Melanoma Research Alliance

New Horizons in Melanoma Treatment

BRIDGING THE TREATMENT GAP

Highlights of the Melanoma Research Alliance Ninth Annual Scientific Retreat
February 13-15, 2017 • Washington, DC

Introduction

Building on the incredible progress made since its founding ten years ago, the Melanoma Research Alliance (MRA) continues to champion the fight against melanoma. Established in 2007 as a public charity by Debra and Leon Black, and under the auspices of the Milken Institute, the mission of MRA is to accelerate treatment options and find a cure for melanoma. As the largest nonprofit funder of melanoma research, MRA has dedicated a total of $87.8 million and leveraged an additional $89.5 million towards this mission. Looking towards the future, MRA recognizes that melanoma still remains a considerable foe, with many patients not benefiting from available therapies and one person losing their life to the disease every hour in the United States alone. MRA remains dedicated to advancing research in melanoma so effective treatment options exist for all patients.

(Left to right) Gideon Bollag, Daisy Helman, Debra Black, Leon Black, Neal Rosen

Since its founding, MRA has catalyzed strategic, collaborative and accountable research efforts that move the field toward effective treatment options for all melanoma patients as quickly as possible. Through its competitive, peer-reviewed research program, and the boundless support of researchers, donors, board members and others, MRA funds innovative research that will impact the prevention, diagnosis, staging and treatment of melanoma in the near and intermediate future. To date, MRA has awarded grants to 233 research programs, including awards to young investigators, established investigators and collaborative teams. These awards have accelerated research involving each of the 11 new melanoma therapies approved by the FDA in the past six years. Importantly, due to the ongoing support of its founders, 100% of donations to MRA go directly towards funding its research program.

100%

OF DONATIONS TO MRA SUPPORT MELANOMA RESEARCH

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Each year, MRA hosts a Scientific Retreat to promote collaboration and communication among key stakeholders in the melanoma community. This year, the Ninth Annual Scientific Retreat was held February 13-15, 2017, in Washington, DC, with nearly 300 registrants. Attendees included academic investigators, pharmaceutical and biotech representatives, melanoma advocates from numerous non-profit organizations, donors and government officials. All were gathered at this invitation-only, think tank-style conference to hear the latest research findings in melanoma prevention, diagnosis and treatment, discuss ways in which industry and academia can better work together to promote the most effective clinical trials and learn from patients and their families with firsthand experience fighting this difficult disease. Several satellite activities accompanied the Retreat's core scientific sessions to ensure a productive meeting for MRA and its partners.

"I'm happy to be a member of an **army against** a waning villain."

17 INDUSTRY PARTNERSHIP AWARDS

20 PILOT/ DEVELOPMENT AWARDS

59 ESTABLISHED INVESTIGATOR AWARDS

60 TEAM SCIENCE AWARDS

77 YOUNG INVESTIGATOR AWARDS

The scientific portion of the Retreat kicked off with Dr. Jedd Wolchok of Memorial Sloan Kettering Cancer Center underscoring the tremendous advances in treating melanoma by saying, "I'm happy to be a member of an army against a waning villain." While recognizing this progress, the scientific presentations also highlighted how much more remains to be done. For instance, despite the approval of 11 new therapies to treat melanoma since 2011, more than half of patients do not experience long-lasting benefit. The scientific presentations revealed the wide variety of approaches that researchers are taking to tackle this problem. These include identifying new therapeutic targets, especially ones that could be targeted in combination with existing therapies to create greater and more durable responses. Such approaches are focused on targeting the tumors themselves and also the surrounding microenvironment, including both immune cells and supporting cells. Researchers also presented data that helped to illuminate why some patients do not respond to any therapy and, for those that do, why many eventually stop responding. Finally, researchers presented new insights into how to better combine currently available therapies and how sunscreen prevents melanoma.

In addition to the scientific sessions, several satellite sessions shared the common objective of promoting enhanced communication between different stakeholder groups. The **Melanoma Advocates and Foundations**

Forum brought together patients, industry representatives and individuals from non-profit organizations responding to melanoma. The Forum supported networking among these groups and provided an overview of current research to help these individuals better understand the scientific sessions. Additionally, an **Industry Roundtable Breakfast** convened academic researchers and representatives from government and industry to discuss how to better facilitate the collection and use of critical tissue specimens from patients participating in clinical studies. Finally, as part of MRA's mission to support the next generation of melanoma researchers, a **MRA Young Investigator Breakfast** featured editors from several top-tier journals who offered advice on how to best prepare their research findings for the most impactful distribution.

Michael Kaplan

MRA Scientific Retreat

Remembering the Patient

With a core mission to fund cutting-edge melanoma research to advance a cure, melanoma patients are a central part of MRA's focus. The retreat kicked off with this this in mind. MRA gave retreat attendees the opportunity to hear from patients whose lives were saved by melanoma research, as well as from family members who lost a loved one to the disease but are carrying out their loved one's wishes to fund research so future melanoma patients and their friends and families would not have to suffer from the disease.

"I'm happy to be alive," said Ms. Trena Taylor Brown, noting that she was diagnosed in 2013 with melanoma at age 65, a diagnosis that led to her toe being amputated. Despite doctors giving her a good prognosis, Ms. Brown was shocked to discover three years later that her labored breathing during gym workouts was a signal her melanoma had returned and had metastasized. Her oncologist quickly put her on a regimen of the immunotherapies nivolumab and ipilimumab, and her latest CAT scan showed no signs of disease. "I'm so grateful for my second chance in life," she said. "I couldn't ask for a better outcome."

In a video shown at the retreat, President Jimmy Carter also expressed his gratitude that he, too, is still alive after being diagnosed in 2015 with metastatic melanoma that had spread to his liver and brain. "I thought it was all over at that point," he said. But his treatment with the anti-PD1 immunotherapy pembrolizumab also was successful and he has been free of melanoma since January 2016. President Carter thanked MRA and the researchers it has supported. "You have saved my life and I'm very grateful to you," he said.

Unfortunately, even when patients are given the latest melanoma treatments, not all of them respond as well as President Carter or Ms. Brown did. Ms. Lauren Miller

"I'm so grateful for my **second chance in life.** I couldn't ask for a better outcome."

Trena Taylor Brown

spoke of the loss of her twin sister Tara to the disease just short of her 30th birthday in 2013. "Her treatment was like an FDA timeline of drug approvals for melanoma," Ms. Miller said, noting that despite getting targeted and immunotherapies, nothing worked for Tara. Recognizing the need for more melanoma research, in between her treatments Tara established a foundation to help future patients with the disease. "She wanted to fund research that will hopefully provide a lifetime

to melanoma patients that she didn't have," Ms. Miller said. In the past three years, the Tara Miller Melanoma Foundation has funded three melanoma investigators through MRA.

Mr. Ross King's daughter, Jacqueline, also wanted to support melanoma research and made that clear to him before she died from the disease in 2014 at the age of 22. Donations in her name funded an MRA Young Investigator whose research findings will provide his daughter with a legacy that, in her words, "will be remembered far after I am forgotten," Mr. King told conferees at the retreat.

Dr. Vicki Goodman of Bristol-Myers Squibb & Co, the Presenting Sponsor for the 2017 Scientific Retreat, acknowledged all the stories of success as well as the failures, saying "They remind us of where we've come from and where we need to go. There's much more we need to do."

"You have **saved my life** and I'm very grateful to you."

Video address from President Carter

Two Avenues of Research

The past decade of research on melanoma has broadly sketched out two categories of effective melanoma treatments—those that target genetic defects in the tumor cells that enable runaway growth, and those that target immune and other cells in the area surrounding a tumor, known as the tumor microenvironment. Increasingly, studies of the tumor microenvironment are teaching scientists about how multiple cell types interact in ways that may suppress an immune response to the cancer or fuel tumor growth via various kinds of molecular signals.

What was apparent at this year's Scientific Retreat was how quickly researchers are filling in the molecular details for both targeted and immune treatments to improve their efficacy, both in terms of durability and reach. Promising new drug targets have emerged from this research, including those for rare forms of melanoma that typically don't respond to current treatments, as well as for melanoma liver and brain metastases which are often deadly. The investigations have also helped explain why some tumors do not respond or become resistant to various treatments, and how to overcome that resistance. An overarching conclusion resulting from the research is that combinations of drugs are more likely to be effective than individual therapies for patients with melanoma.

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MRA Young Investigators

Immunotherapy Past, Present and Future

Dr. Jedd Wolchok of Memorial Sloan Kettering Cancer Center kicked off the scientific sessions of the retreat by noting how dismal melanoma survival statistics were twenty years ago when he started treating his first melanoma patients. “We’ve come a long way since then due to many people working in basic and clinical research along with our partners in the pharmaceutical industry and philanthropy. Some of us feel as if we just washed up on to the beach after having ridden a big wave and now we are figuring out what we accomplished and what we have to do next.”

Dr. Wolchok began his talk by reviewing some of the early successes in immunotherapy, most notably studies conducted by Dr. Steven Rosenberg at the National Cancer Institute. These included treating melanoma patients with high doses of interleukin-2 (IL2), a protein secreted by T cells, which provided the first proof that “a treatment targeting the immune system could provide durable control, which was a step forward,” Dr. Wolchok said. Dr. Rosenberg later improved the efficacy of IL2 by combining it with adoptive cell therapy.

Simultaneously, basic research revealed that CTLA4, a protein expressed on the surface of T cells, provides an “off” switch or “checkpoint” for the immune response. Releasing this brake using antibodies that inhibited CTLA4 allowed T cells to kill tumors. In a pivotal clinical trial, researchers gave ipilimumab, one of these antibodies to CTLA4 and the first in the class of immunotherapies known as “checkpoint inhibitors,” to patients with metastatic melanoma. Twenty percent of patients who received ipilimumab lived five years or longer, a length of time nearly unheard of for metastatic melanoma patients receiving standard therapy. Many ipilimumab-treated patients, however, experience side effects, including serious or even life-threatening gastrointestinal or endocrine disorders. But clinicians learned

Jedd Wolchok

“A treatment targeting the immune system could provide **durable control**, which was a step forward.”

that if detected early, they could reverse many of these with immune suppressants. Surprisingly, this does not seem to interfere with the anti-tumor effects of checkpoint inhibitors, for reasons that are still unclear.

The next generation of checkpoint inhibitors to enter the clinical arena and garner FDA approval were antibodies that block the protein receptor PD1 (nivolumab and pembrolizumab), or its ligand PDL1 (atezolizumab, avelumab, and durvalumab). These antibodies were

developed after researchers found that T cells expressing PD1 were dysfunctional. Clinical studies showed that up to 40-50 percent of patients responded to nivolumab or pembrolizumab. Moreover, previous treatment with ipilimumab did not affect responsiveness to PD1-targeting therapies.

Dr. Wolchok stressed that resistance to one type of immunotherapy does not imply resistance to another because CTLA4 and PD1 affect T cells in different ways. Because of this, combination therapy is approved for metastatic melanoma patients and is currently being tested for other cancers. Encouragingly, responses to checkpoint inhibitors are often durable and most of the patients whose toxic reactions force them to stop therapy still have significant responses. Despite these successes, there are many remaining questions about checkpoint inhibitors that need to be answered, Dr. Wolchok noted, including which melanoma patients need combination therapy.

Other critical questions that remain include understanding what accounts for resistance to current immunotherapies, and if that resistance can be overcome by targeting other key aspects of the immune response in the tumor microenvironment. Dr. Wolchok concluded his presentation by stressing that checkpoint inhibitors are effective treatments that foster durable responses and improve overall survival not just of melanoma patients but of patients with several other cancers. He stressed that for current immunotherapies to achieve their full potential, they will likely need to be combined with additional immunotherapies, targeted therapies, radiation and/or chemotherapy.

WHAT THIS MEANS FOR PATIENTS

The discovery that the immune system uses certain molecules on the surface of cells to turn off an immune response to tumors, and that tumors overproduce proteins that bind these immune "checkpoint" molecules, led to the development of checkpoint inhibitors. These drugs have been remarkably effective at treating advanced melanoma, both alone and when they are used in combination. But, by unleashing an immune response, checkpoint inhibitors can also cause an immune attack on normal cells, leading some patients to develop colitis, thyroid dysfunction, diabetes or other conditions due to an over-reactive immune system. Many of these immune-related side effects can be avoided by early detection and treatment with an immune suppressant. Surprisingly, and for reasons doctors do not yet fully understand, immune-suppressants do not seem to hamper the anti-tumor effects of checkpoint inhibitors.

Despite the progress that has been made in using immunotherapies to treat melanoma, researchers recognize the need to continue to study them with the hope of understanding why some patients never respond and for those that do, why some eventually stop responding. Researchers are seeking to overcome this resistance by using checkpoint inhibitors in combination with other therapies including both immune and targeted therapies. In addition, researchers are beginning to uncover additional molecules to target and are currently testing drugs for these in the clinic, often in combination with checkpoint inhibitors. The hope is that these new treatment combinations will provide durable responses in a greater fraction of melanoma patients.

New Drug Targets

Given the recent successes of both targeted therapies and immunotherapy to treat melanoma, the research community has focused much of its attention on tumors and T cells. While this remains critical, as highlighted in multiple talks, several speakers this year emphasized the importance of casting the net wider—looking beyond these usual suspects in the pursuit of new drug targets. For instance, stromal cells that surround the tumor and other immune cells present in the tumor microenvironment are worth a closer look. Moreover, identifying and pursing rational combinations of therapies is of utmost importance in the effort to cure melanoma whether those treatments target the tumor microenvironment, the tumors themselves or both.

TUMOR MICROENVIRONMENT TARGETS

Myeloid-derived suppressor cells (MDSC) are a type of white blood cell often present in the tumor microenvironment, where they suppress anti-tumor immune responses. Dr. Jedd Wolchok presented data obtained by MRA Young Investigator Dr. Alex Lesokhin of Memorial Sloan Kettering Cancer Center, showing that overall survival responses are worse in ipilimumab-treated metastatic melanoma patients with higher frequencies of MDSCs compared to those patients with low frequencies of these cells. Because MDSCs produce large amounts of colony stimulating factor (CSF) and are dependent on PI3Kγ signaling, investigators have hypothesized that immunosuppressive activity might be blocked with compounds that inhibit these growth-stimulating proteins. Preclinical studies found this to be the case: checkpoint blockade given with a PI3Kγ inhibitor slowed tumor growth and improved survival outcomes in a mouse model of melanoma.

Immunologists have made tremendous progress in deciphering what cell receptors turn on or off an immune response. For example, **Dr. Bin Zhang of Northwestern University** described how rationally targeting these pathways in concert can improve outcomes in preclinical melanoma models. CD137 is a cell surface protein on T cells that has been shown to boost their activity, but antibodies that stimulate CD137 (agonists) have shown little effect in melanoma patients in early stage clinical trials.

"This is very profound evidence that CD73 expression by T cells **might negatively** affect other immunotherapies."

To understand this lack of activity, Dr. Zhang explored the effects of CD137 agonist antibodies on two downstream components of CD137 signaling involved in regulating T cell responses in the tumor microenvironment. One of these is CD73, a cell surface protein on T cells that suppresses the immune response. Dr. Zhang found that CD137 agonist antibodies downregulated CD73 expression on T cells. Moreover, when he combined CD73 blocking antibodies with CD137 agonist antibodies, he was able to shrink melanoma tumors in mice. Tumor shrinkage was likely due to increased frequencies of tumor-infiltrating CD8 T cells and reduced frequencies of tumor-infiltrating, immunosuppressive regulatory T cells. In contrast, neither treatment alone effectively controlled the growth of established melanoma. "This is very profound evidence that CD73 expression by T cells might negatively affect other immunotherapies," Dr. Zhang said.

Aside from blocking CD73 itself, deleting the adenos-

Ana Anderson

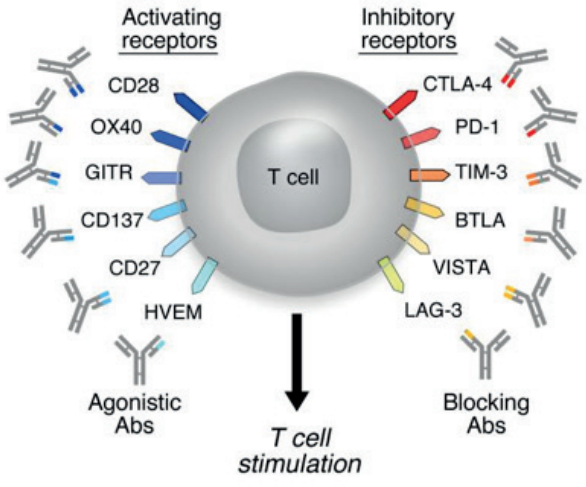
ine 2B receptor, its downstream target, also caused tumors to regress if the mice also received CD137 agonist antibodies. In addition, Dr. Zhang found that the secreted protein, transforming growth factor-β (TGF-β), impaired the effects of CD137 agonist antibodies, at least in part through its effects on CD73. "These findings show combination strategies that make the anti-tumor T cell response better and provide a rationale for which combinations are likely to work in clinical trials," Dr. Zhang concluded.

Like CD73, PD1 and CTLA4, TIM-3 is an inhibitory receptor on T cells. Laboratory studies of this checkpoint molecule have shown that blocking TIM-3 can a) cause tumor-reactive T cells to proliferate more and produce more immunostimulatory cytokines; and, b) improve the anti-tumor effects of PD1 inhibitors. These findings have led to several clinical studies of this combination therapy. But there are four different protein ligands that latch on to TIM-3 and scientists like **Dr. Ana Anderson of Brigham and Women's Hospital** are investigating which of these interactions must be blocked to relieve the immune-suppressing effects of TIM-3. Her laboratory uncovered two key ligands, one of which is a lipid that is expressed on the cell membrane of dying cells, and the other is a glycoprotein that helps cell adhere to one another. Her results suggest that binding of TIM-3 to these ligands must be disrupted for anti-TIM-3 drugs to be effective. "Our findings provide key information for the translation of therapeutic strategies that target TIM-3 for melanoma," she concluded.

Dr. Anderson also discovered that TIM-3 is part of a larger suite of co-regulated inhibitory receptors on tumor-infiltrating T cells that includes other checkpoint molecules, which scientists are currently investigating for their cancer-promoting qualities. A secreted protein that binds T cells is important for triggering expression of this module of proteins. Dr. Anderson's work suggests that inhibiting this secreted protein or other proteins in this group, along with TIM-3, may lead to enhanced anti-tumor activity in T cells.

Many researchers have studied the adaptive arm of the immune system. This is a relatively late immune response primarily carried out by T cells and which is the focus of the approved checkpoint immunotherapy drugs. In contrast, **Dr. Alexander Boiko of the University of California, Irvine** has studied the effect of stimulating the other, earlier arm of immunity known as the innate immune response to target tumors. More specifically, his work focuses on unleashing macrophages to "eat" tumors cells in a process called phagocytosis. But tumor cells can 'trick' the macrophages into sparing them by expressing a protein called CD47 on their surface, which essentially tells macrophages "don't eat me," Dr. Boiko said.

Using clinical melanoma patient datasets, Dr. Boiko found that metastatic melanoma cells overexpress CD47 compared to primary tumors. In his laboratory he then found that blocking CD47 caused macrophages to digest human melanoma cells in cell culture, "providing efficient removal of tumor cells," Dr. Boiko said. His lab then focused on combining CD47 blockade with blockade of CD271, a protein expressed on the surface of some melanoma cells. CD271 is of interest because it has been implicated as marking melanoma cells that initiate tumors, suppressing the immune system and, resisting the BRAF targeted therapy, vemurafenib. The researchers found that CD271 blocking antibodies slowed the growth of melanoma cells in culture. To demonstrate the therapeutic effects of these antibodies in more physiologically relevant conditions, Dr. Boiko's lab established human patient melanoma xenografts in laboratory mice which were then treated with CD47 and CD271 targeting antibodies. In one regimen, combining anti-CD47 and anti-CD271 antibodies significantly slowed the growth of primary tumors and eliminated virtually all melanoma metastases from treated mice as compared to the control treatment arm.



Activating and inhibitory receptors modulate T cell responses to tumors. *Nature* 480, 480 (2011). Used with permission.

"These two antibodies activate the **innate immune** response and at the same time eliminate melanoma initiating cells, providing a **powerful** therapeutic **approach** against metastatic melanoma."

"No one treatment by itself will produce a magical reduction in tumor and metastases, but if you combine these two approaches you have a more profound effect," Dr. Boiko said, noting that in the tumor microenvironment, the combined treatment tipped the balance towards immune stimulating cells better equipped to prevent progressive disease. Immune-dampening myeloid-derived suppressor cell numbers decreased whereas the numbers of tumor-digesting macrophages increased. "These two antibodies activate the innate immune response and at the same time eliminate melanoma initiating cells, providing a powerful therapeutic approach against metastatic melanoma," Dr. Boiko concluded.

Many factors contribute to the immunosuppressive signaling in the microenvironment inhabited by melanoma cells. These include checkpoint molecules like CTLA4 and PDL1/PD1, but also secreted proteins like transforming growth factor-beta (TGF-β), which is produced by fibroblasts, a type of supporting cell that can surround melanoma cells, and MDSCs. **Dr. Brent Hanks of Duke University** presented data that indicates that blocking TGF-β in conjunction

with anti-CTLA4, might be an effective combination therapy for melanoma.

When Dr. Hanks tested a small-molecule TGF-β inhibitor in a transgenic mouse melanoma model, he found that it decreased tumor growth and increased overall survival only when combined with CTLA4 blocking antibodies. In contrast, the TGF-β inhibitor failed to have such effects when combined with PD1/PDL1 blocking antibodies.

When administered in combination with anti-CTLA4 antibodies, blocking TGF-β increased the number of CD8 T cells infiltrating tumors while also suppressing the number of immune-dampening regulatory T cells. When investigating why TGF-β inhibition failed to augment anti-PD1/anti-PDL1 antibodies, Dr. Hanks found that TGF-β inhibitors expanded the number of melanoma-associated fibroblasts which, in turn, diminished PDL1 expression on melanoma cells, likely hampering the effects of PD1- or PDL1-targeting antibodies. When co-transplanting a melanoma cell line with melanoma-associated fibroblasts compared to the melanoma cell line alone, he found that the presence of melanoma-associated fibroblasts significantly suppressed the anti-tumor impact of anti-PD1 antibody therapy. Further work showed melanomas that have escaped anti-PD1 antibody therapy increase the expression of several stromal fibroblast-associated genes. "This study highlights the importance of nearby microenvironment stromal tissues as critical mediators capable of impacting the clinical outcome of checkpoint inhibitor immunotherapy in melanoma," Dr. Hanks stressed. He added that physicians should carefully consider the

INFORMING PATIENTS

Prior to the start of the Scientific Retreat, MRA hosted an enhanced **Melanoma Advocates and Foundations Forum.** With significant input from MRA President and CEO Michael Kaplan, this year's forum brought together more than 60 patients, industry representatives and representatives of non-profits working to combat melanoma. The goal of the forum was to support networking among the many organizations responding to melanoma, while also providing valuable information and tools on everything from early diagnosis to understanding the research agenda. The session was moderated by Drs. Ekemini Riley and Erik Lontok of Milken Institute's Center for Strategic Philanthropy. Dr. Victoria Siegel of Molloy College discussed strategies for using electronic medical records and making better use of nurses in melanoma screening and prevention efforts. Dr. Martin Weinstock of Brown University updated attendees about INFORM, an MRA-funded, web-based curriculum designed to better train primary care physicians and nurses to diagnose melanoma. Finally, Dr. Jason Luke of the University of Chicago provided a patient-centric overview of clinical trials and some of the research topics that were to be discussed at the retreat to help attendees better engage with the scientific agenda. As relayed by one patient in attendance, "…the forum provided a base of understanding that helped to better understand so much of the cutting edge science being presented during the Scientific Retreat that followed."

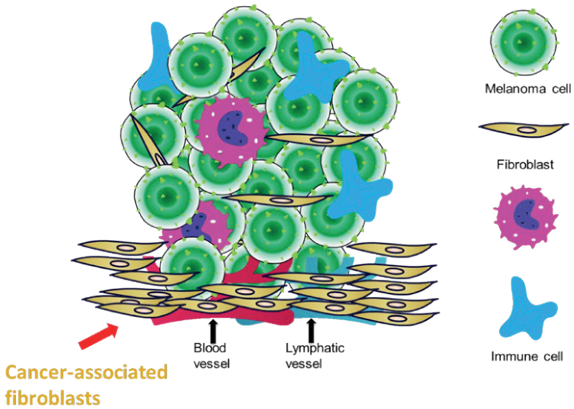
physiological effects on the tumor microenvironment when designing combinations of immunotherapies. Dr. Antoni Ribas of the University of California, Los Angeles added that there is a subtype of melanoma characterized by high amounts of fibrosis and this subtype has the highest response rate to anti-PD1 treatment. Dr. Jeffrey Sosman of Northwestern University noted that this may be related to different fibroblast subtypes. Dr. Hanks indicated that these observations may also be related to differences in the mutational burden of these melanoma subtypes.

Dr. Yuhang Zhang of the University of Cincinnati also presented data describing the different ways in which stromal fibroblasts can influence melanoma onset and growth. Fibroblasts are an important part of the "social network" of melanoma tumors and help tumor cells invade the dermal layer of the skin and beyond, steps that lead tumors to progress and disseminate. "They leave their old friends, keratinocytes, behind and make new friends with fibroblasts," he explained. Fibroblasts are not only drawn to melanoma cells and multiply in their presence, Dr. Zhang showed, but the interaction also triggers melanoma cells to expand due to the biological functions of beta-catenin. Beta-catenin is an important dual-function protein that plays critical roles in both cadherin-based cell-cell adhesion and Wnt-signaling-mediated gene expression.

Dr. Zhang first examined how beta-catenin signaling in fibroblasts influences melanoma growth in mice and found that early in tumor development, beta-catenin signaling in fibroblasts suppresses tumor growth. However, when he deleted beta-catenin from fibroblasts after melanomas were already established, Dr. Zhang got a different result. In this case, mice whose tumors contained fibroblasts that lacked beta-catenin experienced slower growth of their tumors. Moreover, silencing of beta-catenin signaling

"This study highlights the importance of nearby microenvironment **stromal tissues** as critical mediators capable of impacting the clinical outcome of **checkpoint inhibitor** immunotherapy in melanoma."

countered the heightened MAPK signaling seen in the BRAF-mutant melanoma cells, which is of interest since human melanomas also exhibit BRAF mutations and elevated MAPK signaling. Dr. Zhang's data indicate that as melanomas grow, they rewire tumor-suppressive fibroblasts to support their growth. He concluded, "Our data highlight important crosstalk between cancer-associated fibroblasts and the signaling cascade in BRAF-activated melanoma and may offer a new approach to abrogate drug resistance in targeted therapy."



Melanoma cells exist in a microenvironment composed of several cell types. Courtesy of Yuhang Zhang.

Richard Scolyer

"For patients with metastatic disease who fail normal treatments, this analysis could be effective for **identifying new drug targets**."

TARGETING THE TUMOR ITESELF

Dr. Richard Scolyer of the Melanoma Institute Australia and The University of Sydney reported on the Australian Melanoma Genome Project, which is analyzing the whole genome sequences of 500 melanoma samples to discern genetic differences between different types of melanoma, with the hopes of identifying new drug targets. Dr. Scolyer stressed that although researchers often limit their DNA sequencing to just the protein-coding part of the genome, the exome, which comprises one percent of the entire genome, the Australian project is sequencing the other 99%, too. Previously termed 'junk DNA', scientists now understand it plays an important role in regulating gene expression and may have other yet to be determined roles in cancer.

Dr. Scolyer reported that so far the project has analyzed 183 melanoma samples, one-quarter of which were acral melanomas (arising in the nail beds of the fingers and toes, or on the palms or soles), or mucosal melanoma, with the remainder being cutaneous (arising in the skin). They found that cutaneous melanomas had an extremely large number and range of mutations, compared to the acral or mucosal melanomas, which consistently had very few mutations. Cutaneous melanomas were also more likely to have a pattern of mutations indicative of UV damage, whereas acral or mucosal melanomas had a different genetic signature, whose causes are unknown. Surprisingly, the team found that some acral melanomas had a UV damage mutational signature, suggesting "nails may not be as strong a barrier to UV radiation as previously thought," Dr. Scolyer said.

An analysis of mutations found within genes uncovered genetic mutations commonly reported in other studies, including BRAF, NRAS, PTEN, CDKN2A, NF1 and RB1. No new hotspot mutations were detected in the acral melanoma samples, but four mucosal tumors had mutations typically seen in ocular melanoma (GNAQ and SF3B1), but not in cutaneous melanoma. In addition, the analysis uncovered recurrent noncoding mutations, including functionally significant mutations in the promoters of genes like TERT (a gene frequently mutated in several types of cancer), which were more common in cutaneous compared to other forms of melanoma.

Compared to cutaneous melanomas, acral and mucosal melanomas exhibited more chromosomal structural changes, such as gene fusions, which are hybrid genes that often arise from breaks in chromosomes. The researchers uncovered that acral and mucosal subtypes had clustered sites of chromosomal breakage on almost every chromosome, but most strikingly on chromosome 11 where the cell cycle regulator cyclin D1 resides. The high proportion of chromosomal rearrangements might

make acral and mucosal melanomas more susceptible to treatment with chemotherapy or radiation, Dr. Scolyer noted. Why these subtypes have such comparatively high rates of chromosomal breakage remains unclear.

Dr. Scolyer observed that the majority of patient tumor samples the Australian project analyzed had at least one actionable target. "For patients with metastatic disease who fail normal treatments, this analysis could be effective for identifying new drug targets. With the costs of genomic sequencing decreasing and the genetic analyses becoming easier, we expect this technology will be used in some melanoma patient subgroups to select the best treatment for them," Dr. Scolyer said.

Inherited variants of genes contribute to an individual's overall risk of developing melanoma. For instance, the variant of melanocortin-1 that causes red hair and fair skin also increases the risk developing melanoma. But beyond this, researchers have identified few inherited causes of melanoma that directly trigger cancer pathways. Such genes are likely to be rare, estimated at comprising only one percent of all melanoma cases.

Dr. Hensin Tsao of Massachusetts General Hospital set out to find these rare, heritable mutations which predispose individuals to cutaneous and ocular melanoma. Using blood samples, his group, in conjunction with the Broad Institute, performed whole exome sequencing on nearly 400 hereditary cutaneous and ocular melanoma cases along with over 10,000 healthy controls. Dr. Tsao and his collaborators found three genes that harbored more rare mutations among melanoma patients compared to controls. At the top of their list was CDKN2A in cutaneous melanoma. Dr. Tsao stated that 'this was reassuring knowing that the entire pipeline was able to recover a well-established cutaneous melanoma risk gene—this served as our 'positive control' as we developed novel algorithms to execute

Hensin Tsao

"This study further defines the **mutational landscape** of hereditary melanoma."

the first 'gene-based association study' in melanoma." One gene that had not previously been linked to melanoma risk was EBF3, a transcription factor which appears to be more involved in immune development. EBF3 showed significant association with hereditary cutaneous melanoma in the primary cohort and two additional replication cohorts. EBF3 has been shown to have tumor suppressor activity in prostate cancer. Dr. Tsao explored EBF3's ties to melanoma, and found several lines of evidence pointing to EBF3 as a tumor suppressor in melanoma, too. For example, inducing EBF3 expression in cultured melanoma cells reduced their growth in vitro. Elevated expression of EBF3 also slowed melanoma growth in mice, and led to reduced levels of MITF, a transcription factor expressed by melanocytes that is thought to drive melanoma progression. He also found that low EBF3 levels correlated with worse outcomes in melanoma patients, and that normal

skin cells progressing to moles and then to melanoma experience loss of EBF3. “This study further defines the mutational landscape of hereditary melanoma and implicates EBF3 as a possible predisposition gene for cutaneous melanoma,” Dr. Tsao concluded. Among the heritable genes identified by Dr. Tsao, is BAP1 which is frequently lost in ocular, otherwise known as uveal melanoma (UM). UM is a rare form of melanoma that afflicts the uveal tract of the eye. Unfortunately, UM is generally more resistant to treatment than cutaneous melanoma and has a poorer prognosis.

Dr. Scott Woodman of MD Anderson Cancer Center characterized the common chromosomal changes and seven significantly recurrent genetic mutations in primary and metastatic UM tumors, which included the loss of the tumor suppressor gene BAP1. He discovered that the loss of one copy of chromosome 3 (monosomy 3) and gain of an additional copy of part of chromosome 8, correlated with a very high risk of metastasis and a worse prognosis and are highly conserved between primary and metastatic UM. Dr. Woodman reported that compared to the primary tumors, “Metastatic UM harbors few additional chromosome alterations or somatic gene mutations, not recurrently identified in primary tumors.” This suggests that UM metastasis does not occur as a result of the acquisition of additional large-scale genetic mutations by UM cells, although future studies are needed to determine if the few additional alterations observed in metastatic UM may have emerged under a selective pressure of metastatic survival.

Monosomy 3 is associated with aberration of the BAP1 gene, located on the remaining chromosome 3. Dr. Woodman discovered that loss of BAP1 in UM cells had a global reprogramming effect on multiple cellular pathways, including decreasing signaling through the MAPK pathway. If a strong reliance on the MAPK pathway is not necessary for UM growth and survival, this may explain why MEK inhibitors have not shown clinical efficacy in patients with UM, Dr. Woodman noted. In support of this, adding wild type BAP1 back into UM cells lacking a copy of BAP1 enhanced the efficacy of MEK inhibitors. His analysis also suggested that BAP1 loss could suppress anti-tumor immunity, suggesting a link between this observation and the fact that UM patients do not typically respond to immune checkpoint inhibitor therapies. In addition, BAP1 regulates developmental and cell differentiation genes, including the oncogene c-MYC, which is found on the region of chromosome 8 that often has many copies in UM tumor cells isolated from patients with poor prognoses. BAP1 mutant UM cells exhibited elevated expression of c-MYC, which returned to normal levels upon re-expression of wild type BAP1. “We have identified multiple novel functional repercussions of BAP1 loss and a linkage between the two most prominent and co-occurring genetic features within high-risk UM, Monosomy 3/BAP1 and chromosome 8q gain, which may underlie its aggressiveness and recalcitrance to therapy, and inform strategies for developing effective therapeutics,” Dr. Woodman concluded.

Dr. Xu Chen of the University of California San Francisco also reported on UM research, identifying the enzymes protein kinase C delta and epsilon (PKCδ and PKCε) and the molecule RasGRP3 as potential novel therapeutic targets for this disease. Dr. Chen noted that more than 90 percent of UM tumors harbor activating mutations in GNAQ or GNA11, but researchers do not know how these mutations impact the MAPK signaling pathway, which is known to be overactive in cutaneous melanoma. Moreover, it is important to understand signaling downstream of mutant GNAQ and GNA11 because these proteins themselves are not

"PKCδ, PKCε and RasGRP3 are **novel therapeutic targets** for uveal melanoma."

easily druggable. Dr. Chen discovered RasGRP3 links oncogenic GNAQ/GNA11 signaling to the MAPK pathway. RasGRP3 activates the MAPK cascade through Ras. RasGRP3 can be activated by PKCδ and PKCε dependent phosphorylation as well as PKC-independent membrane binding. This PKC-independent activity may explain why PKC inhibition fails to induce sustained suppression of MAPK signaling in GNAQ mutant melanomas. Reducing the expression of PKCδ and PKCε in GNAQ/GNA11 mutant melanoma cell lines decreases their proliferation. Reducing the expression of RasGRP3 slowed tumor growth in a mouse model of melanoma, confirming the important roles of these proteins in regulating oncogenic signaling in UM cells. "PKCδ, PKCε and RasGRP3 are novel therapeutic targets for uveal melanoma," Dr. Chen concluded.

Men with melanoma tend to have lower survival rates than women, perhaps due to differences in the expression of genes found on the sex-linked X and Y chromosomes. **Dr. Alan Spatz at McGill University** and his team investigated this and discovered an important role for the tumor suppressor protein PR70, which is encoded on the X chromosome in females and the Y chromosome in males. Although females have two X chromosomes, cells often 'inactivate' one copy, so men and women would be expected to express similar amounts of the genes encoded on this chromosome. But, genes can escape X inactivation, leading to higher levels of PR70 in some female melanoma cells potentially contributing to cancer sex bias.

To arrive at these conclusions, Dr. Spatz compared the genetics of melanoma tumors from women who survived more than three years without distant metastases to those that did not, and found expression of genes from both X chromosomes was associated with better survival. He then focused on the PPP2R3B gene that encodes the PR70 protein. PR70 functions as the regulatory subunit of an enzyme known to control the activity of proteins involved in melanoma, such as RAF, MEK and AKT.

The research team found that low expression of PR70 correlated with a poor prognosis for cutaneous melanoma patients, and that inducing PR70 expression in melanoma cells decreased their growth in culture and in mice. Further mechanistic studies revealed that PR70 slows tumor growth by regulating chromatin remodeling, which inhibits the ability of tumor cells to replicate their DNA and progress through the cell cycle. These data on PR70 provide "the first example of a sex-related dosage difference in a tumor suppressor gene," Dr. Spatz stressed. He added that "interaction between PR70 and other X-related genes hints at a new mode of tumor suppressor gene regulation through X-linked chromatin remodeling." The researchers are currently

Tal Burstyn-Cohen

"Altogether our data indicates the PROS1-MERTK signaling axis is a **novel** and **targetable** pathway in melanoma."

screening FDA-approved drugs to see if they can target PR70 or the genes whose expression it affects.

The protein tyrosine kinase receptor MERTK regulates many growth promoting and oncogenic pathways, and melanoma tumors express elevated amounts of this protein. These findings led **Tal Burstyn-Cohen of Hebrew University of Jerusalem** and her international MRA Team Science Award collaborators to explore how MERTK functions in melanoma cells and demonstrate that this pathway is likely a therapeutic target worth pursuing.

When these researchers blocked MERTK activity in melanoma cell lines using a small molecule inhibitor, they found that it blocked pro-survival signaling through the PI3K/AKT signaling pathway and induced tumor cell death. Moreover, when the researchers implanted these cell lines into mice, treatment with a MERTK inhibitor slowed tumor growth. Interestingly, the effect was independent of BRAF mutational status (BRAF is mutated in up to 50% of cutaneous melanomas). Blocking MERTK also inhibited tumor growth in mice engineered to develop BRAF mutant melanoma. After showing that Protein S (PROS1), which is expressed by many melanoma cell lines, binds to MERTK, the researchers then found that reducing PROS1 expression in melanoma tumor cells implanted into mice slowed their growth. They are currently assessing if depleting PROS1 also makes melanoma tumors more sensitive to BRAF inhibitors, which are approved treatments for melanoma.

The research team conducted gene expression analyses that revealed that depleting PROS1 decreases the expression of a number of key molecular players and pathways that promote the growth and survival of melanoma cells. "Altogether our data indicate the PROS1-MERTK signaling axis is a novel and targetable pathway in melanoma," Dr. Burstyn-Cohen concluded.

While there are multiple options for the nearly half of melanoma patients whose tumors harbor specific mutations in BRAF, melanoma patients whose tumors are driven by mutations in NRAS, which comprise about a quarter of patients, are not as fortunate. NRAS-mutant melanomas tend to be extremely aggressive and largely resistant to most current therapies.

To help bridge this therapeutic gap, **Dr. Jessie Villanueva of The Wistar Institute** is pursuing the molecular pathways that NRAS regulates and ways to block them. She found that targeting BRD4, an epigenetic reader protein that modulates the expression of many oncogenes, in combination with MEK inhibition, is a promising approach for slowing the growth of NRAS-

"NRAS mutant melanoma has a **remarkable susceptibility** to BET- and MEK-targeting combination approaches."

mutant melanoma. Dr. Villanueva reported that NRAS-mutant melanomas express high levels of BRD4 and depend on it for their survival. Moreover, the presence of high levels of BRD4 protein in melanoma tumors correlates with a poor prognosis.

BRD4 is a member of the molecular family known as BET. When Dr. Villanueva used a small molecule BET-inhibitor in vitro, she inhibited the growth of NRAS mutant melanoma cells, including those that had both BRAF and NRAS mutations but were resistant to BRAF and MEK inhibitors. In addition, she found that co-targeting BET and MEK resulted in a synergistic decrease of tumor growth in NRAS-mutant mouse models and prolonged survival. These same results were seen in patient-derived xenograft (PDX) melanoma models, including those corresponding to melanoma patients whose tumors were refractory to BRAF inhibitors. Several BET inhibitors have been developed and are currently being tested in clinical trials.

"Collectively, our studies show NRAS mutant melanoma has a remarkable susceptibility to BET- and MEK-targeting combination approaches, and will hopefully pave the way for further evaluation and rapid clinical translation of this promising strategy," Dr. Villanueva concluded. Following Dr. Villanueva's presentation, Dr. Iman Osman, of New York University School of Medicine, pointed out that despite the impressive preclinical data on BET inhibitors, some of these compounds are not faring well in early clinical trials, mostly due to their toxicity. "Toxicity is a concern since these inhibitors are targeting growth regulators," she said. Dr. Villanueva responded that such toxicities might be managed by using lower doses of more potent, next generation BET inhibitors or by using intermittent dosing.

Melanoma is the third most common cause of brain metastases, and half of all deaths from melanoma may be due to these metastases, which often resist treatment. Seeking to understand what causes melanoma brain metastases, **Dr. Sheri Holmen of The University of Utah** focuses her research on members of the AKT family of proteins, which play a variety of roles in cells, including regulating cell metabolism and cell division. Dr. Holmen developed a mouse model of melanoma that uses an avian virus to introduce genes into the melanocytes of newborn mice. This model enables the researchers to assess the effects of specific genes on tumor development, progression and metastasis.

Aware of studies showing that AKT signaling is increased when melanomas metastasize and especially heightened in brain metastases compared to lung and liver metastases, Dr. Holmen used the virus to introduce into different subgroups of mice one of each of the

Sherri Holmen

three different forms of activated AKT (AKT1, AKT2, and AKT3). She found that either activated AKT1 or AKT3 promoted melanoma progression and caused brain metastases, although brain metastases were far more frequent in mice receiving activated AKT1 (~80%) compared to AKT3 (~20%).

Dr. Holmen continues to explore specific mutations in AKT1, AKT2, and AKT3 that can heighten the development of brain metastases. She is also currently testing the effects of an AKT1 inhibitor combined with a BRAF inhibitor on the development of such metastases. In addition, Dr. Holmen plans to assess "what it is about the brain microenvironment that makes it such fertile soil for melanoma cells." She noted that molecules secreted by brain cells called astrocytes have been shown to affect the growth of melanoma cells in vitro, and she hopes to experiment with this in the future.

WHAT THIS MEANS FOR PATIENTS

Researchers are pursuing two broad categories of new drug targets: those that target the genetic defects of the tumor and those that target the molecular signaling that occurs in the area surrounding tumors, which is known as the tumor microenvironment.

On the genetic front, researchers are delving more deeply into the molecular pathways that fuel tumor growth, uncovering new signaling branches and nodes that can be blocked with drugs. Many of these studies suggest combinations of targeted drugs. Because combinations may more completely block the signals stimulating tumor growth, drug resistance may be reduced, leading to broader and more durable responses.

Investigators are also uncovering genetic defects specific to subgroups of melanoma patients, such as those that have ocular melanoma or acral melanomas that arise in the nail beds of the fingers or toes, or on the palms or soles. These unique genetic defects suggest a need for new ways to treat these types of melanoma. Researchers have also uncovered genetic changes in the X chromosome of melanoma tumor cells that may explain why men have poorer outcomes than women.

On the tumor microenvironment front, researchers are discovering which combinations of immunotherapies are likely to work synergistically to create greater and more durable responses in melanoma patients. Investigators are also exploring new avenues in the immunotherapy arena, including ways to stimulate "first responder" immune cells.

Finally, investigators are eavesdropping on the crosstalk between tumor cells and their neighbors, such as connective tissue cells called fibroblasts as well as immune cells. They have shown that such crosstalk can stimulate tumor growth and suppress an immune response to tumors, suggesting new targets for melanoma drugs. Much of this genetic and tumor microenvironment research has generated innovative potential treatments that have only been tested in the laboratory on cell cultures or in mice, but some are starting to enter testing in clinical studies.

Tumor Vaccines

Researchers continue to explore vaccines aimed at boosting melanoma patients' immune responses to their tumors and assessing whether such vaccines can augment the effects of other immunotherapies when combined with them. Dr. Wolchok reported on results suggesting that the Newcastle disease virus (NDV) might be a promising vaccine candidate for fighting melanoma, especially when used together with CTLA4 blockade. NDV readily infects cancer cells because tumor cells express high levels of a particular sugar on their surface, which the virus uses to gain entry into the tumor cells. Although normal cells also express this sugar, the virus only replicates in cancer cells. The virus causes tumor cells to secrete high levels of a protein called type 1 interferon, which boosts anti-tumor immunity, and clinical trials testing NDV as a treatment for cancer indicate it is safe.

When members of Dr. Jim Allison's and Dr. Wolchok's laboratories injected NDV directly into tumors in mice, they discovered that it acted like a vaccine in stemming the growth of other distant tumors, but they did not observe any complete tumor regressions. The virus did induce inflammation of tumors, however, which likely augmented the effects of anti-CTLA4 therapy, leading a large proportion of mice to completely reject the virus-injected, as well as distant, non-injected tumors.

Dr. Wolchok also discussed early clinical results generated by another research team that tested the oncolytic herpes virus vaccine known as T-VEC in combination with ipilimumab, which targets CTLA4. These researchers found that T-VEC in combination with ipilimumab had a similar safety profile to ipilimumab alone and appeared to improve the response rates of patients with advanced melanoma compared to those given either treatment alone. "They are getting great results with the combination of ipilimumab and T-VEC," Dr. Wolchok stressed.

Tanja de Gruijl

"You need to **kick start** the local and systemic T cell response to prevent distant recurrence."

While interferon and ipilimumab are used for some, there is a need to develop additional treatments to improve survival of early-stage melanoma patients following excision of their localized tumors, given that many of these patients will later develop metastatic melanoma. This led **Dr. Tanja de Gruijl of VU University Medical Center** in Amsterdam to develop an approach that is showing promising results in preventing metastatic progression in early-stage melanoma patients.

In order for T cells to kill melanoma cells, they first need to be activated by a type of immune cell called a dendritic cell. This interaction often happens in the lymph node closest to the tumor, called the sentinel lymph node. In the lymph node, T cells interact with dendritic cells, which endow the T cells with tumor-fighting capabilities. In cancer patients, however, the sentinel lymph

node is often immune-suppressed and removed as part of the routine diagnostic workup in melanoma, according to Dr. de Gruijl, and this correlates with a reduced ability of dendritic cells to activate T cells.

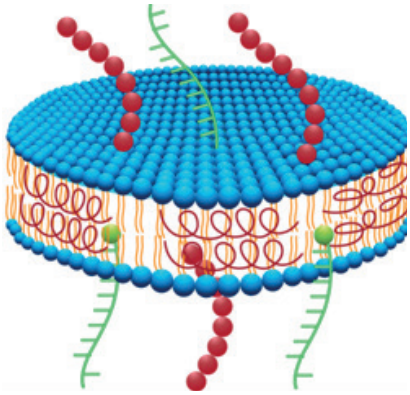
Building on those observations, Dr. de Gruijl sought to develop a way to boost the T cell-stimulating capabilities of dendritic cells in the sentinel lymph node. "You need to kick start the local and systemic T cell response to prevent distant recurrence," Dr. de Gruijl stressed. In three randomized and placebo-controlled phase two clinical trials, she tested the effects of the immune stimulators GM-CSF (granulocyte macrophage-colony stimulating factor), CpG-B (a dinucleotide), or CpG-B combined with GM-CSF in patients with early-stage melanoma. Following the initial surgery, physicians injected the immune stimulants at the tumor excision site seven days before removal of the sentinel lymph node, hypothesizing that this would activate dendritic cells at the tumor site, which would then prime an anti-tumor T cell response in the sentinel lymph node prior to its removal, preventing tumors from recurring. Dr. de Gruijl found that each of these treatments did indeed activate dendritic cells and tumor-targeting T cells in the sentinel lymph node. Intriguingly, the treatments doubled recurrence-free survival. The ten-year recurrence-free survival rate was 94 percent in the treated group compared to 48 percent in the control group of patients given saline injections.

Given these "stunning results" as one participant described them, Dr. de Gruijl plans to conduct a Phase three clinical study of the CpG-B treatment used as a single agent, and also plans to do a smaller trial with CpG-B combined with a checkpoint inhibitor. She emphasized several advantages of this treatment for patients with early-stage melanoma, including that it is more likely to be effective because of the lower tumor loads and heterogeneity, as well as the low levels of immune suppression seen in early-stage cancers. If the present findings are reproduced in future studies, the treatment would be relatively non-invasive, provide long-lasting protection with limited to no side effects and would preempt the need for expensive systemic therapies.

James Moon

"Our approach offers a powerful and **convenient** platform technology for **patient-tailored** cancer vaccines."

Dr. James Moon of the University of Michigan presented preclinical data demonstrating that nanodiscs, disc-shaped nanoparticles composed of lipids and peptides, are a promising platform for the design of personalized cancer vaccines. Dr. Moon envisions the vaccines could be combined with checkpoint inhibitors to boost their effectiveness. These would be personalized vaccines made from an individual patient's specific tumor antigens to elicit T cell responses specific to the tumor since the targeted antigens typically arise from tumor-specific mutations. It is hoped that such nano-



A cancer vaccine nanodisc. *Nature Materials*, 16, 489 (2017). Used with permission.

disc/checkpoint inhibitor combinations will "generate a larger repertoire of T cells and unleash the full toxic potential against cancer cells," said Dr. Moon.

Tumor antigen vaccines can be challenging to make effective, Dr. Moon noted, because after injection in the skin, many of the peptide antigens "get washed away by the circulation so you get a weak T cell response," he said. His strategy is to make nanoparticles that can avoid this washout and deliver the antigens to lymph nodes, where anti-tumor T cell responses arise. The nanoparticles are discs comprised of a smaller synthetic version of HDL, the "good" cholesterol. Tethered to this HDL are the tumor antigens and an immune stimulator. The benefit of using the HDL system ferry as a vaccine platform is that it has been already tested in clinical trials as a platform for a cardiovascular treatment.

Dr. Moon tested his nanodisc platform in a mouse model of melanoma and found that it greatly increased the delivery of antigens and immune stimulant to lymph nodes and led to a robust killer T cell response that was long lasting. The vaccine protected the mice against melanoma tumor engraftment and when combined with checkpoint inhibitors targeting CTLA4 and PD1, it completely eliminated melanoma tumors in a mouse model and provided long-term protection from recurrences. "Owing to the facile nanodisc production process, robust therapeutic efficacy, and good safety profiles, our approach offers a powerful and convenient platform technology for patient-tailored cancer vaccines," Dr. Moon said. Based on these results, Dr. Moon recently founded a start-up that will focus on manufacturing of nanodisc vaccines and clinical translation to improve the outcomes of cancer patients.

WHAT THIS MEANS FOR PATIENTS

Several tumor vaccines for melanoma show promise in preclinical and clinical studies. One strategy targets patients whose melanoma is not metastatic and is given by a physician who injects the vaccine into the site where the tumor was excised: treatment is administered one week prior to surgical removal of the nearest lymph node. Early phase clinical trial results presented at the MRA Scientific Retreat showed that this vaccine greatly reduced the likelihood that the melanoma would recur and spread. Other tumor vaccines are designed to be used with checkpoint inhibitor immunotherapies to direct an immune response to the tumor antigens patients' melanomas harbor. One such vaccine, called T-VEC, generated encouraging findings when it was used in combination with ipilimumab in melanoma patients. Researchers continue to assess the effectiveness of these vaccines in larger numbers of patients participating in clinical trials.

Overcoming Therapeutic Resistance

The goal of precision or personalized medicine is to identify the genetic defects causing a disease and use an inhibitor to block the activity of the protein encoded by the mutated gene—a so-called 'targeted therapy.' Indeed, in melanoma, precision medicine is a reality for patients whose melanoma harbors specific mutations in BRAF, either V600E or V600K. But there are more than 200 different BRAF mutations identified in human cancers. Despite the common use of BRAF inhibitors, researchers do not fully understand which BRAF mutations are significant to melanoma, whether the BRAF proteins encoded by these different gene mutants all behave in the same way or whether they respond similarly to the same drugs. In addition, researchers have not yet fully uncovered the effects of co-mutations (that is, multiple mutations in BRAF), how mutated proteins signal inside cells and whether the right drugs have been developed to most optimally target the proteins these mutated genes encode. While already available to some extent, "precision medicine is a goal, but not yet a reality," stressed **Dr. Neal Rosen of Memorial Sloan Kettering Cancer Center.**

Even for patients whose tumors harbor mutations that targeted therapies hit, resistance almost always develops either as tumors acquire mutations that overcome the drug's effects or by changes in the signals that cells receive. Resistance is also a problem for immunotherapies, including primary resistance seen in patients that never respond to them or secondary resistance that emerges after an initial treatment response, noted Dr. Roger Lo. But as Dr. Rosen pointed out, "embracing precision medicine means embracing complexity and figuring out how to deal with it." Several presentations at the scientific retreat revealed the complexity of the molecular signaling that fosters melanoma, and suggested tactics needed to overcome resistance to treatment.

Neal Rosen

"Embracing precision medicine means embracing **complexity**."

Dr. Rosen presented a series of studies aimed at identifying the underlying molecular basis for resistance to targeted therapies. Such a detailed understanding may aid in making sure the right patients get the right targeted treatments as well as in discovering new drug targets and combination treatment strategies to overcome resistance. The RAS growth pathway plays a prominent role in melanoma and in many cells, controls proliferation. Activation of the RAS protein causes two RAF proteins to bind to each other (form dimers). Dimerization of RAF causes its activation and it activates the MEK protein which, in turn, activates the ERK proteins, which have many functions that result in cell proliferation. Mutations that activate this pathway are very common in many cancers, especially melanoma, where more than 70% of tumors have mutations of the genes encoding BRAF or NRAS.

The ERK proteins also function to inhibit RAS (feedback) and turn off the pathway. Dr. Rosen discovered that BRAF mutants powerfully activate the pathway because they are unresponsive to this feedback—they do not require RAS activation. He divided RAF mutants into two major classes, those that can signal as single proteins (monomers) and those that function as dimers despite the feedback inhibition of RAS. The clinical relevance of this classification is that current RAF inhibitors potently inhibit RAF monomers only. Thus far, only BRAF V600 mutants function as monomers and the only cells that are sensitive to these inhibitors are those with this mutation. Activated RAF mutants that signal as dimers are not as sensitive and tumors driven by such mutations are insensitive to these drugs. Moreover, clinical resistance to these drugs is usually due to other molecular events that cause BRAF V600 to dimerize. Thus, current drugs are not BRAF selective inhibitors, they are BRAF monomer inhibitors.

These drugs are safe and effective, but are not useful for treating tumors driven by the many other BRAF mutants, all of which function as dimers. This suggests the utility of developing an inhibitor of RAF mutant dimers that does not inhibit non-mutant (wild type) forms of BRAF, which also form pairs. Dr. Rosen has identified such inhibitors and determined their mechanism of action and why they are relatively mutant selective. One such inhibitor has shown promising results in the laboratory and is currently in clinical development.

Dr. Piyush Gupta of the Whitehead Institute for Biomedical Research also presented data that shed light on mechanisms used by BRAF-mutant tumors to escape targeted therapy. He began his talk by discussing the three types of responses tumors have to genetic mutations: addiction, resistance and tolerance. Targeted therapies kill addicted tumor cells whereas they have no effect on the growth of resistant tumor cells. Tolerant tumor cells, however, slow or may even completely arrest their growth in response to targeted therapy but they do not die.

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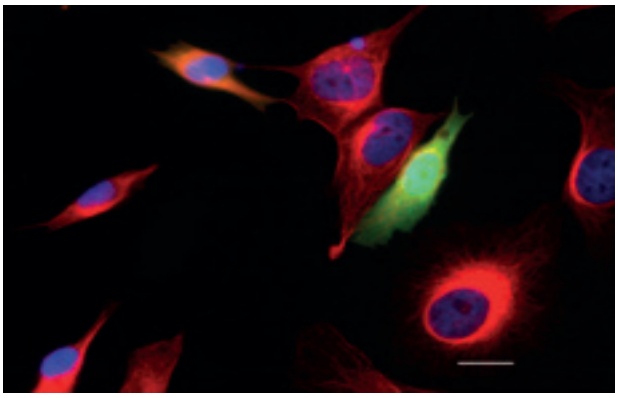
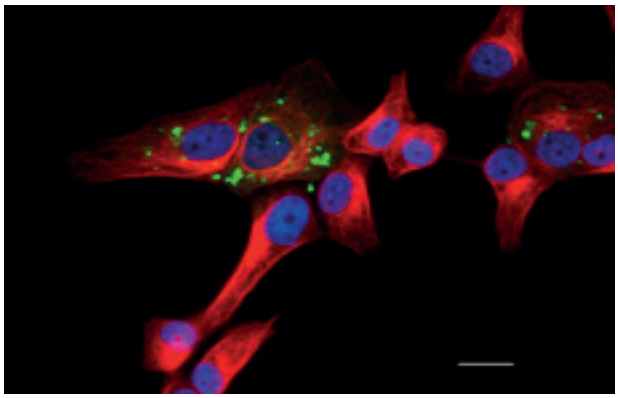


Vemurafenib



Vermurafenib treatment of melanoma cells induces autophagy (as depicted by punctate LC3B staining, shown in green). *Oncogene* 35, 5295 (2016). Used with permission.

Dr. Gupta focused his studies on cultured BRAF-mutant melanoma cells that exhibit characteristics of tolerance rather than addiction in response to BRAF inhibition. One of the major advantages that BRAF mutation confers on tumor cells is that it allows them to increase their energy intake despite being in a low nutrient environment. BRAF inhibitors reduce energy uptake by tumor cells; however, Dr. Gupta discovered that tolerant cells activate an internal energy-scavenging program called

autophagy in response to BRAF or MEK inhibition, allowing them to survive. In contrast, cultured tumor cells expressing the normal, unmutated version of BRAF did not induce autophagy in response to pathway inhibition. Dr. Gupta also found that artificially activating autophagy in BRAF-addicted tumor cells (i.e. those that normally die in response to targeted therapies), rendered them tolerant to BRAF inhibition and able to survive.

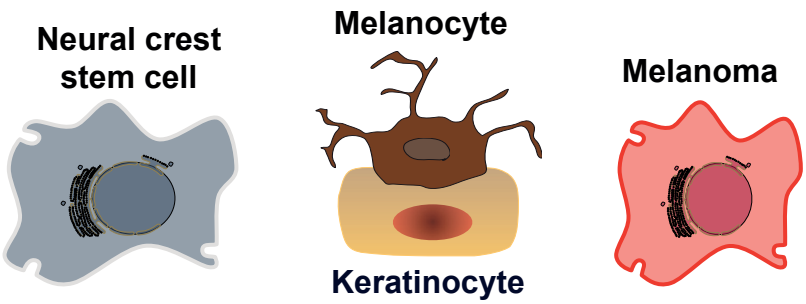
In an effort to translate these findings, Dr. Gupta implanted tolerant BRAF-mutant melanoma cell lines into mice and treated them with a BRAF inhibitor, an autophagy inhibitor or both. He found that although neither inhibitor alone could slow tumor cell growth, when the two were used in combination the mice experienced tumor regressions. A clinical study to test this strategy in patients is currently underway.

Current clinical strategies that target BRAF-mutant melanoma, typically employ a combination of BRAF and MEK inhibitor drugs. **Dr. Roger Lo of the University of California**, **Los Angeles**, began his presentation by noting that "the combination of BRAF and MEK inhibitors addresses only the tip of the iceberg of knowledge about resistance mechanisms." His research reveals that melanoma cells can adapt to BRAF/MEK inhibitors through epigenetic reprogramming, that is by modifying how the genes are expressed rather than altering the sequence of the genes themselves. These epigenetic changes could affect the features of a cell that are recognized by the immune system, and which could have a negative impact on anti-tumor immunity.

"Understanding how melanoma hides from and evades BRAF/MEK inhibitors may provide insights into the efficacy of anti-PD1 therapies and new combinations of BRAF/MEK inhibitors plus immunotherapies," Dr. Lo stressed. While studies have revealed a multitude of mechanisms for tumors to genetically evade targeted therapies, researchers are just starting to explore epigenetic changes that accompany drug resistance. Dr. Lo analyzed tumor samples from melanoma patients whose tumors were regressing or progressing while receiving targeted therapies. Although common mutations affected a few genes in melanoma tumors that had acquired resistance to targeted therapies, he discovered recurrent epigenetic dysregulations of many genes. He also found that resistance to targeted therapies was often accompanied by changes in the immune cell composition of tumors, including a loss of T cell numbers and function. Encouragingly, combination therapies that suppressed resistance to targeted treatments in preclinical models also blunted the loss of T-cell inflammation inside the tumors. These findings suggest that patients whose melanoma tumors develop resistance to targeted therapies may also be unlikely to respond to anti-PD1/L1 treatments, Dr. Lo stressed, underscoring how important understanding mechanisms of resistance is to curing melanoma.

"Understanding non-genetic and immune microenvironmental adaptations early during BRAF/MEK inhibitor therapy may provide insights into the origins of functional adaptations that eventually permit disease progression," he said. In tumors, resistance-inducing adaptions following targeted therapy can be discerned as specific patterns of gene expression. Dr. Lo's analyses of tumor biopsies from melanoma patients given anti-PD1/L1 therapies indicate patterns of gene expression that are similar to BRAF/MEK non-responders. This finding suggests that while anti-PD1/L1 antibodies in combination with BRAF and MEK inhibitors are being tested in melanoma patients, strategies should be incorporated to ameliorate an immune-suppressive tumor microenvironment in order to maximize the clinical benefits of such combinations.

The presentation by **Dr. Meenhard Herlyn of the Wistar Institute** revealed specific ways in which melanoma cells hijack embryonic developmental pathways for uncontrolled growth and suggested how targeting these pathways may help to overcome therapeutic resistance. Although normally turned off in melanocytes, these developmental pathway genes are expressed by neural crest stem cells, the progenitors of melanocytes, and are turned back on in melanoma cells. Using gene silencing techniques, Dr. Herlyn and his colleagues screened 220 genes involved in development to determine the genes expressed in melanomas that overlap with those expressed in neural crest stem cells, but not with those of normal melanocytes. This led him to discover that a signaling network initiated by the cell membrane protein LPAR1 is essential for neural crest stem cell survival as well as for melanoma cell growth and invasion, but whose signaling is turned off in normal melanocytes.



Neural crest cells and melanoma cells, but not melanocytes, share similar patterns of expression of developmental pathway genes. Courtesy of Meenhard Herlyn.

Dr. Herlyn also found heightened expression of LPAR1 in melanoma cell lines resistant to BRAF or MEK inhibitors, both in cells that were intrinsically resistant as well as in cells that developed resistance in response to therapy. When he added an LPAR1 inhibitor and a BRAF inhibitor to resistant melanoma cells, the combination synergistically reduced growth of cell lines, both in culture and when implanted into mice. "Both treatment-naïve and treatment-resistant melanoma cells appear addicted to the LPAR1 network and the few compounds currently available that target it show significant inhibitory activities," Dr. Herlyn said.

He also discovered low expression of LPAR1 in moles and in melanomas that have responded to targeted therapies, but high expression of LPAR1 in the tumors of seven out of 13 patients that had acquired resistance to BRAF and/or MEK-targeting treatments. "It was a differentiating marker of resistance before there were any clinical signs of it," Dr. Herlyn said. These findings suggest that an LPAR1 inhibitor might overcome that resistance in some patients.

"Both treatment-naïve and treatment-resistant melanoma cells **appear addicted** to the LPAR1 network"

A major strategy researchers are pursuing to overcome resistance to individual targeted therapies is to combine them with inhibitors that hit other important targets. The research of **Dr. Andrew Aplin of Thomas Jefferson University** focuses on enzymes called cyclin dependent kinases (CDKs), which cells need in order to divide. The activity of specific members of the CDK family, like CDK4 and CDK6, is elevated in melanomas and inhibitors that block both of these proteins are approved to treat breast cancer. Dr. Aplin demonstrated that CDK4/6 inhibitors also show promise in treating melanoma.

When Dr. Aplin treated mice bearing melanoma tumors with a CDK4/6 inhibitor, their tumors showed, as expected, reduced CDK4/6 activity; however, he only observed decreased tumor growth when the CDK4/6 inhibitor was combined with a MEK inhibitor. Once the treatment ended, the tumors grew back but surprisingly, the new tumors were responsive to retreatment with the combination. Dr. Aplin then experimented with the scheduling of the combination and found that continuous MEK inhibition combined with intermittent CDK4/6 inhibition was the most effective schedule for inhibiting resistance. Additional studies revealed that resistance to both inhibitors was due to activation of the AKT pathway, a signaling pathway known to promote tumor cell survival, proliferation and invasiveness.

As described by Dr. Aplin and discussed by Dr. Holmen, the AKT pathway also appears to play a role in enabling the resistance of uveal melanomas (UM) to targeted therapies. UM, also known as ocular melanoma, is a rare type of melanoma that arises from melanocytes in the eye. Half of all patients with UM will develop metastases, mostly in the liver. Although MEK inhibitors greatly hinder the growth of cell lines made from the metastases of UM patients, clinical studies find that most patients with late-stage UM melanoma do not respond to such drugs. This led Dr. Aplin to wonder what is in the liver microenvironment of the tumor that enables resistance to MEK inhibitors. He found that hepatocyte growth factor (HGF), a protein secreted by cells in the liver, made UM cells resistant to the effects of a MEK inhibitor. Adding an inhibitor of cMET, which is the receptor for HGF, countered these effects. Moreover, when he combined a cMET inhibitor with a MEK inhibitor, he found it enhanced the responsiveness of both tumor cell lines and tumor samples from patients to MEK inhibition. “Selectively blocking cMET signaling in metastatic UM may break its intrinsic resistance to MEK inhibitors provided by factors from cells in the liver,” Dr. Aplin said.

WHAT THIS MEANS FOR PATIENTS

Because the signaling pathways hit by targeted therapies regulate such critical processes like cell survival and cell division, it is not surprising that back-up pathways exist in case of a signaling interruption. Tumor cells appear to be able to usurp these backup pathways to overcome targeted therapy effects. This means that not all patients respond to targeted therapy, and nearly all who do become resistant to them over time. Resistance is also a problem for immunotherapies: not all patients respond initially to immunotherapy and some patients may still have disease come back even if they do respond at first. Consequently, a large part of melanoma research is devoted to assessing in finer detail the genetic and microenvironmental factors that drive melanoma, and which combinations of treatments are more likely to induce greater and more durable responses in patients because they target complementary pathways or block the backup pathways that enable a tumor to resist treatment. Laboratory research is revealing which of many possible combinations of anti-tumor agents are likely to be most effective and should be tested in the clinic. The findings also help explain why some subtypes of melanomas, as well as brain and liver metastases, may resist treatment with current drugs, and illuminate ways to make them more susceptible.

Shedding Light on Melanoma Prevention

Although UV exposure increases the risk of developing melanoma, and it is clear that sunscreen prevents the development of other skin cancers, obtaining evidence that sunscreen use can reduce melanoma risk is controversial. Conducting a controlled study of individuals either using or not using sunscreen to more definitively assess the effects of sunscreen on melanoma risk would be quite difficult, requiring large numbers of subjects, long-term follow up and subjects would be unlikely to fully comply with the study guidelines. "You would have to have a giant pot of money to do such a study, yet in the meantime we're making recommendations to the public that they use sunscreens to prevent melanoma," **Dr. Christin Burd of Ohio State University** noted. "We need to have data to back up that claim," she said. Dr. Burd set out to obtain such data, and presented results suggesting that at least in mice, sunscreen, if applied in sufficient amounts, provides substantial protection against UV-accelerated melanoma.

Dr. Burd pointed out that the driver mutations of melanoma, such as those in BRAF and NRAS, are not directly attributable to UV and are also unable to trigger melanoma on their own. For instance, almost all benign moles have BRAF mutations, but most moles do not progress to melanoma. Exposure to UV is likely what drives melanocytes with altered BRAF or NRAS to become melanoma, Dr. Burd hypothesized, as epidemiology studies link intermittent sun exposures and childhood sunburns to heightened melanoma risk.

To test this, she mimicked intermittent UV exposure in melanoma-susceptible mice, giving them the equivalent of 40 minutes of exposure to intense summer sun. Such exposures increased melanoma tumor burden and incidence in the mice and the mice died of their melanoma much sooner. Reducing the dose of UV radiation so it was equivalent to a single dose of five minutes of sun

"Your sunscreen is **only as good** as its application."

exposure that did not cause a sunburn, also significantly improved melanoma-free survival in the mice. The observed increase in susceptibility only occurred in mice that had the NRAS Q61R mutation that is common in human melanomas. Mice with either a different NRAS mutation or those only defective in the p16INK4a tumor suppressor gene were not affected by the UV exposure. "Clearly not just having any activating NRAS mutation, but having the right NRAS mutation is what can cause melanoma," Dr. Burd said.

Dr. Burd then tested various commercial aerosol sunscreens to see which were most effective at preventing melanoma in the mice exposed to UV radiation. All sunscreens with SPF 30 or higher improved melanoma-free survival and decreased tumor incidence in the mice. The researchers found that the degree of melanoma protection afforded by the sunscreens did not depend on their SPF ratings (if 30 or above) or specific active ingredients, but instead directly correlated with how much was applied, i.e. the degree of coverage. This is an important finding, she said, as "It's well known that consumers apply less than the recommended amount of sunscreen. Your sunscreen is only good as good as its application."

A Fireside Chat on Cancer Causation and Cures

Over the past several decades, scientists have uncovered in ever finer detail the myriad of genetic changes that lead to cancer. Yet researchers still do not understand how to fully take advantage of this information to prevent or cure cancer. **Mr. Michael Milken, Chair of the Milken Institute and MRA Board Member** moderated a conversation on the role of genes in causing cancer and the search for cures with noted author and physician **Dr. Siddhartha Mukherjee of Columbia University** and experienced clinician-scientists **Dr. Antoni Ribas of the University of California, Los Angeles**, and **Dr. Steven Rosenberg of the National Cancer Institute**.

(Left to right) Michael Milken, Siddhartha Mukherjee, Steven Rosenberg, Antoni Ribas

"Cancer is a genetic disease and the understanding of that is crucial to the development of cures," Dr. Mukherjee stressed. But he pointed out the challenges involved in moving from genetic discovery to medical therapies. For example, researchers have churned out tremendous amounts of genetic sequencing information on leukemias, but they still do not understand why specific genetic changes lead to leukemia. Dr. Mukherjee added, "Big Data is only useful when you have sophisticated probes for it."

New drugs and clinical trials act like probes for the genetic information gathered. "We are working in the dark but a single targeted inhibitor is like a beam of light," Dr. Mukherjee said, because by exploring who responds to a targeted treatment and who does not and why, it illuminates the mechanisms underlying cancers. Dr. Ribas agreed, adding "Whether a patient responds to a particular therapy is not random or magical, but based on a series of biological processes."

While genomic advances have led to the approvals of several targeted therapies for melanoma and other cancers, and immunological insights provided the impetus for the development of checkpoint inhibitors, the genetics and immunology of individual tumors are highly specific to each person. Therefore, despite the improvements in outcomes seen with these therapies, Dr. Rosenberg stressed the importance of personalized treatments, arguing that, "we can't be afraid of highly personalized approaches because what cures one patient won't be the cure for other patients."

Although the relative importance of currently available therapies to the future of curing melanoma remains to be seen, Mr. Milken highlighted the recent dramatic improvements in outcomes for metastatic melanoma patients, asking, "What have we learned from melanoma that we can apply to other diseases?" Dr. Mukherjee provided his insight by stating that, "melanoma has become the front runner in a new way of thinking about therapy. For the longest time, because of the tools available, cancer researchers focused on the tumors, which led to understanding the genetics of tumors and growth pathways. But cancer lives in a microenvironment that contains other cells, including T cells and natural killer cells, which also affect liquid tumors such as leukemia. The shift in focus from the cancer cell to the milieu of cancer cells has opened up new universes that are targets for drugs."

New Clinical Directions

To help foster a conversation around the central scientific and clinical themes of the retreat, **Dr. Suzanne Topalian of Johns Hopkins University** led a panel discussion on what is going well for melanoma treatment, diagnosis and prevention and what remains to be done. Panelists included **Drs. Reinhard Dummer of the University Hospital in Zurich**, **Keith Flaherty of Massachusetts General Hospital**, **Howard Kaufman of Rutgers University**, **Grant McArthur of Peter MacCallum Cancer Center in Melbourne**, **Susan Swetter of Stanford University**, and **Jennifer Wargo of MD Anderson Cancer Center**. This discussion covered a range of topics, including melanoma prevention and early detection, treatment strategies for earlier stage patients, biomarkers, optimal first-line treatments for later stage patients and what avenues of research will help clinicians in the future.

Most panelists felt it might be beneficial to treat patients with bulky Stage 3 melanomas with checkpoint inhibitors or targeted therapies that are currently only approved to treat more advanced, Stage 4 patients. But use of these treatments for earlier stage patients is experimental and should be done within a clinical study, they said. Physicians must also ensure that their patients are aware of the serious side effects these treatments can cause.

The panelists did not unanimously agree as to which treatments should be given first to patients with metastatic melanoma. Most panelists said they preferred immunotherapies targeting PD1/L1 as first-line treatment, but not all insurers will reimburse such treatment, especially outside of the United States. For those with BRAF-mutant melanoma, targeted therapies might be a better first-line treatment if tumors are causing patients a lot of pain and suffering because when they work, they tend to cause tumors to shrink more quickly than immunotherapies. While still experimental, a combination of an immunotherapy and a targeted therapy is another option

Keith Flaherty and Susan Swetter

for metastatic melanoma patients, although physicians have not yet determined how to best combine these treatments. Finally, first-line treatment strategies may change as new drugs gain approval. “Year by year this is a shifting issue,” Dr. Flaherty said.

A lack of insurance reimbursement for biopsies has hampered the search for indicators (biomarkers) that reveal which therapies are likely to work for which patients and whether tumors are responding to treatment. A lack of easily accessible tumor tissue to biopsy, particularly in earlier stage patients, can also impede these efforts.

Compared to melanoma treatment, melanoma prevention efforts have not experienced as much progress, although there are new digital apps that may help patients to monitor their moles for signs of malignancy, as well as artificial intelligence-based computer programs that may help doctors better identify malignant moles. Whether these advancements will show positive impacts in preventing melanoma remains to be seen. Finally, there is a need to develop better sun protection methods and policies, and to identify and screen high-risk patients for melanoma, “so we don’t see the disease at all, which will put us all out of a job, but that would be welcome,” concluded Dr. Swetter.

Accelerating Correlative Science

A critically important and long-standing area that deserves greater attention in melanoma research is correlative science, which relies on researchers gaining access to tissue samples from patients participating in clinical trials, often before and after therapy. Correlative science can be used to both predict whether a particular treatment will be beneficial to an individual patient and to determine surrogate endpoints, that is, specific measurements that can be used as an indicator of whether a drug is having a therapeutic effect. Correlative science can also provide insights into why many patients either fail to respond to therapy or relapse, and potential strategies for overcoming such resistance. This topic is at the nexus of many limitations to progress in the area of melanoma biomarker and drug development.

Leaders from industry, academia, and government participated in a roundtable discussion to address the challenges in implementing such correlative science and offer potential solutions. **Drs. Patrick Hwu of MD Anderson Cancer Center, Marcus Bosenberg of Yale University, and Louise Perkins of MRA** co-chaired the session.

Louise Perkins

IMPLEMENTATION CHALLENGES

Although participants largely agreed that most patients are willing to provide their biopsied tissues for research, obtaining appropriate patient consent remains a challenge. In many cases, patients are unaware that their biospecimens belong to them and can be shared with researchers. Because it is often difficult to predict the specific studies biospecimens may be useful for, researchers prefer that patients consent to a range of future research with only minimal restrictions. Such broad informed consent can be difficult to obtain, however, and without it, the investigation of biospecimens already acquired, is limited.

Industry representatives noted the importance of obtaining tissue samples in clinical trials but acknowledged the real-world difficulties related to obtaining such samples. As an example, some Institutional Review Boards at academic centers think it is unethical to not collect biopsy material for study; whereas others may determine that it is unethical to require patients to participate. In addition, participating institutions and physicians may find the collection of biospecimens during clinical studies as too burdensome to the patient, resulting in trial designs that allow biopsies to be optional. Even if required, patient participants have the right to opt out of providing biospecimens, which is worrisome to researchers, because it could potentially bias the results of the trial. Another challenge is that not all patients have easily accessible tumors from which to biopsy, especially those responding to treatment. Finally, it can be difficult to predict when in the course of treatment to take the biopsies so that they will be maximally informative for the researchers.

Beyond these practical challenges, another major barrier to conducting and studying biopsies is cost. On this basis, only large pharmaceutical companies may be

able to afford such work, and even they may be reluctant to pay for it unless the extra cost is justified, participants noted. Dr. Christina Coughlin of Immunocore, referencing her experience with both large pharma and small biotech, noted that collecting biospecimens can add as much as 20 percent to the cost of a trial. For smaller pharmaceutical companies in particular, these costs can be quite prohibitive, even if they could assure a more successful project. What might justify the cost and risk of incorporating biopsy collection in a trial design? One suggestion was to prioritize obtaining biospecimens that would help to determine whether to continue testing a therapeutic agent.

Participants largely agreed that biospecimen and data sharing is expensive and difficult, therefore it remains a major challenge confronting correlative science. Using collected samples poses its own problems. Ideally, researchers would have access to tumor samples across the continuum of care; however, this does not often occur. The substantial logistical hurdles, often related to working out the specific agreements between institutions for the sharing such reagents and determining who will own any intellectual property resulting from use of the biospecimens or the data, can be a major sticking point.

Even when data are shared, challenges remain. Sifting out what is relevant and replicable can be difficult, because there are many different ways of analyzing biomarkers and experiments are often challenging to perform and standardize. Furthermore, although surrogate endpoints are important in immunotherapy clinical research, the RECIST criteria (standards used by clinicians to determine when patients respond, stabilize or progress) are not appropriate for these treatments. The patterns of tumor response to immunotherapy differ from chemotherapy, for which the RECIST criteria were originally developed.

Christina Coughlin and Paul Chapman

POSSIBLE SOLUTIONS

Participants at the Industry Roundtable Breakfast offered several ideas for overcoming the hurdles involved in research on biospecimens, including broader patient consent forms, using social media and patient-driven websites, such as Count Me In, to foster collection and sharing of patient samples and data with investigators, and developing and deploying new ways to analyze blood specimens that can free researchers from needing tumor specimens. Having patients and their families consent to rapid autopsies would also make tumor tissue more readily available for analysis, as would creating a central repository for biospecimens that could enable sharing.

There were several suggestions for how MRA could help. One example was that MRA could devise a consensus statement on the critical need for treatment biopsies and partner with patient advocacy groups to ensure biopsies are done in clinical trials. It was further suggested that MRA could contribute to the development of a Master Material Transfer Agreement that would enable tissue and data sharing. Finally, MRA could encourage patients to participate in clinical trials and advocate for rapid autopsy studies.

Getting the Word Out

Young investigators are at the heart of MRA's strategy not only for their inventive scientific research, but also as part of MRA's commitment to build human capital capable of defeating melanoma. To help these researchers advance their careers and disseminate their findings in the most impactful way possible, MRA organized a panel discussion by the editors of several prestigious scientific journals, including *Cell, Clinical Cancer Research, Nature and Science*. Editors provided practical suggestions for how to get published, including how to:

- Engage editors at meetings or by email and provide them with a pre-submission summary of their research
- Have a sense of the readership of the journal and whether the research paper is appropriate
- Tell a story of the research in a way that people not in the specific area of research will understand it, including relating how it fits into the bigger context
- Request feedback on the research and the research paper from colleagues and mentors prior to submission
- Seek training on how to write a good paper because the way results are communicated makes a difference

Beyond taking into consideration the core advance and its relevance, editors and reviewers will also consider what the investigator is trying to show and the best way to show it given the current tools available. Some of the editors admitted that having a senior mentor on a paper carries some weight and can improve the chances of a paper being sent for in-depth review. However, a well-written paper can overcome the need to have well-known names in the field on the paper if the science is stellar, Dr. Victoria Aranda, a Senior Editor at *Nature* stressed. "A beautiful paper is a beautiful paper and the names come later," she said.

(Left to right) Kristen Mueller, João Monteiro, Priscilla Kelly, Keith Flaherty, Victoria Aranda

Conclusion

MRA Board Member Dr. Elliott Sigal gave the concluding remarks to the retreat. He highlighted the tremendous progress made in the past decade towards treating melanoma and the cutting-edge research being done, which has led to melanoma serving as a beachhead in the war on cancer. "A lot more has to be done, but the outline of the new frontier has never been clearer," he said. That research frontier involves achieving functional if not actual cures, increasing the reach of targeted therapies, identifying biomarkers that would predict which patients will respond to immunotherapies and targeted therapies and learning how to change resistant tumors into responsive ones.

Dr. Sigal highlighted that innovation often arises at the intersection of different fields and stakeholders. After an early career in engineering and then moving into medicine, he "appreciated how people with different backgrounds and training could view the same problem differently with different insights." Dr. Sigal praised Debra and Leon Black's vision to have MRA bring in new investigators to think about issues differently, and to have immunologists speak to oncologists. "It happens routinely now, but it rarely happened eight years ago," he said.

Dr. Sigal noted that drug development involves an ecosystem of multiple organizations and a myriad of ideas from government, academia, industry and patient advocacy groups and that MRA has an important role to play in this labyrinthine environment. "MRA can catalyze across the ecosystem and make it more efficient," he said, stressing that, "new treatments resulting from team science and collaboration are key to progress in this arena. But silos are natural and need to be broken down to accelerate progress. Patient-focused groups can catalyze collaborations and walk through doors others can't walk through and create interactions."

Elliott Sigal

"A lot more has to be done, but the outline of the new frontier has never been clearer... Progress is slow and often painful. So get back to work—because there are **patients waiting**."

He finished with important advice to young investigators: always keep in mind the patients who will be helped by their work. "Let your North Star always be the patient's best interest and affect how you design experiments. You need to remember those patients because progress is slow and often painful. So get back to work—because there are patients waiting."

Acknowledgements

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

Agenda

MONDAY, FEBRUARY 13TH

7:30 am-5:00 pm	Grant Review Committee Meeting (by invitation)……Plaza Ballroom
10:30 am-12:30 pm	MAC internal meeting (by invitation)……Roosevelt
12:00 pm-6:00 pm	Registration open……Salon Ballroom Foyer
1:00 pm-5:30 pm	Melanoma Advocates & Foundations Forum (by invitation)……Salon I
6:00 pm-7:30 pm	**Opening Reception**……**Salon I & II Foyer**

TUESDAY, FEBRUARY 14TH

6:30 am-6:00 pm	Registration open……Outside Salon Ballrooms
7:00 am-8:15 am	General Breakfast……Salon III
7:00 am-8:15 am	Young Investigators Breakfast (by invitation only)……Plaza Ballroom
8:30 am-8:45 am	**Opening Remaks**……**Salon I & II** Michael Kaplan, MRA President and CEO Louise Perkins, MRA Chief Science Officer Introduction by Ross King & President Carter welcome video
8:45 am-9:15 am	**Lecture:** Jedd Wolchok, Memorial Sloan Kettering Cancer Center: Immunotherapy for melanoma – where do we go from here?
9:15 am-11:25 am	**Session 1: Biological Basis of Therapeutic Resistance** Chair: Roger Lo
9:15 am-9:40 am	Neal Rosen, Memorial Sloan Kettering Cancer Center: Development of an equipotent inhibitor of mutant RAF monomers and dimers
9:40 am-10:00 am	Piyush Gupta, Whitehead Institute: Mechanisms of tolerance to Ras pathway inhibition in BRAF-mutant melanomas
10:00 am-10:20 am	Brent Hanks, Duke University: Inhibiting the TGF-ß signaling axis in the melanoma microenvironment
10:20 AM-10:40 AM	**BREAK**
10:40 am-11:00 am	Bin Zhang, Northwestern University: Overcoming resistance to agonist immunotherapeutics
11:00 am-11:25 am	Roger Lo, UCLA: Resistance to MAPK and PD-1 targeted therapies
11:25 am-11:55 am	**Lecture:** Richard Scolyer, University of Sydney: Using whole genome sequencing to reveal differences between acral, mucosal and cutaneous melanomas: Data from the Australian melanoma genome project

12:00 pm-1:15 pm	**Lunch and Fireside Chat** ..... **Salon III** **Genes: A Conversation on Cancer Causation and Cures** Moderator: Michael Milken, Chairman, Milken Institute and MRA Board Member Siddhartha Mukherjee, Columbia University Antoni Ribas, UCLA Steven Rosenberg, U.S. National Cancer Institute
1:30 pm-2:20 pm	**Session 2: Germline Influences on Melanoma**..... **Salon I & II**
1:30 pm-1:55 pm	Hensin Tsao, Massachusetts General Hospital Mutational landscape of hereditary melanoma
1:55 pm-2:20 pm	Alan Spatz, Lady Davis Institute: The protein phosphatase 2A regulatory subunit PR70 is a gonosomal melanoma tumor suppressor gene
2:20 pm-4:45 pm	**Session 3: Models, Markers and New Targets**..... **Salon I & II** Chair: Meenhard Herlyn
2:20 pm-2:40 pm	Scott Woodman, MD Anderson Cancer Center: Unraveling the functional effects of hallmark genetic aberrations in uveal melanoma
2:40 pm-3:00 pm	Yuhang Zhang, University of Cincinnati: A tale of two stories: Targeting cancer-associated fibroblasts in the melanoma microenvironment
3:00 PM-3:20 PM	**BREAK**
3:20 pm-3:40 pm	Alexander Boiko, University of California, Irvine: Activation of innate immunity and targeting of tumor initiating cells effectively suppresses melanoma metastasis
3:40 pm-4:00 pm	Christin Burd, Ohio State University: Ultraviolet radiation accelerates NRAS mutant melanoma genesis: A cooperative effect blocked by sunscreen
4:00 pm-4:20 pm	Tal Burstyn-Cohen, Hebrew University of Jerusalem: TAM receptors in melanoma: Mechanisms and therapeutic efficacy of novel inhibitors
4:20 pm-4:45 pm	Meenhard Herlyn, Wistar Institute: Targeting developmental pathways in melanoma
4:45 pm	**Closing Remarks Day 1** Louise Perkins, MRA Chief Science Officer
5:30-6:30 pm	MRA Board Meeting (invitation only)
6:30-9:00 pm	**Reception and Dinner**..... **Teddy & The Bully Bar** Dress: Casual 1200 19th Street, NW, (202) 872-8700 Reception 6:30-7 pm; Dinner 7:15 pm

WEDNESDAY, FEBRUARY 15TH

6:30 am-10:00 am	**Registration open**..... Salon Ballroom Foyer
6:30 am-10:00 am	General breakfast..... Salon III
7:30 am-8:30 am	Industry Roundtable Breakfast (by invitation only).....Plaza Ballroom
8:40 am-8:45 am	**Opening Remarks Day 2** .....**Salon I & II** Kristen Mueller, MRA Scientific Program Director
8:45 am-11:40 am	**Session 4: Overcoming Difficult to Treat Disease** Chair: Sheri Holmen
8:45 am-9:10 am	Tanja de Gruijl, VUMC: Harnessing the sentinel lymph node to limit metastatic melanoma
9:10 am-9:30 am	James Moon, University of Michigan: Vaccine nanodiscs for personalized cancer immunotherapy
9:30 am-9:50 am	Xu Chen, UCSF: RasGRP3 mediates MAPK pathway activation in GNAQ mutant uveal melanoma
9:50 am-10:15 am	Andrew Aplin, Thomas Jefferson University: Targeted inhibitors in cutaneous and uveal melanoma: Combinations, reporters and schedules
10:15 AM-10:35 AM	**BREAK**
10:35 am-10:55 am	Jessie Villanueva, Wistar Institute: A promising BETi/MEKi combination strategy for NRAS mutant melanomas
10:55 am-11:15 am	Ana Anderson, Brigham and Women's Hospital: Harnessing Tim-3 pathway blockade for melanoma immunotherapy
11:15 am-11:40 am	Sheri Holmen, University of Utah: Identification and characterization of drivers of melanoma brain metastasis
11:40 am-12:20 pm	**Panel Discussion: News from the Field: What's going well and what remains to be done?** Reinhard Dummer, University Hospital Zurich Keith Flaherty, Massachusetts General Hospital Howard Kaufman, Rutgers University Grant McArthur, Peter MacCallum Cancer Centre Susan Swetter, Stanford University Jennifer Wargo, MD Anderson Cancer Center Suzanne Topalian, Johns Hopkins University (Chair)
12:20 pm-12:30 pm	**Closing Remarks** Elliott Sigal, MRA Board Member
12:30 pm-1:30 pm	**Lunch available and departures**.....**Salon II**

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