedented opportunity for transformational progress on behalf of patients, and all who are at risk, with more than 100 new melanoma compounds in the pipeline and nearly 300 clinical trials underway. ”



# New Melanoma Molecular Targets

Researchers reported on a wide range of new potential drug targets for melanoma, most of which regulate melanomagenesis and the life cycle of a cell and were discovered with genomic or proteomic techniques, or by looking for epigenetic mechanisms that affect the transcription of genes into proteins.



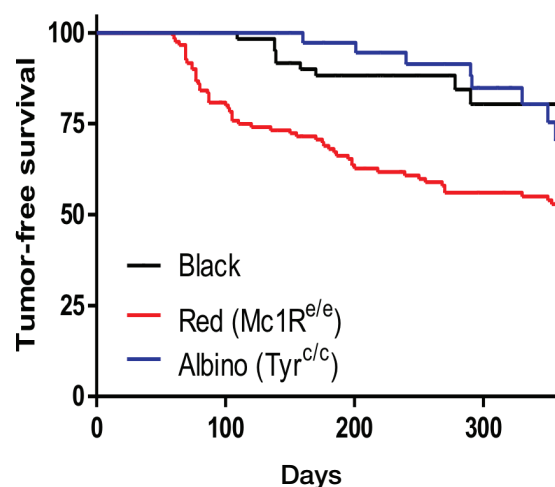
## Identifying pathways regulating melanoma formation and survival

MRA Established Investigator **David Fisher, Massachusetts General Hospital**, has uncovered several novel pathways that drive melanoma. Individuals with red hair have an increased risk for melanoma. To investigate how redheads' unique pigment might boost their risk of developing melanoma, he created genetically engineered red-haired mice and found that they were more prone to developing melanoma even in the absence of exposure to ultraviolet (UV) radiation. UV radiation might still add to the increased risk of melanoma redheads have. Data from Fisher's lab indicates that there is more oxidation in the skin of red mice as well as nucleotide adducts, both of which might damage DNA and explain how the pigment pathway fosters carcinogenesis. This information also provides new targets for prevention. Fisher plans to test the effects of antioxidants to see if they might help prevent melanoma formation. But, he cautioned that the red pigment prevalent in the skin of redheads contains cysteine, which is an endogenous antioxidant; supplemental antioxidants might boost the production of the red pigment, which in vitro studies suggest worsen melanoma risk.

Once melanoma spreads beyond the skin, it is especially aggressive and drug resistance is a critical challenge in the field. To address this question, Fisher looked at the expression

profiles of many melanoma subtypes and found that high BCL2a1 expression correlated with worse clinical response to vemurafenib. Suppression of BCL2a1 diminished the growth of melanoma tumors in mice and improved sensitivity to BRAF inhibitors in cell lines. There is some evidence that a compound called obatoclax targets BCL2a1 function, which might be a promising combination with BRAF inhibitors. Fisher's lab found that BRAF inhibitors induce production of more mitochondria in tumor cells, and combining a mitochondrial toxin with a BRAF inhibitor led to more cell death in melanoma cell lines. Both BCL2a1 and mitochondrial biogenesis are regulated by the MITF transcription factor, which is known to control the growth of melanocytes and melanomas.

Red-head mice have accelerated tumorigenesis compared to black and albino mice



Courtesy of David Fisher, Massachusetts General Hospital

## Targeting cell death and cell signaling

Several presentations focused on regulators of melanoma cell survival that might be promising drug targets for melanoma. The laboratory of MRA Established Investigator **Hermann Steller, Rockefeller University**, focuses on XIAP, which prevents cell death (apoptosis) of tumor cells. XIAP is an attractive drug target because it is elevated in many human tumors including melanoma, and mice genetically engineered to lack XIAP are viable but are protected against developing cancers. In addition, XIAP plays a role in “life and death” decisions of stem cells, and aberrations in stem cell apoptosis have consequences for tumor development. Due to compensatory mechanisms that prevent a significant drop in the number of stem cells, targeting XIAP alone may not have a substantial effect on cancer stem cell pools. Because XIAP activity plays an important role at the outer membrane of the mitochondria, an anti-XIAP compound linked to a carrier that deposits it on the mitochondrial membrane was developed. Although studies show this compound degrades XIAP well, it is so large that only a small percentage enters cells. An alternative approach to ridding tumor cells of XIAP that appears more effective so far is linking it to compounds that target XIAP for natural degradation by proteasomes in the cell. Steller found two compounds that did this effectively and killed melanoma cells in vitro. Future work will focus on further optimizing these compounds for therapeutic purposes.

Another important natural grim reaper for tumor cells is TRAIL, a protein made by immune cells that causes cell death when it binds to “death receptors” on cancer cells. Much oncology research has been focused on TRAIL, but it is challenging to turn this protein into an anti-tumor drug because of its rapid clearance and because TRAIL receptors are widely expressed in normal cells as well as tumor cells. MRA Young Investigator **Edwin Bremer, University Medical Center Groningen**, created an antibody-based TRAIL fusion protein that targets TRAIL to the MCSP protein, which is found on more than 85% of melanomas but not most normal cells other than melanocytes. By linking TRAIL to the antibody domain, the fusion protein had a longer circulating time and Bremer was able to significantly reduce tumor size in mice with melanoma xenografts. This targeting approach was also used to equip T-cells with TRAIL. T-cells normally do not express TRAIL, or do so only minimally, but when Bremer armed them in this way, his in vitro studies showed a five hundred-fold enhancement of tumor cell death.

PDK1 is a master regulator of AGC kinases including include AKT and PKC, which play an important role in melanoma. The expression of PDK1 is significantly increased in melanoma tumors linked to poor prognosis. To investigate its functional importance in melanoma, MRA Established Investigator **Ze’ev Ronai, Sanford Burnham Research Institute**, inactivated the

PDK1 gene in the BRAFV600E/PTEN mutant mouse melanoma model. Inactivation of PDK1 resulted in delayed melanoma formation, inhibited the development of metastases, and prolonged survival. PDK1 inhibitors have been in development, and one such inhibitor showed effects that resembled the genetic inactivation of PDK1 in mice. Despite concern about the side effects of targeting such a master regulator, selective inhibition in melanocytes by genetic means nor the use of the pharmacological PDK1 inhibitor exhibited toxicity. These early results indicate promise for the possible targeting of PDK1 in melanoma therapy.

Ronai also reported on his latest research testing small molecule drugs in NRAS mutant melanomas. One of these early compounds stemmed the growth of many different genotypes of melanoma, but “most striking and exciting is its effect in NRAS melanoma,” Ronai said. When it was given to mice shortly after NRAS induction made them prone to developing melanoma, it inhibited tumor development by 100%. When administered at later stages in melanoma development, 40% inhibition of melanoma development was noted. The compound reduced inflammation and tumor proliferation, but did not have an effect on cell death. The drug seems to function as a multi-kinase inhibitor. This compound seems to have synergistic effects when combined with low doses of vemurafenib. A medicinal chemistry campaign led to two

analogues of the compound that have improved oral bioavailability and are currently being tested in different melanoma models.

### Re-engineering anthrax toxin

Funded by an MRA Pilot Award, **Kenneth Bradley of the University of California, Los Angeles** is studying the therapeutic applications of anthrax toxin, which is another natural compound whose cell-killing ability researchers want to use to destroy tumor cells. This toxin targets the vasculature and provides a “molecular syringe” that delivers enzymes to the host cell that interrupt MAP kinase signaling. Since MAP kinase signaling plays a key role in fueling the growth of melanoma and other tumors, anthrax toxin has long been recognized as a potential anti-tumor agent and research in mouse studies show that it stems the growth of melanoma xenografts. “The glitch is the therapeutic index—the dose required to cause tumor regression is the same as the dose that kills the animal,” Bradley said. To make anthrax toxin more targeted to tumor vasculature as opposed to normal cells, Bradley engineered a version of it that only binds to a cell receptor called TEM8 that is not expressed in normal adult tissues or in wound healing in adults. This compound was not toxic to mice, and it targeted the blood vessels that support tumor cells. The TEM8-specific anthrax toxin suppressed B16 melanoma cell growth. However, it stimulated antibody responses that might limit how long it remains in circulation.

Pegylated formulations of the toxin might reduce such antibody formation.

### Targeting brain metastases

Brain metastases are a major cause of death in melanoma patients. MRA Young Investigator **Michael Davies, University of Texas M.D. Anderson Cancer Center**, focuses his research on identifying drug targets that might prevent or counter such brain lesions. By analyzing melanoma brain metastases and extracranial metastases from patients who previously had both types of tumors removed by surgery, he demonstrated that genomic hotspot mutations, copy number variations as well as transcriptional (mRNA) profiles of the matching tumors were largely similar. However, comparison of the tumors' protein networks identified increased activation of several components of the PI3K-AKT pathway and evidence of loss of control of cell cycle regulation in the brain metastases. These findings support the rationale for the clinical testing of inhibitors against these pathways in patients with brain metastases. Davies also announced that a clinical study will open soon to test BRAF inhibitor therapy given prior to surgical resection of brain metastases, which will allow further characterization of the molecular changes in patients, and additional research will be funded by a recently-awarded MRA Team Science Award.

### Taking cues from gender differences

There is a striking gender effect in melanoma. Men with the cancer are twice as likely to die from it as women, despite no evidence of a hormonal influence. This led **Alan Spatz of McGill University** to hypothesize that X chromosome inactivation might explain part of the gender effect. In women, most of the genes on one X chromosome are silenced due to X-chromosome inactivation. But some genes escape such inactivation and are doubly expressed from both X chromosomes. These genes are thought to be responsible for gender-linked health differences. Spatz and an international team of investigators funded by an MRA Team Science Award found a gene called PR70 located on both the X and Y chromosomes that escapes inactivation in females. This gene is a tumor suppressor, which regulates pRb phosphorylation status and cell cycle progression. Loss of PR70 expression in primary cutaneous melanoma correlates with poor three-year overall survival. In mouse xenografts, Spatz found an inverse correlation between PR70 expression and the number of melanoma grafts that took and grew in mice.

### Interrogating the melanoma genome

**Levi Garraway, Dana-Farber Cancer Institute**, noted that while researchers tend to search for cancer-causing changes in the protein coding regions of the genome, probing

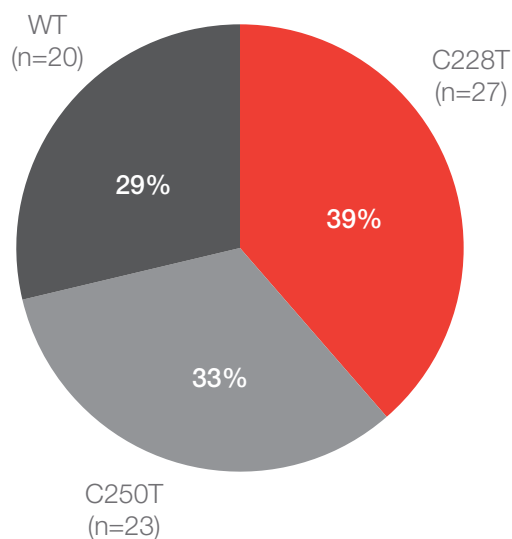
other regions, including those responsible for regulating the activity of genes—what he called the “dark matter” of the cancer genome—might also lead to the discovery of important targets for melanoma treatments. Garraway’s lab, funded by several MRA Awards, discovered two mutations located in the promoter for TERT, a gene that codes for the telomerase reverse transcriptase, which enables cells to become immortal. The TERT promoter mutations were more common in melanoma cell lines (70 % of lines studied) than the BRAFV600E mutation that is the target of RAF inhibitors. The mutations augment transcript activity from the TERT promoter between 1.5

to 4-fold and were not unique to melanoma; Garraway also found them in other cancers as well. Globally, TERT expression does not appear to be elevated in tumor samples, although specific measurements of expression from the mutated promoter itself will require more refined studies in the future. This work demonstrates the importance of studying the dark matter of the cancer genome.

### Regulating gene activation

Another new frontier for melanoma drug targets is not focused on the genome, but on the cellular machinery that regulates gene activation and expression (called epigenetics). Epigenetic regulators may serve as an alternative or complementary strategy to targeted therapies against genetic signaling pathways. Supported by an MRA Pilot Award, **Eva Hernando of New York University** discovered promising epigenetic proteins in the BET family that are upregulated in melanoma cell lines and tissues compared to benign nevi. BET enables transcription of key melanoma cell cycle regulators. Hernando’s in vitro studies found BET inhibition suppressed melanoma cell growth and metastasis in a mouse xenograft model. Her preliminary research indicates that BET inhibitors may be less likely to trigger treatment resistance than targeting particular genes in a signaling pathway and may be effective in patients without BRAF mutations.

Distribution of TERT somatic mutation status in melanoma tumors and short term cell cultures



Courtesy of Levi Garraway, Dana-Farber Cancer Institute

MicroRNAs are another type of cellular machinery that regulates gene expression. By comparing the microRNA profiles of parent melanoma tumors to their metastatic clones in mice, MRA Young Investigator **Sohail Tavozeie of Rockefeller University** found three microRNAs that appear to regulate melanoma invasiveness and metastasis that occurs independent of BRAF mutation status. More specifically, the microRNAs promote endothelial cell recruitment and regulate metastatic angiogenesis in mice by regulating two genes—one that codes for a heat shock protein (DNAJA4) and one that codes for a metabolic protein (ApoE). The three microRNAs he identified in his mouse studies correlated to likelihood of metastasis in samples of primary human melanoma. He noted that microRNAs can be difficult to target systemically with drugs, but his studies suggest that they, or the genes they regulate, could be therapeutic targets.

### **Developing a personalized medicine trial for BRAF wild type melanoma**

Researchers continue to discover molecular differences in patients' tumors that affect their ability to respond to targeted treatments and necessitate a "personalized medicine" approach to treatment. This approach requires testing patients' tumor samples to determine their molecular subtype, which then determines what investigative new drugs they receive. Such innovative personalized

medicine clinical trials are already in progress for breast and colon cancer, and now a similar trial is underway for melanoma patients, thanks to the groundbreaking partnership between MRA and Stand Up to Cancer (SU2C). **Patricia LoRusso, Barbara Ann Karmanos Cancer Center**, summarized the SU2C-MRA Melanoma Dream Team project, which is a multi-centered clinical trial for patients with a particularly intractable form of melanoma known as BRAF wild type that is, non-V600E BRAF melanoma. In addition to Karmanos Cancer Center, eighteen other institutions are involved. The study will test several investigative new drugs singly or in combination in a randomized trial. An initial pilot protocol, which is a "proof-of-concept" for the treatment matching process without actual therapeutic intervention, had its first patient enrolled in November 2012. The main endpoint of the pilot trial is to determine the feasibility of the treatment matching process prior to embarking on the large-scale, statistically-driven therapeutic clinical trial. Although this type of study is incredibly challenging to construct, LoRusso said, "We're all here for one reason—the patient."

### Conclusion: The post-BRAF era of melanoma molecular targets

The development of specific inhibitors of mutationally activated BRAF is a major breakthrough in the treatment of a subset of patients with advanced melanoma. Indeed, in recent years, researchers have made tremendous strides in the identification of additional melanoma molecular targets including NRAS, NF1, non-V600E BRAF mutations and others like PI3K pathway targets. This research is critical not only for non-V600E BRAF melanoma, but also to set the stage for future combination therapy of currently available drugs and other agents in late-stage development. In light of these new findings, some of which were presented at the MRA Retreat, MRA-funded investigator **Martin McMahon of the University of California, San Francisco**, summarized important questions that need to be addressed more fully through additional research; many MRA-funded studies are addressing these questions to accelerate new therapeutic approaches to patients:

- Will targeting of BRAF in combination with other signaling pathways be successful in maintaining patients in durable remission?
- Will changes to dose and schedule of already approved drugs sustain patients in durable remission?

- How can researchers target NRAS or GNAQ/11 mutated melanomas, which are notoriously resistant to treatment? Are small interfering RNAs a promising strategy?
- Does p16INK4A silencing predict for sensitivity to CDK4/6 inhibitors? Moreover, what is the role of ARF silencing in melanoma?
- Can drugs be developed against non-enzymatic targets such as MITF and BCL2?
- How different are brain metastases from primary melanomas or melanoma metastases located at other sites, and what are the implications for therapy?
- What do we need to learn about targeting the tumor stroma, vasculature, or non-tumor cell targets?
- What should be the strategy for developing adjuvant approaches for patients with high-risk primary melanoma?



Martin McMahon

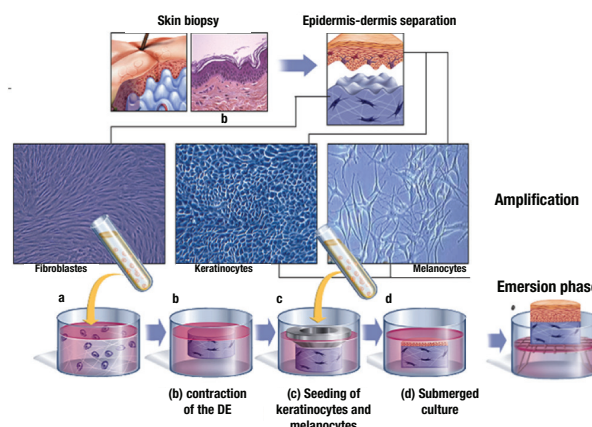
## Building Three-Dimensional Human Skin Models

Françoise Bernerd from L'Oréal Research and Innovation reported on human skin models her company developed to better understand the effects of different types of UV radiation on skin and to test compounds that might counteract those effects. One model includes a differentiated multilayered epidermis comprised of keratinocytes that are on top of a dermal equivalent that includes collagen and fibroblasts. Researchers validated the model using well-known sunburn-related biomarkers and saw the same DNA lesions, p53 activation, sunburn cells, and overexpression of galectin 7 seen

when human skin is exposed to UVB radiation. Unlike UVB radiation, UVA radiation penetrates past the epidermis and into the underlying dermis. When researchers exposed the human skin model to UVA radiation, they found it affected dermal fibroblasts and matrix as well as inflammatory functions, cytokines, and growth factors deeper down in the dermis. This finding confirms that of other studies that show UVA radiation induces dermal photoaging but also immunosuppression in humans. The researchers also discovered p53 mutations in the epidermis after pure UVA exposure, suggesting that UVA radiation may be more carcinogenic than has previously been thought.

Another human skin model mimics the full thickness of pigmented skin in three-dimensional architecture and has keratinocytes, melanocytes, fibroblasts and matrix proteins. This model can reveal the regulation of pigmentation, including melanocyte biology and microenvironment components that influence its biology. In this model, researchers can see the effects of UV exposure such as the tanning response including activation of melanocytes and melanin synthesis. The model also revealed the ability of dermal fibroblasts to regulate the level of pigmentation. Taken together, these 3D skin models allowed researchers to reproduce molecular and cellular damage induced by both UVB and UVA wavelengths in the two cutaneous compartments. They also emphasized that the combined UV-induced alterations of epidermal keratinocytes and melanocytes with dermal components led to a loss of functional integrity of the whole skin leading to a tumor promoting environment.

## In vitro skin model



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# Melanoma Immunotherapies

As the basic understanding of how the immune system responds to tumors continues to expand, so too do the opportunities for advancing effective immunotherapeutic treatment approaches to combat melanoma and other cancers. Melanoma is at the forefront of immunoncology, and the last few years have seen major advances on behalf of patients.

Two important goals of cancer immunotherapy are to raise the frequency of quality anti-tumor T-cells and to improve the effectiveness of those T-cells against the tumor. MRA-funded researchers are leading the way in these areas.

### **Developing anti-PD-1 immunotherapy**

There are a large number of co-stimulatory and co-inhibitory molecules that determine how the T-cell will react when it sees a tumor antigen. **Drew Pardoll, Johns Hopkins University**, noted that, “These molecules are turning out to be very important and promising targets for immunotherapy, and we’re just scratching the surface of opportunity.” The research of Pardoll and a group of investigators funded by an MRA Team Science Award focuses on anti-PD-1, which is an antibody that blocks a checkpoint that normally suppresses an immune response to tumors. Anti-PD-1 antibodies are currently undergoing clinical testing, and have shown promising results in several different types of cancer, including melanoma. There is a dynamic bi-directional crosstalk between tumor cells and neighboring cells in the microenvironment that leads to upregulation of a PD-1 ligand (called PD-L1) on tumor cells, which engages the inhibitory pathway on T-cells. Pardoll and his collaborators propose that PD-L1 expression in tumors may be a treatment-related biomarker. However, there are challenges that need to be overcome including the fact that expression can vary over time and might be missed in a

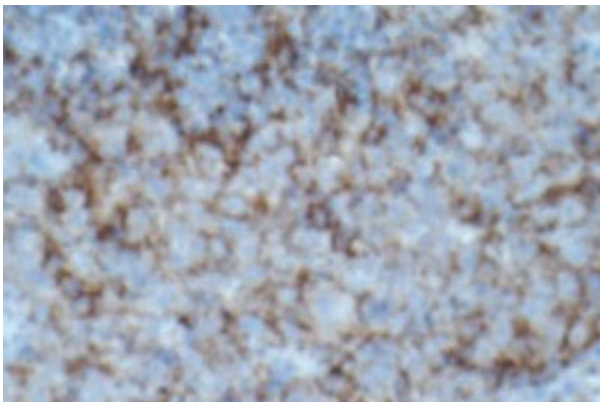
biopsy taken at a single point. Nonetheless, based on these original findings, a number of companies are developing PD-L1 assays as part of their strategy to clinically develop antibodies blocking this pathway. Despite the enhanced response to anti-PD-1 among patients whose tumors express PD-L1, the data show that less than half of patients with PD-L1+ tumors respond to anti-PD-1, which may be due to tumor expression of other co-dominant checkpoints such as LAG-3. Dual antibody blockade of PD-1 and LAG-3 provided synergistic anti-tumor activity in mice, supporting an approach involving multi-checkpoint blockade therapy.

### **Stimulating dendritic cells/T-cells with CD27**

To promote more functional T-cells infiltrating tumor cells, **Timothy Bullock of the University of Virginia** has focused on trying to increase their stimulation by mimicking the action of dendritic cells, which activate T-cells via CD27 stimulation. Stimulation of this receptor strongly supports vaccine-driven and endogenous responses to melanoma antigens, and Bullock’s mouse studies, funded by an MRA Academic-Industry Partnership Award with Celldex Therapeutics, show that boosting the amount of CD27 stimulation increases the number and activity of CD8 T-cells in tumors, which enhances tumor control. To determine whether the expression of CD27 on T-cells correlates with their function, Bullock

used dual staining for CD27 and CD8 T-cells in collections of archived melanoma patient samples, and has been developing imaging software to quantify whether expression of CD27 correlated with increased numbers of CD8 T-cells, and ultimately patient survival. He found that stimulating CD27 on T-cells increases their expansion to the extent achieved with inhibitors of immune system checkpoint blockade, such as PD-1. Preliminary data from a multi-center Phase I clinical trial with this antibody (CDX-1127) showed that it was bio-active in melanoma patients, but responses have been variable, Bullock said. Natural killer cells and memory CD8 T-cells appear to be targets in CDX-1127-treated patients. Next steps may be to combine CD27 stimulation with checkpoint blockade or TLR agonists to augment vaccine-induced CD8 T-cell responses.

Tumor-cell surface PD-L1 expression (brown staining) in a metastatic melanoma lesion

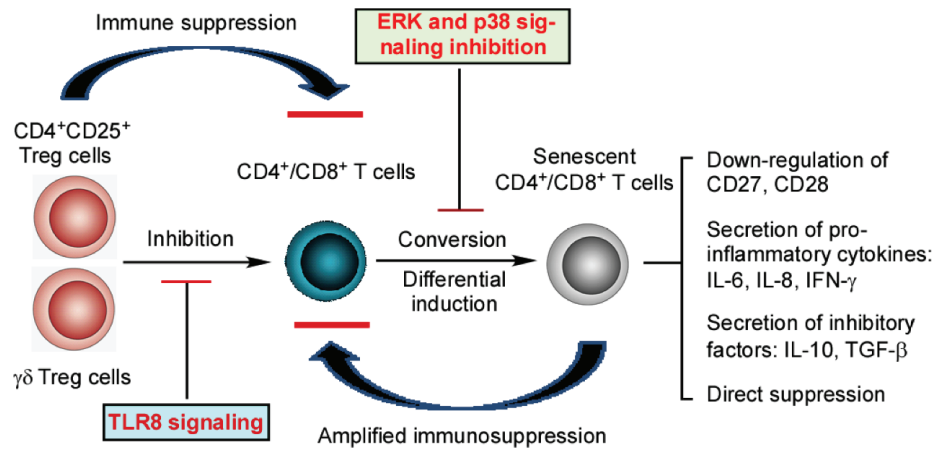


*Courtesy of Janis Taube, Johns Hopkins University*

## Countering Treg immune suppression

MRA Young Investigator **Guangyong Peng, St. Louis University**, pointed out that T regulatory cells (Tregs) play an important role in checking immune system activity to prevent autoimmune diseases and limit chronic inflammatory disease, and are also known to inhibit effective immune responses against cancer. Tregs are thought to be a major obstacle to successful tumor immunotherapy through a variety of mechanisms including generating cytokines that inhibit effector T-cells, inducing the death of T-cells or apoptosis in other cells, disrupting effector T-cell metabolism, and inhibiting dendritic cell maturation and function. Peng's research focuses on uncovering which of these mechanisms are important in melanoma. When he co-cultured human Tregs with CD4 T-cells or transferred human T-cells in immunodeficient mouse models, he found that Tregs do not induce cell death in the T-cells thought to be important in tumor control, although they do freeze their progression in the cell cycle. Peng discovered that Tregs induced premature aging of CD4 T-cell with potent suppressive activity. Elevated numbers of senescent tumor-infiltrating T-cells were also found in breast cancers and lymphomas. Peng found that the T-cell senescence was induced by changes in MAPK signaling, including ERK1/2 and p38 activation. He was able to block the senescence and suppressor functions of T-cells by TLR8 signaling, which

## Control of tumor infiltrating lymphocyte fate and function for melanoma immunotherapy



Reprinted by permission. Ye J et al. *Blood* 2012; 120(10):2021

stimulates an immune response, and/or by specific ERK1/2 and p38 inhibition using in vitro and in vivo animal models.

### Designing T-cell receptors

One way to make T-cells more effective anti-tumor weapons is to engineer them so they are more likely to target tumor cells. MRA Established Investigator **David Kranz, University of Illinois at Urbana-Champaign**, takes this approach in his research, which creates artificial T-cell receptors that are designed to bind to melanoma antigens. After a melanoma patient's T-cells are harvested, these designer receptors are genetically introduced to be expressed by the T-cells for use in adoptive T-cell therapy. To discover how best to engineer T-cell receptors, Kranz developed an in vivo screening system in

which he creates a library of T-cells that are activated to express T-cell receptors with a wide range of affinities. He introduces these T-cells into mice with melanoma tumors and determines which receptors are on T-cells that are most active and persistent. He discovered that constructing artificial T-cell receptors could be modeled by targeting a synthetic peptide (SIY) that imitates a natural, melanoma-specific ligand recognized by a natural T-cell receptor. Kranz found that the artificial T-cell receptors had most anti-tumor activity in CD4 T-cells, but when they were used in CD8 T-cells they fostered undesirable cross reactivity with self-antigens and subsequent deletion of these cells. A single-chain artificial T-cell receptor construct reduced such cross reactivity and subsequent deletion of the CD8 T-cells in vivo, while

maintaining the reactivity of CD4 T-cells. More recently, Kranz has been using a human single-chain T-cell receptor as a scaffold for in vitro engineering of artificial T-cell receptors against new tumor specificities. This process could expedite the development of T-cells with artificial receptors that target tumor cells because it eliminates the need for isolating T-cell clones. One challenge of this approach to T-cell receptor engineering that needs to be overcome is that T-cell receptors with high affinity can lose their specificity and foster undesirable reactions that are difficult to predict.

### **Characterizing MDSCs as a response biomarker**

There are many factors that raise the need for a biomarker for likelihood of response that could be used to test patients prior to initiating immunotherapy. These include the long time period most patients need to respond to immune therapies such as ipilimumab, the potential for adverse side effects of this treatment, and the relatively small fraction of patients with long term benefit. There might be immunologic subtypes of melanoma that will escape immune approaches and tailoring treatments to those immune phenotypes may be important. MRA Young Investigator **Alexander Lesokhin, Memorial Sloan-Kettering Cancer Center**, reported on his studies focused on the role of myeloid-derived suppressor cells (MDSC) as a biomarker of response to ipilimumab. His results indicate

MDSC levels might not only serve as a novel prognostic marker for worse overall survival in melanoma, but that when the levels are combined with the absolute lymphocyte count (ALC), response to ipilimumab may be predicted. In a mouse melanoma model whose generation of MDSC can be stemmed with the application of a toxin, Lesokhin found levels of MDSC negatively correlated with CD8 T-cells and tumor outgrowth. Findings suggest that MDSC limits T-cell access into the tumors and affects T-cell proliferation. ALC is an early indicator of ipilimumab activity and preliminary studies find that melanoma patients with favorable ALC/MDSC ratio have a better prognosis when they are treated with ipilimumab. A prospective study to validate this finding is being planned.

### **Studying the effects of BRAF inhibitors on immune function**

**Susan Kaech, Yale University**, focuses her work on countering the immunosuppressive environment of the tumor microenvironment with immunotherapy. Her hypothesis is that part of that immunosuppression might be due to the metabolism of cancer cells that consumes a disproportionate share of available glucose, the main fuel for tumor-infiltrating T-cells. “The competition for glucose and other nutrients may starve the T-cells and contribute to their inability to function in tumors,” she said. In addition, inhibitory ligands produced by tumor cells

may hamper activation of the mTOR pathway that enables T-cells to boost their metabolism and attack tumors. By reducing the uptake of glucose by tumors, the treatment benefits seen by BRAF inhibitors might be due in part to the effects on tumor-infiltrating T-cells. Funded by an MRA Development Award, her in vivo studies in a murine model of melanoma found that vemurafenib had many stimulatory effects on the infiltrating immune cells. The treatment increased the ability of T-cells to uptake glucose and increased their metabolism via the mTOR pathway and effector functions. It also increased the expression of important costimulatory molecules, CD40L and CD70, which are important for T-cell activation and anti-tumor functions. Most importantly, her work finds that vemurafenib prevents tumor growth in a CD40L-dependent manner indicating that the effects of this drug are not entirely due to the inhibition of BRAF in the tumor cells. “The tumor microenvironment seems to be behaving in a more immunogenic state after treatment with vemurafenib,” Kaech concluded.

MRA-funded investigator **Jennifer Wargo of Massachusetts General Hospital** also studies the effects of BRAF inhibitors on the

immune response to tumors in patient biopsies and found the drugs dramatically increased expression of melanoma antigens and the number of tumor-infiltrating T-cells in treated tumors. The upregulation of tumor antigens by vemurafenib can be upwards of a 100-fold, her studies found. BRAF inhibitors also resulted in decreased immunosuppressive cytokines and VEGF, suggesting that BRAF inhibitors facilitate a more favorable tumor microenvironment. Importantly, Wargo found that BRAF inhibitors increase the immunomodulatory molecule PD-1 on the surface of infiltrating T-cells. Simultaneously, expression of the immunosuppressive ligand PD-L1 is increased on tumor cells, which may contribute to resistance to therapy. This has important implications, and suggests that immune checkpoint blockade may augment responses to BRAF-targeted therapy. Tumor biopsies revealed that one patient treated with BRAF inhibition and anti-CTLA-4 therapy had fluctuating numbers of tumor-infiltrating T-cells over time. “Timing is everything,” Wargo said, and suggested that further preclinical models will help guide rational use of combination approaches with targeted agents and immunotherapies.

**Conclusion: Going beyond the T-cell**

In summarizing the immunotherapy session, MRA-funded investigator **Thomas Gajewski, University of Chicago**, outlined the goals of cancer immunotherapy by suggesting there may be a theoretical ceiling to current therapies based on the fraction of patients that have an “inflamed” tumor microenvironment. For example, research has shown expression of inflammation associated genes correlates with clinical benefit to ipilimumab. New strategies may be needed to promote appropriate inflammation in tumors that lack a T-cell infiltrate, which might be guided by knowledge of the mechanisms of spontaneous immune activation when it does occur. Studies indicate there are host genetic differences in immune regulatory

genes that affect immune tumor responses, as well as genetic differences in tumor cells that affect the mutational landscape and its antigenic repertoire. In addition, new research is uncovering environmental differences, including the gut microbiome and immunologic/pathogen exposure history of patients that can have a powerful impact on host immune response. In order to study these factors, researchers will need to expand the type of tissues and samples they collect. Similar to molecularly targeted therapies, combination approaches will be important to improve the number of patients who respond to immune-based therapies. Gajewski called for more advanced preclinical models that researchers can use to prioritize which combination immunotherapies should be tested in the clinic.



# Drug Resistance and Combination Therapies

A major effort of research and clinical translation is focused on developing combination therapies to counter drug resistance and improve clinical responses to single agent therapies. The large number of drug targets for melanoma, including multiple players in the immune system, offer significant opportunity to avert or treat drug-resistant melanoma.



## Countering drug resistance

Melanoma drug resistance spans the spectrum of adaptive to acquired resistance. Adaptive resistance occurs early in response to treatment due to rebound survival signaling through pathway network crosstalk. Late acquired resistance involves expansion of tumor subclones with alterations that provide fitness for growth in the presence of the drug. Several mechanisms of acquired resistance to BRAF inhibitors have been described by investigators relying on limited in vivo validation. MRA Young Investigator **Roger Lo of the University of California at Los Angeles** analyzed 100 tumor biopsies, including repeated disease progression tumor sampling from multiple patients, to assess the relative contributions of these known mechanisms to clinical resistance, to find new mechanisms, and to better understand the scope of tumor heterogeneity. He found most patients' tumors had multiple mutations and resistance mechanisms that evolved in response to treatment, and that these can be grouped into at least two core survival pathways – the MAPK pathway and the PI3K/AKT pathway. Phylogenetic reconstruction revealed genomic diversification and branched evolution during BRAF inhibitor therapy. "This underscores the importance of upfront, co-targeting of core pathways," he concluded.

Rather than assessing genetic differences already in tumors that might indicate pathways to drug resistance and/or effective drug

combinations, MRA Established Investigator **Thomas Graeber, University of California at Los Angeles**, is studying mechanisms at the protein level. Tyrosine kinase receptor upregulation has been described as one mechanism of BRAF inhibitor resistance. Using proteomic profiling of the signaling network to gain a better understanding of this resistance mechanism, Graeber found that receptor upregulation triggers a de-differentiation switch. Resistant cells look different than parental cells, form connected cellular networks and are more invasive in vitro. The differentiation-associated changes offer targets for novel co-treatment strategies, which his lab is now pursuing. In another line of investigation, his lab perturbs known target and pathway nodes in melanoma cell lines, profiles how that affects protein activity as indicated by phosphorylation, and constructs network models. This strategy led to the discovery that glucose starvation of melanoma cell lines caused the production of reactive oxygen species (ROS) that induced tumor cell death. "We need to design treatments that push melanomas over the metabolic edge," Graeber said. He suggested co-targeting ROS generation and metabolic inhibition.

## Testing new therapeutic approaches for regionally metastatic disease

MRA Established Investigator **Douglas Tyler, Duke University**, is conducting clinical studies on melanoma patients with locally advanced melanoma tumors limited to their limbs. These

patients are often given isolated limb infusions of melphalan. Preclinical studies showed that temozolomide (TMZ) given in this manner may be effective in a subset of patients who do not respond to melphalan or with tumors that recur after treatment. To assess which patients are likely to respond to temozolomide or melphalan, Tyler determined both the expression of the DNA repair gene MGMT as well as the methylation status of its promoter in biopsies of patients prior to their limb infusions with temozolomide or melphalan. The researchers also conducted pre-treatment gene expression profiles for cytokines and other compounds, including the enzyme IDO, which suppresses T-cell activation and proliferation and promotes the development of Tregs. Tyler found that low baseline pretreatment MGMT may be a marker of response to temozolomide, and that response to melphalan seemed linked to RNA markers of immune cell infiltration. “We can separate patients based on a genetic analysis that indicates which will be more likely to respond to melphalan versus those more likely to respond to temozolomide,” Tyler said. In addition, he found that IDO expression in melanoma patients appeared to be a negative prognostic marker.

### Finding the right combinations

MRA Young Investigator **Aaron Mackey**, **University of Virginia**, is focusing his efforts to identify the mechanisms of response and resistance to drug combinations. Using melanoma cell lines, he found that responses

to combinatorial treatments are highly variable and not explained by common melanoma driver mutations. For example, when the BRAF inhibitor PLX4720 (a vemurafenib analog) was combined with lapatinib, which targets HER2 and EGFR, he boosted the response of cell lines to PLX4720. But that response was not linked to a single mechanistic genetic or protein pathway change. Quite to the contrary, no two cell lines had the same genetic changes that could explain the enhanced response; Mackey added that he has yet to explore microRNAs or copy number variation in genes that might explain the synergy. Mackey did find, however, methylation at specific genomic CpG sites linked to synergy response in consistent subgroups across melanomas. CpG sites serve as points in the genome for methylation that turns specific genes off. Because the methylation pattern was so consistent across melanomas, Mackey concludes that a melanocyte differentiation process, occurring prior to tumor formation, leads to melanoma tumors having different sensitivities to combination therapy, demanding an individualized interpretation to develop personalized therapy. Mackey also points out that investigations performed within each biological modality (gene expression, methylation, protein phosphorylation, etc.) provide only one view of the mechanisms at work. “Our ultimate goal is to enable cross-platform, mutation aware, network-based pathway inference, to get an integrated understanding of gene expression, protein

expression and epigenetic regulation that together predict the efficacy of any particular treatment,” said Mackey.

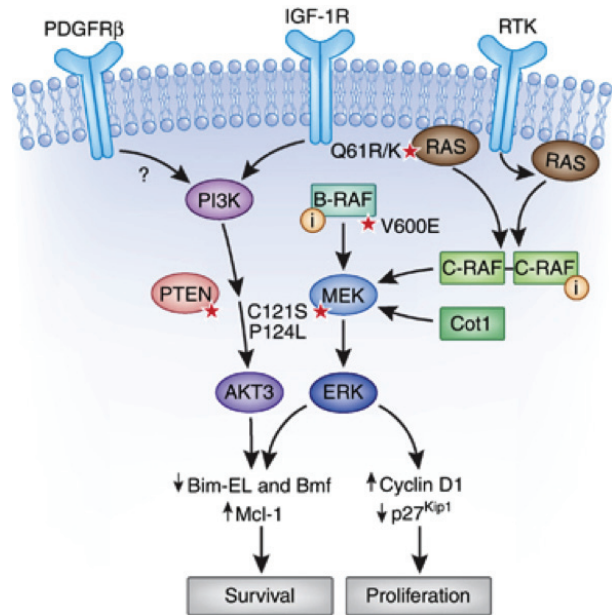
**Marcus Bosenberg, Yale University,** has found both expected and unexpected synergistic drug combinations using a high-throughput screening approach. Forty drugs at three doses were tested in combination in a panel of 20 melanoma cell lines that included those with mutated NRAS, and either mutant or wild type BRAF. The drugs tested included a large number of receptor tyrosine kinase inhibitors, MAPK inhibitors, as well as cytotoxic and metabolic inhibitors that regulate cell death. In BRAF mutant cell lines, inhibitors of BRAF, AKT, and EGFR were synergistic. The AKT inhibitor MK2206 combined with vemurafenib and lapatinib produced dramatic response in melanoma lines that were resistant to vemurafenib. In RAS-driven melanoma cell lines, he found synergy with simvastatin (cholesterol drug) and the CDK inhibitor flavopiridol that was also seen in a mouse melanoma xenograft model. It was notable that simvastatin was synergistic in several combinations, which could be due to statins altering the lipid modifications on RAS molecules. Funded by an MRA Established Investigator Award, another series of studies is investigating how best to combine BRAF inhibitors with immune modulators using the BRAFV600E/PTEN/Beta catenin mouse model. Surprisingly, Bosenberg found gender differences in melanoma growth with a 10-20% faster growth in female mice. This suggests that

researchers should watch for this and that the results of studies utilizing this and other models may be gender-specific.

**Maria Wei, University of California at San Francisco,** reported that her research on protein trafficking in melanoma, which was funded by an MRA Pilot Award, suggests yet another innovative approach to combining treatments. Protein trafficking molecules play a key role for many cellular processes, such as directing proteins to cell membranes or carrying them to their final destinations. A number of protein trafficking molecules are active only in melanocytes, and researchers are increasingly recognizing the parts these protein trafficking molecules play in fostering melanoma due to their crosstalk with signaling molecules in growth-promoting pathways, such as mTOR and AKT. Wei noted that when a protein trafficking molecule is targeted, it can potentially influence more than one molecular driver of a melanoma tumor active only in cells derived from melanocytes, suggesting that side effects might be limited. When two protein trafficking regulators (VPS33A and CNO) were targeted in melanoma cell lines and melanoma xenografts in mice, she found they increased sensitivity to cisplatin and carboplatin by decreasing the amount of drug that entered melanosomes, the organelles that contain melanin in melanocytes. In addition, when she targeted ASIP binding to the melanoma cell surface to alter protein trafficking, she blocked melanosome maturation and also

increased sensitivity to cisplatin and DTIC. We noted that melanomas with more immature melanosomes were more sensitive to cisplatin and carboplatin. Inhibition of protein trafficking reduced the expression of multiple receptor tyrosine kinases, including IGF-1R, KIT, and MET, as well as their downstream signaling components, such as mTOR, AKT, and ERK. Such protein trafficking inhibition also reduced the expression of components of the BRAF pathway. Combining protein trafficking inhibition with carboplatin increased the sensitivity of melanoma tumors to PI3K/mTOR inhibition by more than 30-fold.

### Mechanisms of resistance to BRAF inhibitors




Reprinted by permission. Aplin AE. *Journal of Investigative Dermatology* 2011;131:1817.

## **Conclusion: Grappling with tumor heterogeneity**

**David Solit, Memorial Sloan-Kettering Cancer Center**, summarized the session on drug resistance and combination therapies. Studying drug resistance is critical to guide rational strategy for combination therapies as well as to identify new targets for therapy, work that Solit and his collaborators are conducting with the support of an MRA Team Science Award. Combination therapies should improve response rate and depth of response by inhibiting pathways that attenuate oncogene dependence and/or improve the durability of response by preventing or delaying the emergence of drug-resistant clones. Melanoma tumors are highly heterogeneous, which gives them multiple mechanisms to escape the effects of therapy and regrow. A

major challenge to interrogating resistance mechanisms is the limited number of patient tumors that researchers have profiled to date and limited information on how those profiles change when resistance ensues. Much work is still needed to predict drug response and resistance mechanisms in individual patients. Pretreatment tumor biopsies would inform the most appropriate combination strategy, but the same patient's tumors can evolve in multiple different directions in a heterogeneous manner throughout the course of treatment. "That's going to remain a major challenge, but not one that can't be overcome in the next few years," said Solit. He added, "It's a testament to the research that the MRA has funded in recent years that all the major mechanisms for melanoma drug resistance were identified by MRA-funded investigators."



# Clinical Care Decision-Making for Today's Melanoma Patients

The 2013 retreat concluded  
with a panel discussion  
applying the latest  
advances in melanoma  
science to the clinic.

The discussion was moderated by MRA Established Investigator **Michael Atkins, Georgetown-Lombardi Comprehensive Cancer Center**. Panelists included **Keith Flaherty, Massachusetts General Hospital; John Kirkwood, Pittsburgh Cancer Institute; Kim Margolin, University of Washington/Seattle Cancer Center; Antoni Ribas, University of California, Los Angeles;** and **Caroline Robert, Institute Gustave-Roussy**. The MRA retreat provided a unique platform to engage key clinical and research leaders in this discussion. Key questions that were discussed included:

- What types of molecular testing should melanoma patients have?
- What should be first-line treatment for patients with BRAF mutant melanoma?
- How should patients resistant to a BRAF inhibitor be treated?
- What combinations of treatments are likely to yield the best results?
- How do you test new potential therapies now that there are effective and approved molecularly-targeted and immunotherapies for patients with melanoma?
- What is the most pressing unmet need in treating patients with melanoma today?

### **Molecular testing**

With the availability of vemurafenib for patients with BRAF mutated melanoma, molecular testing for this target is becoming routine. In addition to the V600E mutation, there are other

BRAF mutations, and c-KIT mutations in Exon 11 and 15 that may be informative. In addition, testing for all of the mutations that define genetic subgroups for which there are or will be clinical trials in the near future (such as NRAS and NF1) will be important. Increasingly, academic medical centers are creating their own panels of molecular alterations to be examined for patients with melanoma and other cancers in order to guide clinical trial eligibility and treatment selection.

### **First-line treatment for patients with BRAF mutations**

Clinical assessment of the pace of disease can guide the type of therapy that is offered first. For example, patients with slowly progressing disease might be the good candidates for immunotherapies, such as ipilimumab, that take longer to produce a response and have a greater chance of producing prolonged treatment free survival. But patients with aggressive disease might



(From left to right) John Kirkwood, Caroline Robert, Kim Margolin, and Keith Flaherty

benefit more from a BRAF inhibitor first because of the quicker and more reliable responses that can result. Better biomarkers for identifying the subset of patients who are most likely to respond to immunotherapies are needed in order to spare those less likely to respond from the treatment-related side effects. Much research is focused on identifying and validating new melanoma biomarkers.

### **Treating patients resistant to a BRAF inhibitor**

One strategy to treat patients resistant to a BRAF inhibitor is to follow with other targeted agents. Tumor biopsies can inform whether resistance is driven by reactivation of MAPK pathway or an alternative growth pathway, such as PI3K/AKT. Better technologies for identifying targets and detecting resistance mechanisms are needed, and this represents a major current challenge. Melanoma tumors can be highly heterogeneous, making the determination of the importance of low level alterations difficult. Different metastases might have distinct mechanisms of resistance and it may not be feasible to biopsy each lesion. Blood-based markers such as circulating tumor cells might help identify dominant resistance mechanisms. Research in preclinical models has suggested that intermittent BRAF inhibitor treatment might delay this onset of resistance and that a “drug holiday” might restore treatment sensitivity.

However, more research needs to be done to determine the usefulness of this approach. Other options for patients who progress on a BRAF inhibitor include treatment with ipilimumab-based immunotherapy or enrollment in a clinical trial testing other immunotherapies such as anti-PD-1 or adoptive cell transfer.

### **Combinations of treatments**

A goal of combination therapy is to improve anti-tumor response without increasing toxicity. Clinical testing of BRAF and MEK inhibitors suggests that this combination increases clinical benefit and may be less toxic than BRAF inhibition alone. However, not all combinations may accomplish these dual goals. Therefore, more research is needed to rationally develop combination therapies. Research is needed to understand how targeted agents affect the immune system, as researchers have seen both positive and negative effects. Adaptive trials such as the I-SPY trial for breast cancer and the BATTLE trial for lung cancer may be models for consideration in the melanoma space. Collaborative research networks are also important to accelerate research. For example, the Cancer Immunotherapy Trials Network is a group of 28 institutions that has been funded to study prioritized immunotherapies, alone and in combination, in 15 investigator-initiated protocols.



### **Testing new therapies**

While new FDA-approved therapies have provided better options for patients, their availability has made testing investigational treatments more difficult. This is because patients may opt to select a treatment with a known benefit/risk profile over one that is less proven. As a consequence, promising new therapies may be tested only in situations where they are less likely to be effective (e.g. patients with BRAF inhibitor resistant disease). This is an issue for the entire oncology community, not just the melanoma subset. Clinical trial design is another aspect of drug development that is the topic of much discussion. Questions remain concerning the necessity of large, randomized Phase III trials and if and when smaller, non-randomized studies might be a better path.

### **Unmet needs in melanoma**

Given the prognosis for patients with brain metastases, more effective therapies for these patients are urgently needed. However, they are often not included in clinical trials. Additional study of the biology and responsiveness of brain metastases is needed in order to develop more effective treatments. Novel adjuvant therapy approaches are also a priority for the field, which would help forestall the development of these distant metastases that are so difficult to address. Another major need is the development of effective melanoma prevention strategies. For example, a screening program in Germany was recently shown to reduce melanoma mortality by approximately 50%. There are more options for melanoma patients than ever before, and the research field is opening up new avenues at an accelerated pace. Given this new era, expeditiously bringing scientific advances to patient management remains a high priority.



# New Models for Drug Testing and Approval

Leaders from industry, academia, and government participated in a small roundtable discussion of cross-cutting issues in clinical trials and regulatory issues for the development of new melanoma diagnostics and therapies.

The discussion was moderated by MRA Medical Advisory Panel Member and MRA-funded investigator **Antoni Ribas from the University of California at Los Angeles** and included **FDA's Richard Pazdur and Alberto Gutierrez**. Several themes arose during the discussion, including:

- **Global strategy for drug approval:**

While FDA has made use of innovative trial design and endpoints in oncology drug approvals, non-U.S. regulators tend to be more conservative. Greater harmonization between these agencies could accelerate the implementation of new trial designs and endpoints to benefit global drug developers and speed approvals.

- **Phase 3 clinical trial design:** In an era of promising investigational therapies for melanoma, the traditional randomized controlled trial has been called into question. Patients may not want to participate in trials with the possibility of being randomized to the control arm, which could mean treatment



Renzo Canetta at the Industry Roundtable Breakfast

with chemotherapy that is already known to be not effective for most melanoma patients. Nevertheless, trials must be able to establish a drug benefit for regulatory approval and to support the decisions of insurance providers and physicians. If a new drug has an unprecedented benefit rate in single arm clinical trials way beyond what could be expected with standard of care therapies, then there may not be a need for randomizing patients to the control therapy to demonstrate that the new agent benefits patients with melanoma. In some trials this one-arm design may be appropriate, but it may not be useful when the trial is designed to assess progression-free survival or another time-to-event. In addition, randomized studies can be designed so that there are more patients receiving the experimental drug than in the control arm, or to allow for cross-over.

- **Approval pathways for diagnostics:** With the increasing number of personalized




Richard Pazdur at the Industry Roundtable Breakfast

medicine approaches for cancer, there has been much discussion in the community about the appropriate approval pathway for diagnostics. The current system in the U.S. is complex, involving FDA and CLIA, and leads to a large investment in validation assay studies and correlation with clinical outcomes. Regulatory oversight by other agencies in Europe and Australia does not require this high bar for approval of a companion diagnostic. In part because of the lack of clear regulatory oversight of in vitro diagnostics, reimbursement for companion diagnostics that indicate response to specific treatments is highly fractured in the U.S. The FDA recently released guidance on how to use biomarkers to enrich patients likely to respond to treatment in clinical trials. Greater clarity for both reimbursement and regulation is needed to maximize the potential of cancer diagnostics.

While these issues are relevant to other cancers, melanoma is an ideal case study given the recent clinical developments in the field.



(From left to right) Suzanne Topalian, Antoni Ribas, and Wendy Selig



# The Role of the Government in Melanoma Prevention, Diagnosis, and Treatment

Governments play a critical role in the cancer landscape from administering publicly-funded research to implementing policies that shape public health practices.

MRA maintains significant relationships with leaders of the relevant government agencies and this year's retreat provided several opportunities to engage them directly in sessions regarding ongoing scientific progress in the melanoma field.

### **From melanoma to public health service: Assistant Secretary for Health Howard Koh**

Howard Koh stated that his journey to public health service “started with patients we could not save.” He believes that early detection and prevention can help stem the number of individuals dying from melanoma. “I was tantalized by the fact that a screening exam by an expert could save lives and was determined to help develop the field of melanoma screening. I thought it was going to be easy, but I discovered an ounce of prevention is sometimes a ton of work,” he said.



Howard Koh

Prior to being appointed Assistant Secretary for Health of the U.S. Department of Health and Human Services, Koh was the Harvey V. Fineberg Professor of the Practice of Public Health and Associate Dean for Public Health Practice at the Harvard School of Public Health and Commissioner of Public Health for the Commonwealth of Massachusetts. As a board certified dermatologist, his academic efforts included leading melanoma screening studies.

The incidence rate in melanoma continues to rise in a dramatic fashion—it is six times higher in young adults than it was 40 years ago, with women especially vulnerable. Mortality rates still have not declined. Clearly, more needs to be done to fully address this public health problem. With that goal in mind, Koh recently convened a key meeting of 30 leaders in melanoma research that included representatives from government (Food and Drug Administration, National Institutes of Health, National Cancer Institute, Centers for Disease Control (CDC)), academic leaders in the field, and research and patient advocacy groups, including the MRA, who helped shape the discussion. The focus of the meeting was melanoma prevention, and included exploring whether the 50% drop in melanoma mortality over ten years recently achieved in Schleswig-Holstein, Germany due to a screening intervention could also be achieved in the United States. As a result of this meeting, the CDC is exploring with the Surgeon General ways to advance skin cancer awareness and prevention, and he hopes it

will lead to the US Preventative Services Task Force to consider recommending melanoma screening so that health insurers will cover this service in their plans. As of this writing, the FDA released draft guidance to increase oversight of tanning beds, which have been shown to increase the risk of melanoma by 75%. “In hindsight, melanoma humbled me but also opened the door to me becoming more of a public health professional. I plan to continue to coordinate these efforts to make a difference in melanoma,” Koh concluded.

**Speeding new therapies to patients: A discussion with Margaret Hamburg, Food and Drug Administration, and Christopher Austin, National Institutes of Health**

**Michael Milken, MRA Board Member and Chairman of the Milken Institute,** led a discussion with Margaret Hamburg, Commissioner of the U.S. Food and Drug Administration and Christopher Austin, Director of the new National Center for Advancing Translational Sciences (NCATS) at the U.S. National Institutes of Health. The discussion was focused on how best to foster clinical translation of research findings into medical products, on their regulation in a global economy, on budgetary dilemmas facing the U.S. research enterprise, and on the importance of patient groups and foundations in translation efforts.

With support by the Milken Institute’s FasterCures and other advocacy groups focused on accelerating innovation in bioscience, NCATS was established in 2011 to develop new approaches to overcome bottlenecks in the translational research pipeline and speed the delivery of new drugs, diagnostics and medical devices to patients. NCATS’ approach is to think about the translational process in its entirety from gene to a drug, including innovative programs for target validation, preclinical development and clinical testing. “We are focused on new and different ways of doing things,” Austin said. Unlike other NIH institutes, NCATS does not narrow its focus on a subset of diseases and instead tries to foster synergistic collaborations across disciplines.

The final step in clinical translation of research findings is acquiring approval from the FDA to market the therapies tested in the clinic. Hamburg noted that the global economy creates a need for international cooperation in regulating products, including drugs. This relates to both the scientific/regulatory review of products and efforts to protect the integrity of the supply chain. Over the past decade there has been a quadrupling of imports of non-U.S. products and 80% of active ingredients manufacturers are overseas.

On the broader issue of collaboration, Hamburg noted that, “We’ve seen some interesting models that speak to the value

of disease- and patient-oriented groups, academia, and industry all coming together to get better products to people. Because of involvement of patient groups and foundations, agendas have been created that strengthen regulatory science and get products into the clinic.” She noted that the FDA is looking at innovative models for the regulatory approval process that give more consideration to patient-reported outcomes and how patients would like clinical trials to be structured. Milken added that the role of disease specific organizations is dramatically increasing, and that they are more sophisticated than ever. For example, the MRA has accelerated the progress for patients on multiple fronts, including funding cutting-edge research, and is an active partner at every level of the process.

Budget constraints also hamper clinical translation and regulation of medical products. The FDA has a broad scope but a relatively

small budget to accomplish its tasks. “Every American effectively spends 2 cents a day for FDA services—it’s the best bargain around, but Americans would be better served if we had a more robust budget,” said Hamburg. Austin added that because NCATS was formed less than two years ago, it still needs substantial investments in its infrastructure, “Budget cuts are problematic, especially considering the enormous agenda of things we need to address,” he said. Milken pointed out that “Other countries recognize the importance of bioscience and are increasing their investments,” noting that India and China are both ramping up their biomedical research budgets by 20% even as the U.S. reduces such investments. The last few years have seen major breakthroughs, and researchers continue to open up new avenues for exploration. The federal government plays a key role in the process. “It’s an exciting time but a very challenging time,” Hamburg concluded.



(From left to right) Suzanne Topalian, Wendy Selig, Louise Perkins, Christopher Austin, Michael Milken, and Margaret Hamburg





## Conclusion

MRA-funded research has accelerated the pace of melanoma progress by supporting a strong, international, cross-disciplinary group of outstanding biomedical researchers possessing the scientific and clinical expertise to explore, identify, and pursue innovative solutions to critical questions that will lead to a cure for melanoma patients. Transformative research results from MRA-funded programs in the areas of prevention and treatment have been leading the way in this extraordinary era of progress against melanoma. These findings were highlighted at the 2013 Scientific Retreat in a forum that allowed stakeholders from across the continuum to share, discuss, learn and plan ways to accelerate the pace of discovery. No single organization, investigator, or research sector can defeat melanoma alone. The interactions, discussions, and presentations held at the 2013 MRA Scientific Retreat highlight the importance of continued robust cross-sector and cross-disciplinary collaborations, catalyzed by MRA's unique model of engaging the field's leaders toward the day when no one suffers or dies from melanoma.



# Acknowledgements

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FOR MORE INFORMATION, visit the MRA website at [www.curemelanoma.org](http://www.curemelanoma.org). The website contains additional information about the MRA research program and past MRA Retreats.



# Appendix

Agenda

Participants

Retreat Participants

Industry Roundtable Breakfast

**AGENDA**

Omni Shoreham Hotel, 2500 Calvert St. NW

**Tuesday, February 26<sup>th</sup>**

2:30-5:30 pm Registration open.....East Registration Desk

4:30-6:00 pm Young Investigators Meeting (by invitation only).....Calvert Room

**6:30-8:30 pm Welcome Reception at the Embassy of Australia**

1601 Massachusetts Ave, NW Washington DC 20036  
Shuttle service at the hotel entrance from 6:00-7:00 pm

**Welcome:** Graham Fletcher, Deputy Chief of Mission, Embassy of Australia  
and Debra Black, MRA Co-founder and Chair of the Board

**Wednesday, February 27<sup>th</sup>**

6:30 am Registration open.....Blue Pre-function Room

7:00-8:00 am Breakfast.....Blue Pre-function Room

**8:00-8:10 Opening Remarks.....Blue Room**

Wendy Selig, MRA President and Chief Executive Officer

**8:10-12:00 Session: Discovering New Melanoma Molecular Targets**

Chair: Martin McMahon, University of California, San Francisco

8:10-8:35 David Fisher, Massachusetts General Hospital: Pathways inducing melanoma formation and survival

8:35-8:55 Michael Davies, MD Anderson Cancer Center: Identifying therapeutic targets for melanoma brain metastases

8:55-9:15 Eva Hernando, New York University: Epigenetic differentiation therapy for melanoma

9:15-9:35 Sohail Tavazoie, Rockefeller University: Therapeutic targeting of novel metastatic microRNAs in human melanoma

9:35-9:45 Levi Garraway: Highly recurrent TERT promoter mutations in melanoma

9:45-10:00 BREAK

10:00-10:20 Edwin Bremer, University Medical Center Groningen: Metastatic spread and outgrowth by MCSP-targeted therapy

10:20-10:45 Hermann Steller, Rockefeller University: Targeting XIAP for the treatment of melanoma

10:45-11:05 Kenneth Bradley, University of California, Los Angeles: Targeting tumor vasculature with anthrax toxin

11:05-11:30 Alan Spatz, Jewish General Hospital/Lady Davis Institute for Medical Research: Role of the X chromosome in melanoma biology and prognosis

## Wednesday, February 27<sup>th</sup> (cont.)

- 11:30-11:45 Jeff Trent, Translational Genomics Institute, and Pat LoRusso, Barbara Ann Karmanos Cancer Institute: Dream Team Overview: Personalized medicine for patients with metastatic BRAF wild type melanoma
- 11:45-12:00 Commentary by the Chair: The post-BRAF era of melanoma molecular targets
- 12:00-12:20 pm Keynote Address.....Blue Room**  
Howard Koh, Assistant Secretary for Health,  
U.S. Department of Health Human Services
- 12:30-1:40 pm Lunch.....Hampton Ballroom**  
Discussion with Margaret Hamburg, Commissioner, U.S. Food and Drug Administration and Christopher Austin, Director, National Center for Advancing Translational Sciences, U.S. National Institutes of Health  
Moderated by Michael Milken, Chairman, the Milken Institute and MRA Board Member
- 1:45-2:10 pm Special Lecture.....Blue Room**  
Françoise Bernerd, L'Oreal Research and Innovation: Skin photocarcinogenesis from early molecular events to prevention strategies: a key role of human in vitro skin models
- 2:10-5:25 pm Session: Melanoma Immunotherapy.....Blue Room**  
Chair: Thomas Gajewski, University of Chicago
- 2:10-2:30 Susan Kaech, Yale University: Regulatory macrophages: A new therapeutic target in melanoma
- 2:30-2:55 Drew Pardoll, Johns Hopkins University: The PD-1 pathway as a target for melanoma therapy: Biomarkers of response
- 2:55-3:20 Jennifer Wargo, Massachusetts General Hospital: Evidence for potential synergy of BRAF inhibition and immunotherapy in metastatic melanoma
- 3:20-3:45 Timothy Bullock, University of Virginia: Enhancing melanoma specific T cell function by CD27 stimulation
- 3:45-4:05 *BREAK*
- 4:05-4:25 Alexander Lesokhin, Memorial Sloan-Kettering Cancer Center: Myeloid derived suppressor cells and immunotherapy outcomes in melanoma
- 4:25-4:45 Guangyong Peng, St. Louis University: Novel strategies targeting Treg cell suppression for melanoma immunotherapy
- 4:45-5:10 David Kranz, University of Illinois at Urbana-Champaign: Optimal T cell receptor affinity for adoptive T cell therapy of melanoma
- 5:10-5:25 Commentary by the Chair: Targeting of immunoregulatory pathways in the clinic
- 5:25-5:30 pm Closing Remarks:** Laura Brockway-Lunardi, MRA Scientific Program Director
- 6:15-9:00 pm Reception and Dinner.....Hampton Ballroom**  
Keynote Speaker: Michael Milken, Chairman, the Milken Institute and MRA Board Member

## Thursday, February 28<sup>th</sup>

- 6:30 am Registration open.....Blue Pre-function Room
- 7:00-8:15 am Industry Roundtable Breakfast (by invitation only).....Hampton Ballroom
- 7:00-8:15 am General Breakfast.....Blue Pre-function Room
- 8:30-11:35 am Session: Drug Resistance and Combination Therapies.....Blue Room**  
Chair: David Solit, Memorial Sloan-Kettering Cancer Center
- 8:30-8:50 Roger Lo, University of California, Los Angeles: Innate and acquired BRAF inhibitor resistance
- 8:50-9:15 Thomas Graeber, University of California, Los Angeles: Delineating BRAF inhibitor resistance mechanisms using proteomic profiling
- 9:15-9:35 Aaron Mackey, University of Virginia: Markers and mechanisms of melanoma resistance to combination chemotherapy
- 9:35-9:55 Maria Wei, University of California, San Francisco: Targeting protein trafficking in melanoma combinatorial therapy
- 9:55-10:20 Marcus Bosenberg, Yale University: Development of effective targeted and immune combination therapies
- 10:20-10:35 *BREAK*
- 10:35-11:00 Ze'ev Ronai, Sanford Burnham Research Institute: AGC kinases in melanoma development - implication for novel therapies
- 11:00-11:25 Douglas Tyler, Duke University: Defining tumor-host interactions in regional advanced melanoma
- 11:25-11:40 Commentary by the Chair: Developing rational combination therapy approaches for melanoma
- 11:40 am-12:30 pm Panel Discussion: Clinical Care Decision-Making for Today's Melanoma Patients**  
Chair: Michael Atkins, Georgetown University
- Panelists:
- Keith Flaherty, Massachusetts General Hospital
  - John Kirkwood, University of Pittsburgh
  - Kim Margolin, University of Washington/Seattle Cancer Center
  - Antoni Ribas, University of California, Los Angeles
  - Caroline Robert, Institute Gustave-Roussy
- 12:30 pm Closing Remarks:** Suzanne Topalian, Chair, MRA Scientific Advisory Panel, and Louise Perkins, MRA Chief Science Officer
- 12:30-1:30 pm Lunch.....Hampton Ballroom**

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