Raising the Bar

Accelerating New Paradigms in Melanoma Research

Highlights of the Melanoma Research Alliance Seventh Annual Scientific Retreat

FEBRUARY 25-27, 2015 WASHINGTON, DC

Melanoma Research Alliance

Contents

Introduction

MELANOMA, a cancer of pigment-producing cells, accounts for nearly 200,000 new cases of cancer reported each year worldwide. It is the deadliest form of skin cancer. Alarmingly, in the U.S., the incidence has tripled over the last three decades, and the death rate has increased at a time when mortality for other common cancers has declined. If caught early, melanoma can be successfully treated by surgery, while those diagnosed with widespread metastatic disease (Stage IV) have a median survival of less than one year.

Fortunately, innovative new drugs that have come onto the market in the last four years have revolutionized the field, provided new hope for patients, and showcased melanoma as a case study for all of oncology. These therapies fall into two classes: 1) drugs that block growth-promoting pathways in melanomas that have activating mutations in BRAF (vemurafenib, dabrafenib, and trametinib); and 2) immune checkpoint inhibitors (ipilimumab, pembrolizumab, and nivolumab) that target the "brakes" on the immune system.

The Melanoma Research Alliance (MRA), a unique foundation launched in 2007 by Debra and Leon Black under the auspices of the Milken Institute, aims to end suffering and death due to melanoma by collaborating with all stakeholders to accelerate powerful research, advance cures for all patients, and prevent more melanomas. To date, MRA has awarded more than $67 million in funding in 14 different countries. MRA supports a number of different types of research programs: Team Science Awards conducted by multi-disciplinary teams; and a number of awards to individual investigators, including Established Investigator Awards, Young Investigator Awards, Pilot and Development Awards; and Academic-Industry Partnership Awards that are awards matched by an industrial partner. As a result of the data that has been generated with this investment, an additional $73 million in research funding has been secured by investigators as a result of their MRA award, including grants from the U.S. National Institute of Health or other foundations.

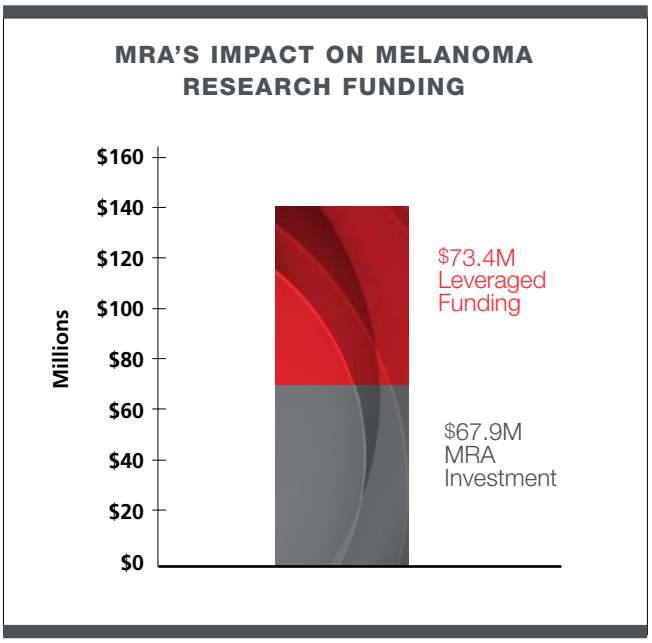
MRA accelerates collaboration within and across sectors, and the annual Scientific Retreat is one important forum for this engagement, providing an invitation-only, think-tank setting to share the latest findings and forge new partnerships in pursuit of better outcomes for patients. This year's Seventh Annual Scientific Retreat held in Washington, DC on February 25-27, 2015 included almost 300 thought leaders in attendance. Participants included academic scientists from 10 countries and 68 institutions, representatives from 37

OVERALL MORTALITY FOR MELANOMA HAS INCREASED IN THE U.S. AT A TIME WHEN MORTALITY FOR OTHER COMMON CANCERS HAS DECLINED (1975-2003)

US SEER CANCER REGISTRY, 2003
COURTESY OF ALLAN HALPERN

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

Throughout the meeting, speakers and participants highlighted the remarkable progress that has led to new therapeutic options for patients. But, because many people are still suffering from this disease, many speakers stated that "it's not good enough," and more must be done to improve these therapies and develop additional options for patients as Lynn Schuchter stressed in her opening lecture. "We need all hands on deck, including industry, NIH, philanthropy, academic medical centers, and advocates working together to collectively improve survival for patients," said Schuchter. By promoting collaboration in the field and providing critical investments, MRA is accelerating new paradigms in melanoma research that will continue to raise the bar and accelerate better outcomes for patients and those at risk.



MRA-sponsored Young Investigators

Improving Survival for Patients with Melanoma

Lynn Schuchter of the Abramson Cancer Center at the University of Pennsylvania summarized the recent advances made in melanoma treatment with BRAF inhibitors and immune checkpoint blocking antibodies, discussed challenges with these therapies, and posed questions yet to be answered about how best to use them.

BRAF INHIBITORS

In clinical trials, BRAF targeted drugs (vemurafenib and dabrafenib) elicited a high response rate—on the order of 80%—and improved survival compared to chemo-therapy. Studies have also shown that BRAF and MEK combination therapy works better than single agent BRAF inhibitors with a higher response rate, longer duration of response, and improved progression free survival and overall survival. Patients typically experience

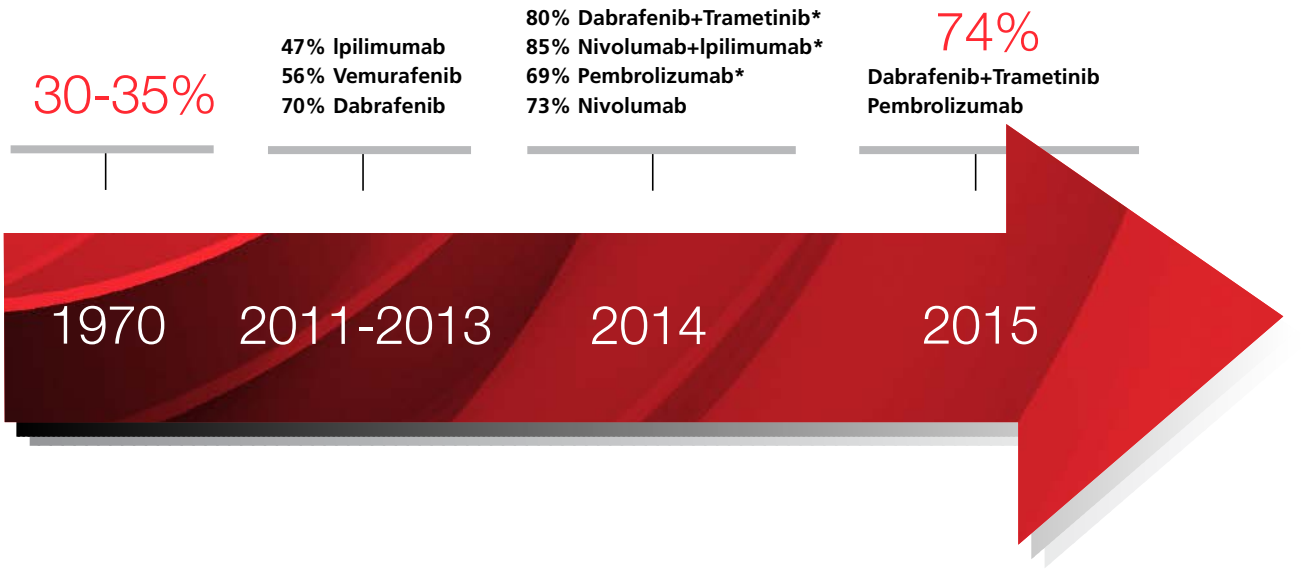
Lynn Schuchter

fewer side effects than with traditional chemotherapy. However, there is concern that BRAF inhibitors cause secondary tumors with approximately 20% of patients developing squamous cell cancer. While response rates to BRAF inhibitors can be rapid and high, the therapies are dogged by frequent development of drug resistance, with many patients experiencing disease progression within six months of starting treatment. At least 15 different mechanisms of drug resistance have been reported to date, which often involves reactivation of the MAP kinase pathway. More than one mechanism can lead to this pathway activation in the same patient. Consequently, this is an important area of research, and many trials are addressing it through the use of serial tumor biopsies to identify new drug targets and exploration of combination therapy approaches. In addition, studies are trying to determine the right dose and schedule for treatment, including whether intermittent dosing might be less likely to cause resistance than the current regimen of continuous daily dosing, as some mouse studies indicate. With this goal in mind, there is a clinical trial opening soon that will test intermittent versus continuous dosing of dabrafenib and trametinib. Another question that needs to be addressed better in the lab and clinic is whether treatment should be continued once patients' tumors progress. Disease progression usually triggers stopping traditional chemotherapy treatment because patients are not likely to receive any further benefit from therapy. But this may not be the case for patients receiving BRAF inhibitors. There is one study that showed patients who continue to receive continuous dosing with these drugs after progression do better than those that do not, while the reverse has also been seen, Schuchter pointed out.

IMMUNE CHECKPOINT INHIBITORS

The advent of checkpoint inhibitors targeting CTLA4 and the PD-1 pathway has made another group of innovative therapies available to patients. Although response rates to checkpoint inhibitors tend to be lower than to kinase

SIGNIFICANT IMPROVEMENTS IN ONE YEAR SURVIVAL RESULTING FROM NEW MELANOMA TREATMENTS



*PHASE 1 AND 2 STUDY RESULTS ONLY

COURTESY OF GEORGINA V. LONG

inhibitors (approximately 15 to 40 percent of melanoma patients respond to the approved anti-CTLA4 or anti-PD-1 checkpoint inhibitors), responses tend to be more durable and complete. Checkpoint inhibitors have unique adverse events, such as the development of thyroiditis, dermatitis, adrenal failure, hepatitis and colitis that most oncologists are not used to treating, so it is critical to partner with the relevant specialists when these side effects occur, Schuchter stressed. It is also important to identify more sophisticated biomarkers that can predict response to checkpoint inhibitors and indicate risk of recurrence, particularly now that these agents are being considered in the adjuvant setting. A large trial recently reported on ipilimumab in the adjuvant setting, and pembrolizumab is currently being tested as an adjuvant therapy. Such studies are addressing the important question of whether using systemic therapies earlier in the disease is or is not better than in late stage disease. Additional open questions involve dose and schedule, mechanisms of resistance, and how to combine them with other therapies. Sophisticated animal models with humanized immune systems will be required to enable these studies. With both BRAF targeted therapies and immunotherapies on the market, there is much enthusiasm for combining these modalities. Preclinical and clinical research is ongoing to study therapy sequencing and combinations. For example, an ECOG/SWOG trial will test ipilimumab + nivolumab (Ipi/Nivo) followed by dabrafenib + trametinib (D/T) versus D/T followed by Ipi/Nivo.

MRA Scientific Retreat

Discovery and Integration of Novel Targets into Melanoma Therapy

Researchers continue to fine-tune the understanding of the cellular pathways that foster the growth of melanomas or enable their resistance to targeted therapies as well as the interaction between the immune system and tumors. Through this work, new putative drug targets have been discovered and are being studied and validated, including those that may be responsible for BRAF inhibitor resistance, epigenetic regulators of melanoma, and components of the CTLA4 or PD-1 pathways.

TARGETING CDK4/6 IN MELANOMA

Two important enzymes, CDK4 and CDK6 (CDK4/6), participate in driving cell cycle progression and are abnormally activated in numerous cancers. The FDA recently approved an inhibitor of these enzymes called palbociclib for the treatment of certain breast cancers. Because CDK4/6 is involved exploited by many melanoma tumors, this drug may work in melanoma as well, but studies on cell lines suggest response to palbociclib is variable. For future clinical studies, researchers need a way to predict which melanoma tumor subtypes are likely to respond, as well as a way to biochemically quantify how much palbociclib inhibits its target in melanoma cells. **Andrew Aplin of Thomas Jefferson University** is tackling both issues with research funded by a Pfizer-MRA Academic Industry Partnership Award. His lab's genetic analysis of melanoma cell lines found factors that are regulated in the cell lines most sensitive to the combination of CDK4/6 and MEK inhibitors. They also developed a mouse melanoma model that uses a firefly reporter gene linked to the E2F transcription factor to signal whether CDK4/6 is active in tumor cells transplanted into nude mice. They found mice treated with a CDK4/6 inhibitor had a decreased amount of signaling. With the combination of a CDK4/6 inhibitor and a MEK inhibitor, there was blockade of the reporter activity and this activity was associated with tumor shrinkage. There was also tumor regrowth when they stopped giving the mice both drugs. "We generated a reporter system that can monitor in real

time the response and resistance to CDK4/6 inhibitors," Aplin said, noting that this should aid researchers trying to determine appropriate combinations and dosing regimens for CDK4/6 inhibitors in melanoma.

BLOCKING A NOVEL CTLA4 PATHWAY

Supported in part by a Stewart Rahr-MRA Young Investigator Award, **Kok-Fai Kong of La Jolla Institute for Allergy and Immunology** identified a novel signaling pathway controlling the functions of the checkpoint molecule CTLA4 in the immune system. He found that CTLA4 must recruit another molecule called phosphorylated PKCeta in order to activate T regulatory cells, which suppress the immune response. When he knocked out the gene encoding PKCeta, a significant reduction in the growth of melanoma tumors in a mouse model was seen, and there were greater numbers of T cells infiltrating into the tumors. Kong's pre-clinical tests of a PKCeta inhibitor found that it suppressed T regulatory cells without blocking activation of other T cells vital for an effective immune response, nor did it stimulate an autoimmune response. These results implicated the CTLA4/PKCeta pathway as a feasible target to continue to pursue as a new melanoma therapeutic approach.

INTERROGATING RNF125 DOWN-REGULATION

Supported by an MRA Established Investigator Award, **Ze'ev Ronai of the Sanford-Burnham Medical Research Institute** and his colleagues explored the possibility that BRAF inhibitor resistance may be due to the action of the ubiquitin proteasome system (UPS), which cells use to selectively destroy certain proteins. By screening for UPS genes that may overcome resistance of melanoma cultures to vemurafenib (BRAFi), they identified the ubiquitin ligase RNF125, which was also down regulated in tumor cell lines obtained from BRAFi-resistant tumors. Analysis in PDX and melanoma specimens confirmed that lower RNF125 expression is associated with greater the resistance to BRAF inhibitors. Analysis of possible targets for the RNF125 ubiquiitn ligase identified JAK1. Reduced RNF5 expression in tumors coincided with increased JAK1 and phospho-STAT3, one of its key downstream substrates. Elevated JAK1 in the BRAFi-resistant melanoma coincided with increased expression of EGFR, AXL and PDGFR, receptor tyrosine kinases that were previously reported to be upregulated in BRAFi-resistant tumors. Would inhibition of JAK1 be a way to overcome resistance to BRAF inhibitors in melanoma patients? Initial studies in cell cultures and animals found that combination of JAK and EGFR inhibitors with BRAF inhibitor effectively overcame the resistance of these tumors, suppressing these tumors' growth. "Targeting JAK1 is likely to have a beneficial effect in BRAF inhibitor-resistant tumors and offers a novel therapy for such resistance," Ronai said.

IMPLICATING THE EIF4F TRANSLATION INITIATION COMPLEX

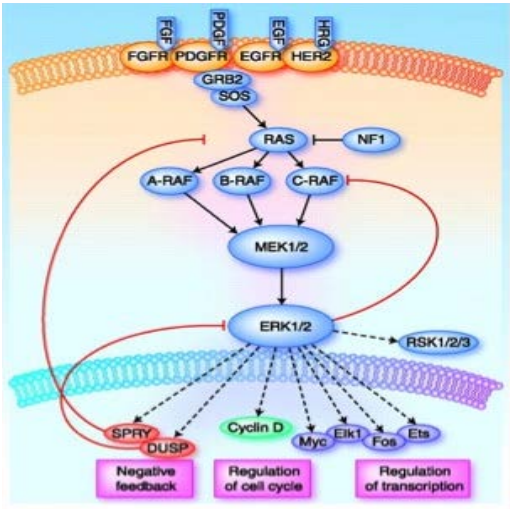
The nexus of BRAF inhibitor resistance may lie in the complex of molecules that controls cap-dependent mRNA translation, reported **Caroline Robert of the Institute Gustave Roussy**. This complex, called eIF-4F, is under the control of both MAPK and PI3-kinase pathways to generate the growth and survival factors needed for cancers to grow. Other proteins that support cell housekeeping functions are usually less dependent upon this complex than the ones that foster tumor survival and progression. Robert's and Vagner's studies show that the formation and persistence of eIF-4F is linked to the resistance to BRAF and/or MEK inhibitors due to multiple mechanisms in upstream pathways. She and her colleagues have also shown that inhibitors of the eIF-4F translation initiation complex like several compounds from the flavagline family, when combined with anti-BRAF agents, synergize with BRAF-inhibitors to inhibit the proliferation of cells that are usually resistant to BRAF inhibitors. In vivo, in xenograft mouse models, the BRAF inhibitor vemurafenib is synergistic with eIF-4F inhibitor flavagline-3 which can reverse vemurafenib resistance. This research might open new therapeutic avenues for metastatic melanoma.

MODELING EPIGENETICS IN MELANOMA

To better understand the role that epigenetics has in melanoma, **Marcus Bosenberg of Yale University**

has been creating mouse models genetically engineered to have an inability to methylate DNA or to form micro-RNAs, in addition to having heightened susceptibility to developing melanomas because of activation of BRAF and loss of PTEN. With support from a Sokoloff Family-MRA Team Science award, Bosenberg and his colleagues created melanoma-susceptible mouse models that lacked one of each of the three enzymes responsible for methylating DNA. Although one of these enzymes, Dnmt1, is thought to be the main enzyme responsible for such methylation in mammalian cells, studies on his models showed that a lack of Dnmt3b had the most effect on stemming the initiation and growth of melanoma tumors in these mice. A lack of this enzyme did not stop moles from forming on the mice, but it seemed to block moles from turning into deadly melanomas. Nearly all mice with PTEN loss and activation of BRAF died from melanoma tumors within a few months, but about 20 percent of the mice that had lost Dnmt3b continue to survive more than a year. "It's the greatest suppression of tumorigenesis we've ever seen in our mouse models," Bosenberg said. His team is currently conducting studies to assess why this is so. Specific micro RNAs appear to play critical roles in melanoma formation and progression. To investigate their role, BRAF/PTEN mice genetically engineered to lack the enzyme Dicer, which is needed to create micro-RNAs, still formed melanomas, albeit with a marked delay.

THE RAS-RAF-MEK-ERK SIGNALING PATHWAY



CHRISTINE A. PRATILAS AND DAVID B. SOLIT
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WHAT THIS MEANS FOR PATIENTS

Researchers continue to fine-tune the understanding of the genetic pathways that foster the growth of melanomas or enable their resistance to therapies. Current genetically targeted therapies, such as vemurafenib, dabrafenib, and trametinib block the growth-promoting messages that arise from mutated BRAF proteins. But often when BRAF signaling is blocked, tumor cells adapt and create bypasses that overcome the blockade and patients relapse. New laboratory studies have identified how this happens and suggest additional therapies that may also be effective when used singly or in combination with BRAF inhibitors. One example of this is the approved drug combination of trametinib and dabrafenib to treat BRAF mutant melanoma. Researchers are also identifying the way tumors stall the immune system's response to cancer. So-called immune checkpoints are one process that interrupt tumor killing by immune cells, and certain checkpoints are targeted by the drugs ipilimumab, nivolumab, and pembrolizumab. Studies are ongoing to better understand their mechanism of action and improve their effectiveness, including identifying biomarkers associated with clinical response and designing combination therapy regimens. In addition, a new frontier in melanoma research is to search for new ways to control key genes by blocking epigenetic processes that influence the genome but do not alter its fundamental coding. Studies of epigenetics have uncovered new leads, but this area of research in melanoma is still in relatively early stages.

Melanoma Biology, Prevention and Early Detection

Preventing the occurrence, recurrence, or metastasis of melanoma are major avenues of research and explorations in this area often include mouse models that can be used to uncover the biology of melanoma recurrence or metastasis and the role of ultraviolet radiation in initiating melanoma. Researchers reported their findings on the causes of melanoma and its spread as well as new advances in early detection of melanomas.

MODELING HUMAN MELANOMA IN THE MOUSE

Because most melanoma deaths are caused by the recurrence and metastasis of tumors, **Glenn Merlino of the U.S. National Cancer Institute** developed mouse models that can tease out these events. Unlike commonly used xenograft mouse models, Merlino's mice have capable immune systems, and melanomas are induced by UV light exposure to mice genetically engineered to be highly susceptible to UV due to Met Receptor activation. To make melanomas easy to detect, the melanocytes in these mice are also labeled with a fluorescent signal. The melanomas that form in the mice are not only similar to those of humans in appearance but in their genetic profile as well. Merlino and his colleagues hypothesized the aggressive growth of metastatic tumors may be enabled by reactivating previously silent genes that trigger rapid growth and migration of melanocytes in the embryo. To test this hypothesis, they compared the gene expression profiles of embryonic melanocytes (melanoblasts), normal melanocytes, and melanoma cells isolated from their mouse model. This work implicated a gene that encodes an endoplasmic reticulum receptor thought to play a role in regulating cellular stress and the degradation of faulty proteins. Melanoma cells that lacked this receptor developed fewer metastases in mice. This stress receptor is overexpressed in mouse and human melanoma, and its expression is linked to patient survival. Merlino suspects that this receptor could affect

multiple genes and pathways involved in melanoma metastasis and might be a new target for therapy.

DISSECTING THE INTERACTION BETWEEN UV RADIATION AND MELANOMA DRIVER GENES

Although the BRAF pathway is known to drive the development of about half of melanomas, it is often not sufficient by itself to generate melanoma, suggesting other events are needed to form the tumors. UV light exposure is a known risk factor for the development of melanoma, but the interaction of UV radiation and genetic drivers of melanoma, such as BRAF and NRAS, is unclear. To test this, Richard Marais of the Cancer Research UK Manchester Institute made mice susceptible to developing melanoma by inducing melanocytic expression of BRAF V600E on a portion of their skin. He exposed half of this skin to an amount of UVR "equivalent to having lunch outside in Lisbon in the summer" and found that UVR accelerated the development of melanoma and increased the number of tumors compared to the skin that was not exposed to UVR. UVR did not induce melanoma in any mice with wild-type BRAF. Nearly half of the UV-induced tumors expressed altered p53, which is also the third most commonly mutated gene in human melanomas. Thus, this research indicated that p53 is a bona-fide UVR-targeted tumor suppressor in melanoma. The researchers then tested sunscreen to see if it could prevent the development of melanomas in their mouse model. When broad-spectrum SPF50 sunscreen was applied, it decreased, but did not prevent the development of melanoma and reduced the number of genetic mutations expressed in the melanomas. "Although sunscreen works, it does not provide complete protection and needs to be combined with other methods of protecting skin from UV light," Marais said. These results in animal models underscore the wisdom of not only applying sunscreen but also wearing sun protective clothing and staying in the shade to avoid the deleterious effects of UV light.

Levi Garraway

BALANCING BENEFITS AND RISKS OF MELANOMA SCREENING

The recent "call to action" from the U.S. Surgeon General suggested several policy measures to reduce exposure to UV radiation outdoors and in tanning beds and reduce the incidence of melanoma and other skin cancers. But these will take several years before having an effect and many still require a change in human behavior that can be difficult to elicit, noted **Allan Halpern of Memorial Sloan Kettering Cancer Center**. Other measures may be warranted, including screening for melanoma in the general population: so-called secondary prevention. Data from Germany revealed that skin screening substantially reduced deaths from melanoma in the areas where the screening was instituted. But such population-based screening

Michael Giordano and Jamie Troil Goldfarb

WHAT THIS MEANS FOR PATIENTS

A better understanding of the complex causes of melanoma will enable improved ways to tackle it through prevention and early detection efforts. In this vein, investigators reported on mice genetically engineered to be susceptible to melanoma that they are using to look at the interaction between genes and the environment. Initial studies reveal that the aggressive growth of metastatic tumors is enabled by reactivating a gene that triggers the rapid growth and spread of cells in the embryo but is usually turned off by the end of fetal development. UV radiation from the sun and tanning beds is the biggest environmental contributor to melanoma. Research in mice suggests that UV radiation can accelerate melanoma when skin cells harbor certain abnormal genes. Studies also suggest that sunscreen as it is currently formulated helps to diminish but not prevent all melanomas, re-enforcing the advice that sunscreen should be combined with other methods of protecting skin from UV light. The earlier melanomas are detected, the more effective their treatment. Screening of everyone's skin for melanoma is not routinely done, however, because there is not sufficient published evidence that such screening of the general population would reduce the number of deaths from melanoma with an acceptable benefit-to-risk ratio. Studies to address this are difficult and expensive to conduct; however, research funded by MRA and others is currently ongoing to gather data to inform skin cancer screening policy.

runs the risk of harms related to over-diagnosis and excessive or unnecessary treatment, as has been seen with prostate cancer screening. Population screening for melanoma is not done currently in the U.S. because there is not enough data to support its implementation; however, there is ongoing research that aims to inform this discussion. Harms of screening could be decreased by conducting screening in the most susceptible populations. If such screening is to be undertaken, effort will have to be made to extend the work force to conduct such testing, with greater use of nurse practitioners and physician assistants trained in melanoma screening. Technologies that aid melanoma detection could also be used, Halpern added, including those that detect concerning or changing moles using digital imaging. The International Skin Imaging Collaboration Melanoma Project is aiming to create a central public resource that can be used to teach melanoma diagnosis as well as to provide digital clinical decision support resources. He added that with the support of the MRA, a three-dimensional total body photography system has entered the clinical arena to aid melanoma surveillance, as well as digital dermatoscopes that magnify and process mole images. "Secondary prevention has enormous possibility to reduce melanoma mortality," Halpern stressed.

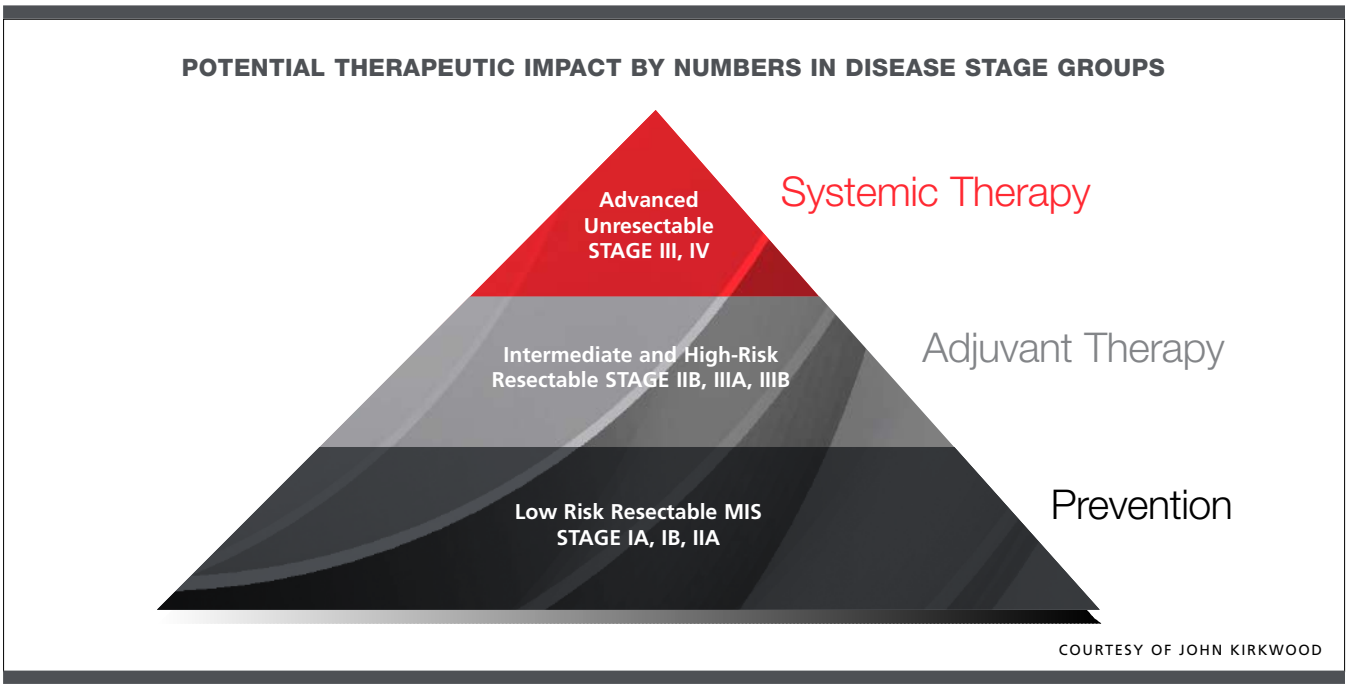
Industry Roundtable Breakfast

Adjuvant Therapy of Melanoma

Adjuvant therapy, which is therapy administered following surgery of deep primary melanomas or lymph node metastatic melanoma, has the goal to reduce relapse and to increase survival of the disease after potentially curative surgery. **John M. Kirkwood of the University of Pittsburgh Cancer Institute** reviewed the state of adjuvant therapy for melanoma patients and potential new avenues to improve development of new therapeutic options. Interferon is the only drug currently approved for adjuvant therapy for melanoma. But given the effectiveness of the new targeted and immune therapies used for metastatic melanoma, researchers suspect such treatments could also be effective when used in the adjuvant setting.

BRAF INHIBITORS AND IMMUNE CHECKPOINT BLOCKADE

Could BRAF and checkpoint inhibitors in use for melanoma patients with advanced disease also be useful earlier in the adjuvant setting to prevent the recurrence of disease after surgery? Immunotherapy is likely to be more effective when tumor burden is lower than in more advanced disease. Some treatments, such as anti-PD1 therapies may also be synergistic with interferon because interferon is known to induce PD-L1, a recognized biomarker of anti-PD1 response. In addition, an effective immune response to tumors requires both immune stimulation as well as relief from signals that inhibit T cell activation. Consequently, an immune stimulant such as interferon might work better when combined with a checkpoint inhibitor. Phase I-II clinical trials are currently evaluating BRAF and checkpoint inhibitors used singly or together, as well as BRAF+MEK inhibitor combinations with immunotherapies. BRAF inhibitors and checkpoint inhibitors given in combination with interferon as adjuvant therapies for melanoma patients might overcome the immune inhibitory effects of BRAF mutation and activation, to



gain better response from these agents together. Promising results have been seen so far, but their effects on overall survival will not be known for several years.

CLINICAL TRIAL DESIGN AND BIOMARKERS

When designing trials, overall survival has been the single unquestioned goal of therapies for melanoma over the years. Given the many new approaches to improving the outcome of metastatic disease, overall survival may not in the future be the solitary primary endpoint in adjuvant trials. Instead, the pursuit of both overall survival and relapse-free survival might be important, and the quality of life needs to be considered. PET imaging enhances the ability to detect an early anti-tumor response, and there could be biomarkers that can predict patients' likelihood of responding to adjuvant treatments. Some studies suggest tumor ulceration or the presence of tumor infiltrating lymphocytes (inflammation) can predict response to interferon and other immunotherapies. There is also evidence that these treatments may induce autoimmune reactions and that the presence of a certain profile of serum cytokine profiles can predict beneficial antitumor response to immunotherapies, as well as some of the toxicities such as colitis with the new anti-CTLA4 blocking antibodies. Biopsies taken before and as early as a month after starting adjuvant therapy have allowed investigators at the University of Pittsburgh to assess at both a molecular and cellular level whether mechanisms, such T cell infiltration and altered STAT signaling, are occurring that indicate likely effectiveness of the treatment. New trial designs that more rigorously assess these biomarkers are needed to more rapidly identify the potential anti-tumor effects of these therapies and their mechanisms so as to move these more quickly and efficiently into clinical testing and regulatory approval.

Early Biomakers of Resistance and Treatment Response

Only about one out of every five melanoma patients treated with a single BRAF inhibitor or a single-agent anti-CTLA4 checkpoint inhibitor experiences a durable response, studies show. This makes it critical to detect early on in treatment which melanoma patients are likely to benefit in the long-term from the treatment they are undergoing and monitor for early signs of drug resistance.

DEVELOPING SINGLE-CELL TECHNOLOGIES

Prior to showing substantial clinical signs of resistance to BRAF inhibitors, melanoma cells start to de-differentiate into a more embryonic state, as evidenced by the heightened coordinated expression of certain proteins sometime between 5 and 10 days after exposure to the drug and the later expression of surface markers of de-differentiation. Such a key adaptive response can be missed in bulk assays of tumor samples that detect the quantities of various proteins overall, but not whether there is coordination of any of these proteins within tumor cells. **James Heath of the California Institute of Technology** reported on research using a nanotechnology-based assay that he and collaborators developed to detect critical protein-protein interactions in melanoma cells. In this assay, each cell is isolated in a chamber that has a microscopic antibody chip to detect proteins made by the cell. Once it is further developed, clinicians could potentially use this single-cell analysis system to detect the signaling that is promoting transition to resistance and then use drugs to counter the signaling prior to it reaching a critical point after which reversal of the pathway to resistance might not be possible. “We can anticipate resistance before it happens by the signaling networks that are activated by the drug,” Heath said. One could test the cells from multiple metastases if heterogeneity of the tumors is a concern. Information gathered in such assays was also used to assemble a Markov-based kinetic model of the transition to resistance, which can

assist in the design of rational pulsatile therapy to avoid resistance. However, optimal timing of pulsatile therapy might vary from patient to patient.

PREDICTING RESPONSE TO CHECKPOINT INHIBITORS

To search for markers of response to immune checkpoint inhibitors, **Timothy Chan of Memorial Sloan Kettering Cancer Center** and his colleagues analyzed the expressed genome in melanoma tumor biopsies taken before and after treatment with these agents. When they compared the results seen in patients that had responses that lasted more than 6 months to those that did not, they discovered that mutational burden was significantly different between responders and non-responders. "However, no specific gene mutations are universal to responders or progressors on immune therapy," Chan said. However the researchers did find that complete responders had more tumor antigens than patients who did not respond to checkpoint inhibitors. After doing patient-specific HLA typing they identified candidate tumor antigens for each patient and determined a tumor antigen profile that predicted exceptional response to anti-CTLA4 treatment. Antigens arising due to mutation (neoantigens) may not reflect the drivers of the tumors, according to Chan and the tumor cell antigen signature that predicted response to anti-PD1 therapy was not the same as the one that predicted response to anti-CTLA4 therapy. "We thought there is only one immune system so the neoantigen signature may be similar across immunotherapies, but our data showed otherwise." Nonetheless, the tumor cell antigen findings might be useful when designing new clinical trials of checkpoint inhibitors, he added.

It can be challenging to determine response to immune checkpoint inhibitors using standard CT scans because tumors on these scans often appear to grow before shrinking. To improve early recognition of response to these drugs **Evan Lipson of Johns Hopkins University School of Medicine** analyzed PET scans performed 4 weeks into treatment, as well as changes in levels of tumor-derived DNA circulating in the blood.

Elliott Sigal and Suzanne Topalian

Both studies were conducted on patients with metastatic melanoma receiving immune checkpoint drugs targeting either CTLA4 or the PD-1 pathway. In the first study of 20 patients, preliminary results showed that a decrease in metabolic tumor volume seen on early PET scans appeared to predict eventual response. In the second study, circulating tumor DNA from 4 patients contained mutations identical to those found in tumor specimens. In 3 of those patients, changes in circulating tumor DNA levels correlated with—but did not predict—changes in tumor burden seen on CT scans. However, in one patient, a sustained decrease in circulating tumor DNA level preceded clinical evidence of anti-tumor response by about 3 weeks. Larger studies are needed to assess the value of early PET scans and circulating tumor DNA in predicting responses to checkpoint inhibitor therapies.

Detecting early signals of metastasis

Understanding what causes melanomas to metastasize and developing ways to detect and prevent such metastasis is a major area of research that has been limited by a lack of appropriate probes and animal models to detect the critical first steps in this process. It is thought that the creation of new lymphatic vessels enables tumor cells to travel and seed themselves in other parts of the body. **Maria Soengas of the Spanish National Cancer Research Center (CNIO)** and collaborators funded by an MRA Team Science Award presented a series of strategies to visualize melanoma metastasis in

vivo, with particular emphasis on very early lesions. She presented near infrared fluorescent probes generated by their Team member Michael Detmar (ETH, Switzerland) that allow for the assessment of lymphatic valve pulse and lymphatic structure in vivo, with exquisite detail. She then summarized results from Hector Peinado (Weill Cornell, USA and CNIO) who has been able to identify tumor cell-secreted vesicles (exosomes) that promote lymphatic expansion. Soengas then focused on a unique set of "metastasis alert" mouse models generated in her laboratory. Involved tissues in these animals emit bioluminescence when pro-lymphangiogenic activities are induced in response to aggressive melanomas. This is possible via a luciferase cassette knocked in to be expressed specifically upon activation of VEGFR3, the main driver of neo-lymphangiogenesis. With this strategy they can visualize how melanoma cells and patient-derived xenografts (PDX) activate distal sites (pre-metastatic niches) before colonizing them. Given that these events acted "at a distance", they searched for secreted factors that may represent novel drivers of melanoma metastasis. They are now pursuing proteins that allow melanoma cells to disseminate, adhere to lymphatic endothelial vessels and ultimately intravasate through them. Moreover, they used their lymphoreporter model to screen for drugs that inhibited melanoma growth and metastatic progression. In particular, they found a potent anti-tumorigenic effect of nanoparticles based on dsRNA. These nanoplexes repressed lymphangiogenesis and favored the activation of the immune system in a manner different to current melanoma drugs. Therefore, this presentation illustrates how in vivo studies in animal models can serve as a platform for gene discovery and validation of potential alternatives to melanoma treatment. In this context, Soengas concluded by emphasizing how this MRA Team Science award has prompted synergistic interactions also with other members of this collaborative group, that include Corinne Bertolloto and Robert Ballotti (Nice, France) and Stefan Endres and Sebastian Kobold (Univ Munich, Germany).

WHAT THIS MEANS FOR PATIENTS

Only about one out of every five melanoma patients treated with a single genetically targeted drug or a single-agent anti-CTLA4 checkpoint inhibitor experiences a durable response, studies show. This makes it critical to detect early on in treatment, which patients are likely to benefit from the treatment they are undergoing, as well as early signs of the development of drug resistance or disease progression so patients can be switched to a different therapy when these signs occur. Researchers reported on several advances in this regard using a variety of different technologies. These include looking at single melanoma tumor cells to detect early biochemical signals just before tumor cells make a critical transition to being resistant to targeted treatments. They also include methods to detect earlier in the course of immunotherapy if a patient is responding favorably via PET scans, circulating tumor DNA, and new analyses of tumor biopsies. The goal of this research is to develop tests that can be used by doctors to decide which treatments to give to melanoma patients and when to switch to a different treatment or to use a combination of treatments.

The Future of Translational Melanoma Research

Antoni Ribas of the University of California, Los Angeles discussed what needs to be done to make the most of current innovative treatments. Understanding the biological mechanisms underlying patient responses or resistance to therapy is critical to move the field forward. Tumor biopsies before, during, and upon progression provide invaluable insights for research as well as for clinical decision-making. For example, Ribas and his collaborators analyzed patient tumor samples before and during therapy with pembrolizumab and showed that when patients' tumors were surrounded by T cells and expressed PD-1/PD-L1 before therapy, they were more likely to respond. Based on this finding, they developed and validated a predictive model. Their findings indicated that PD-1 blockade works by inhibiting adaptive immune resistance. The implication of this is that the pre-existing

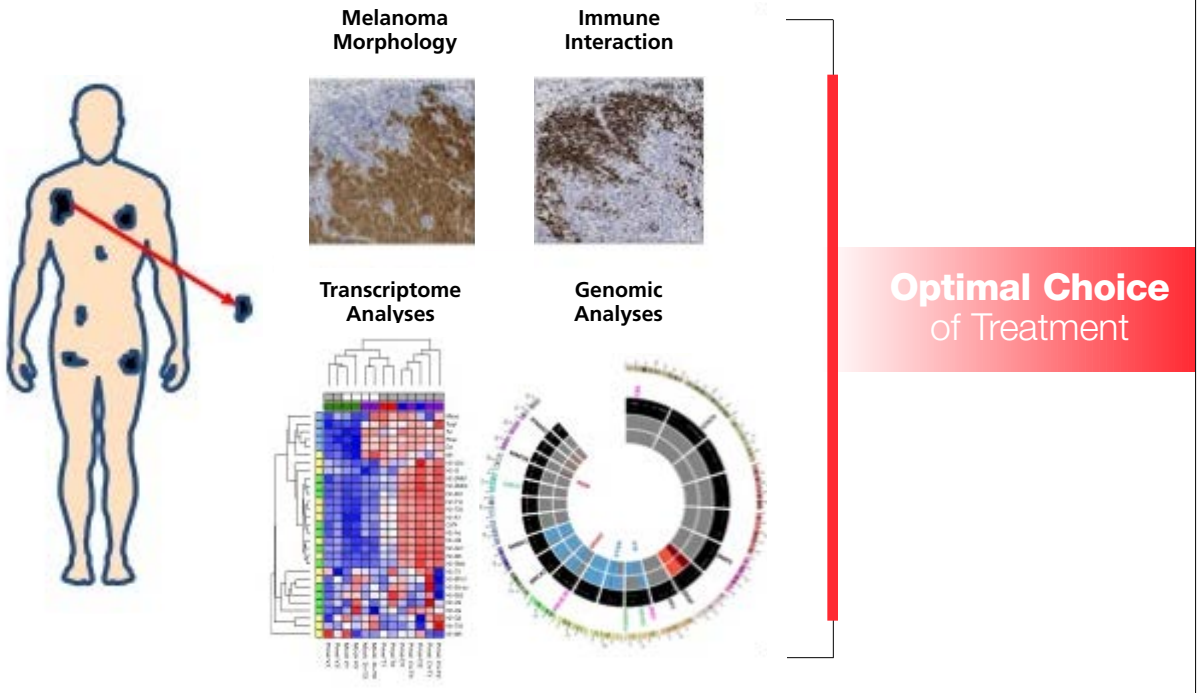
Antoni Ribas

interaction of the immune system with the tumor may be the most important factor to inform a decision about first-line therapy. If a patient biopsy shows that they are mounting an immune response to the tumor, then they should receive anti-PD-1/PD-L1 either alone or in combination with other therapies depending on the pattern of expression of other molecules.

For those patients who initially respond to a checkpoint inhibitor but then progress, there are various combination therapies that are being tested, including combination checkpoint inhibitor therapy, adoptive cell transfer therapy, and many other new targets. Indeed, combination therapy will be necessary when using inhibitors of BRAF for most patients as shown with the improvement in responses with the combination of dabrafenib and vemurafenib versus dabrafenib alone. However, a major challenge is that "resistance is not just one process but a series of processes," Ribas noted, with an evolution of drug-resistant tumors over time. This suggests the need to more effectively block nodes that are early in the pathway before these mechanisms develop.

He predicted that the future of research and clinical care of melanoma patients will involve a multivariate analysis of a patient's tumors to determine the optimal therapy. "Science has brought incredible advances in a short period of time. But we just have our foot in the door, and it is time to put in even more effort and funding to beat this disease. I want every patient I see in my clinic to be a long-term responder," he said.

IN THE NEAR FUTURE, BIOPSIES WILL NOT ONLY BE SUBJECT TO THE STANDARD MORPHOLOGIC ASSESSMENT BUT IMMUNE INTERACTION WITH THE TUMOR AND ANALYSES OF THE TUMOR TRANSCRIPTOME AND GENOME TO GUIDE OPTIMAL CHOICE OF TREATMENT FOR PATIENTS



COURTESY OF TONI RIBAS

Combination Therapies

Building on the greater successes clinicians have had by treating patients with a combination of agents rather than single-agent therapies, a major area of research is assessing which combinations of treatments might work best for melanoma patients.

COMBINING PI3K AND BRAF INHIBITORS

The PI3K molecular pathway is a major growth-promoting pathway that tumors can activate to become resistant to treatment with inhibitors to MEK and BRAF. Recognizing this, Suzette and Steven Kolitch-MRA Young Investigator **Tara Gangadhar of the University of Pennsylvania** and her colleagues conducted a multi-center clinical trial of an inhibitor of PI3K called PX-866 that was combined with the BRAF inhibitor vemurafenib in 23 patients with advanced BRAF-mutant melanomas. Patients' tumors were biopsied at both the start of the trial and after 8 days of treatment with PX-866. After the first biopsy, treatment with both PX-866 and vemurafenib was started and continued until tumors progressed or patients experienced unacceptable toxicities. The treatment was tolerated for the most part, with only two patients developing dose-limiting toxicity. When the researchers examined the tumor biopsies, they found treatment with PX-866 had decreased pAKT expression (a marker of PI3K activation) in most but not all patients, but it was not predictive of response to the combination therapy, nor was PTEN status. The investigators continue to search for molecular markers that might predict response to the therapy. However, Gangadhar stressed that, "This type of study shows it is feasible to use biopsies to learn how to personalize treatment."

COMBINING MOLECULARLY TARGETED THERAPY AND IMMUNOTHERAPY

To aid in the understanding of the interaction between targeted therapy and the immune system, **Jennifer Wargo at the University of Texas MD Anderson**

Cancer Center has focused her research on better understanding what determines response and resistance to therapy by doing molecular and immune profiling of tumor and blood samples taken from melanoma patients prior to and during treatment, as well as when their disease progresses. There is growing recognition that patients' immune responses influence their responses to both BRAF and checkpoint inhibitors, and these immune responses cannot be detected with conventional imaging. Wargo's research, which was partially funded by an MRA Team Science Award, has revealed that treatment with BRAF inhibitors increases melanoma antigens and $CD8^+$ T cells infiltrating into the tumor, while decreasing immunosuppressive cytokines and VEGF. However simultaneously, there is an increase in expression of the immunomodulatory molecule PD-L1, suggesting a possible mechanism of resistance to BRAF inhibition. Patients receiving a BRAF inhibitor whose disease progressed had a decrease in the number of $CD8^+$ T cells infiltrating their tumor samples. In contrast, biopsies of patients progressing while receiving a checkpoint inhibitor revealed that the numbers of $CD8^+$ T cells infiltrating into tumors increased early on in treatment, and stayed high even at the time of disease progression. "Early biopsies will be critical to identify treatment strategies," said Wargo. Using mouse melanoma models to assess the effects of combination therapy, she found that treatment with a checkpoint inhibitor in mice previously receiving BRAF inhibitor therapy resulted in a more active CD8 T cell infiltrate and enhanced survival and delayed tumor outgrowth.

MAKING ADOPTIVE T CELL THERAPY LESS TOXIC

Adoptive cell transfer (ACT) therapy is a way to expand activated T cells that target tumor cells. In this procedure, a patient's tumor is removed, and the tumor-infiltrating T cells isolated and stimulated with interleukin (IL)-2. The activated and tumor-cell-directed T cells that result are expanded in number and infused back into the patient. ACT therapy can be highly effective in

WHAT THIS MEANS FOR PATIENTS

Building on the greater successes clinicians have had by treating patients with other cancers or HIV infections using a cocktail of drugs rather than a single medicine, a major area of research is assessing which combinations of treatments might work best for melanoma patients. Researchers reported the results of their studies on a number of promising combination therapies, including combinations of genetically targeted treatments and combinations of therapies that boost the immune response to tumors. Combining treatments of different modalities is an emerging and important area. New data indicate that targeted therapies have effects on the function of the immune system, and investigators are using those insights to inform how best to combine immunotherapies with targeted therapies. Encouragingly, combinations of melanoma drugs currently on the market as well as new and investigational approaches, including adoptive cell therapy, are showing promise to boost the number of patients who benefit or the durability of benefit in both mouse and human studies.

treating patients with advanced melanoma, but prior to infusion of the cells, it requires toxic chemotherapy or radiation to deplete the patients' white blood cells. Such immunodepletion is thought to be necessary to prevent the production of immunosuppressive T regulatory cells and to reduce the competition for cytokines needed for T cell survival. With a Stewart Rahr-MRA Young Investigator Award, **Mark Rubinstein of the Medical University of South Carolina** has been investigating ways to avoid the toxic lymphodepletion step in ACT therapy. His studies in mice suggest this step may not be necessary if T cells are appropriately activated prior to adoptive transfer and systemic cytokines are provided. Thus, when T cells were activated with interleukin (IL)-12, and then adoptively transferred, these donor T cells had much greater sensitivity to systemically administered IL-2 in mice. Using this technique, ACT was effective in inducing complete responses in 6 of 9 tumor-bearing mice in the absence of lymphodepletion. With the administration of an IL-2-based therapy, there is concern that IL-2 might trigger activation of T regulatory cells which express the high-affinity IL-2 receptor. This activation could negate the tumor cell-killing effects of the therapy. But Dr. Rubinstein's mechanistic studies revealed that if there is enough high affinity IL-2 receptor on the donor T cells, the donor cells can likely out-compete T regulatory cells for available cytokine. Dr. Rubinstein's results suggest that genetically engineering T cells with the high affinity IL-2 receptor may allow effective ACT responses with adjuvant IL-2 in the absence of lymphodepletion.

COMBINING CHECKPOINT INHIBITORS WITH ADOPTIVE CELL TRANSFER

Activated T cells infused back into melanoma patients receiving ACT highly overexpress checkpoint molecules, which can suppress the immune response against the cancer. Consequently, ACT might be more effective if is combined with checkpoint inhibition, which animal studies and a pilot clinical study supported by an MRA Team Science award suggested. **Jeffrey Weber of the Moffitt Cancer Center** and his colleagues funded through an MRA Team Science Award treated 11 melanoma patients with ACT combined with ipilimumab. Two patients developed dose-limiting adverse reactions, but 9 weeks after treatment 6 patients responded and an additional patient had stable disease. Patients who received the combination had twice as many T cells targeting tumor-specific antigens, and overall had a modest boost in the total number of tumor-infiltrating cells. A large number of T regulatory cells are generated in response to the immunodepletion step of ACT. To avoid the immune suppression of these cells, Weber is considering combining ACT with treatment with a compound that mimics 4-1BB. His research team found this protein reduces the number of regulatory T cells and boosts proliferation of CD8 tumor-infiltrating T cells. The in vitro studies also showed that the combination of an anti-PD-1 drug with 4-1BB enhances T cells' anti-melanoma response. In their next clinical trial of ACT, the researchers plan to test this combination.

James Allison

The Future of Immune Checkpoint Blockade

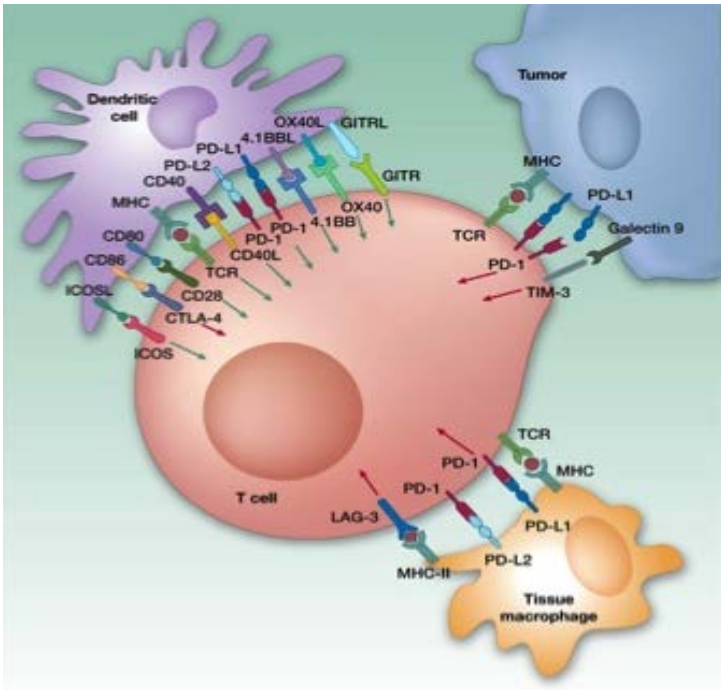
James Allison of the University of Texas MD Anderson Cancer Center summarized the progress that has been made in cancer immunology over the past decade, and advances expected in the near future. The approval of immune checkpoint blocking antibodies against CTLA4 and PD-1 has opened up an exciting area of therapy for not only melanoma patients but patients with other cancers as well, including non-small cell lung cancer, renal cell cancer, and prostate cancer. Combinations are expected to substantially boost the long-term survival of melanoma patients given the results seen in mouse models and in clinical studies. There are numerous promising approaches to combining immune checkpoint blockade with other immune checkpoint inhibitory or costimulatory molecules as well as alongside the blockade of immunosuppressive factors. In addition, possible other combinations could link immune checkpoint blockade with cell therapy, targeted therapies, personalized vaccines, approaches that enhance innate immunity, as well as traditional approaches such as surgery, radiation, and chemotherapy.

More than 50,000 cancer patients have been treated with ipilimumab and about 20 percent of those have durable responses, with the longest known responder surviving 15 years after initial treatment. About 30 percent of patients treated with nivolumab have survived for at least 4 years with an overall survival of 79 percent at two years. When both therapies have been combined in clinical trials, however, about half of patients had partial or complete responses. To maximize the effectiveness of checkpoint blocking antibodies, researchers are working on a better understanding of the mechanisms of the anti-tumor effect, biomarkers that distinguish between responders and non-responders, and how to combine them with other therapies. Numerous additional other immune checkpoints have been discovered (such as Lag-3, Tim-3, Vista, B7-H3, and B7-H4), and therapies

directed at them could be added to current melanoma drugs to improve response, Allison noted. Several stimulators of an effective anti-tumor immune response have also been identified and show promise for single or combination melanoma therapy. Innovative immunotherapies currently being pursued include those that target the proteins ICOS or IDO, both of which are thought to play a role in tumor cell immunity. An inhibitor of IDO combined with ipilimumab doubled the percent of mice with melanoma that survived at 60 days compared to ipilimumab used alone. Similarly, a vaccine that targets ICOS substantially boosted the number of tumor-infiltrating CD8 T cells and increased their activity when it was combined with ipilimumab in a mouse melanoma model.

Another tack investigators are taking is using a virus that infects tumor cells and boosts the immune response to these infected cells. Using intratumoral injection of Newcastle disease virus along with systemic ipilimumab treatment in the B16 melanoma mouse model, the combination substantially increased their survival and rejection of tumors injected with the treatment as well as distal tumors not injected. When the virus was genetically engineered to express the ligand for ICOS, it further increased survival, with up to three-quarters of the mice living more than 100 days after treatment. Given that upregulation of ICOS predicts response to CTLA4 blockade therapy in patients with melanoma, the combination therapy of engineered oncolytic viruses and immunomodulatory antibodies present an attractive therapeutic strategy for clinical exploration. Researchers also are pursing personalized vaccines comprised of the tumor antigens expressed within individual patients. Given the many approaches showing promise, Allison concluded that "It's an exciting time to do cancer research."

CO-STIMULATORY AND CO-INHIBITORY LIGAND–RECEPTOR INTERACTIONS BETWEEN A T CELL AND A DENDRITIC CELL, A TUMOR CELL, AND A MACROPHAGE, RESPECTIVELY, IN THE TUMOR



PATRICK A. OTT ET AL. CLIN CANCER RES 2013; 19:5300-5309

U.S. Funding and Policy Initiatives to Speed Cancer Research

Francis Collins, the director of the U.S. National Institutes of Health (NIH) expressed his excitement for the recent progress in targeted melanoma treatments based on genetic explorations akin to what he himself helped pioneer for cystic fibrosis. These genetic studies "provide us with insights in molecular mechanisms for melanoma that go beyond what we thought possible a decade ago and are enabling precision medicine," he said. He noted the bipartisan support for President Obama's new Precision Medicine Initiative, adding that he expects it "will energize the new generation of scientists to roll up their sleeves and get involved, ask questions, and develop new technologies. Science has never been at a more wonderfully portentous place in terms of what we can do that we never imagined we could before." Collins also praised the progress being made in immunotherapies for melanoma, including immune checkpoint inhibitors. He noted that the cures being made with the new drugs for melanoma are "hard won" and based on decades of basic research, but the budget for such research continues to decline. The chances of getting an NIH grant application accepted is the lowest it has been in 50 years. Given that financial stress "we hope creative funding efforts by MRA and other foundations can fill in the gaps to fund researchers. We need the MRA more than ever," Collins concluded.

Post-Approval Optimization of New Melanoma Drugs

Given the accelerated drug approval mechanisms that speed drug access to patients, key questions remain as to how to optimize the use of new therapies and these issues need to be investigated in the post-approval era of melanoma treatments. To identify and prioritize these questions, leaders from industry, academia, and the U.S. Food and Drug Administration participated in a roundtable discussion of challenges and opportunities to accelerate the optimization of new melanoma drugs. The session was moderated by Keith Flaherty, Massachusetts General Hospital, and Elliott Sigal, MRA Board Member and Former Executive Vice President and Chief Scientific Officer, Bristol-Myers Squibb. Several themes arose during the discussion, including:

- **REFINEMENT OF DOSE AND SCHEDULE:** While there are now several effective treatment options for melanoma patients that are improving overall quality of life and survival, there is a need to determine how to use these newly approved drugs optimally as single agents, particularly as it relates to proper dose and schedule for more personalized treatment.

- **COMBINATION OF PATHWAY AND/OR IMMUNOTHERAPY INHIBITORS:** Melanoma patients often develop resistance to single agent therapy, a combination of therapeutic approaches may be necessary to provide durable control and cures for patients. Key questions surrounding appropriate dose, schedule and sequencing of these treatments remain and more research is needed to determine optimal therapeutic combinations.

- **BIOMARKERS:** Given the range of treatment options, it is imperative to understand the molecular alterations that predict patient response so that clinicians can more definitively determine which patients will respond or not respond to certain therapies. Additionally, it would be beneficial for physicians to be able to identify which patients will benefit from single agent therapy from those who could benefit from combination treatment approaches.

As a follow up to the discussion, MRA aims to develop a set of key questions that can facilitate collaboration among stakeholders to address them and improve care and outcomes for melanoma patients.

Conclusion

The field of melanoma research has undergone extraordinary transformational progress in a relatively short amount of time, ushering in new paradigms for the treatment of patients. New therapies and exciting combinations have had a notable impact in melanoma and the oncology community as a whole. Innovative MRA-funded research programs have been leading the way in this period of incredible advancement. These findings were highlighted at the 2015 MRA Scientific Retreat in a forum that allowed stakeholders across sectors to share, discuss, and plan ways to accelerate the pace of discovery. Throughout the meeting there was a sense that the amazing progress being made has raised the bar for the field. Yet, while there is more hope than ever before, much more remains to be done until melanoma is effectively addressed for most patients. As MRA Board Member Jeffrey Rowbottom characterized it, “We’ve punched a hole in the wall, and now we’re ready to storm through it.”

Acknowledgements

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

MRA is grateful to its allies for their generous financial and in-kind support of the retreat: Adaptive Biotechnologies, Aduro Biotech, AdvaMedDx, Amgen, Ashland, BASF, Biotechnology Industry Organization, Birds Nest Foundation, Bristol-Myers Squibb, Caste Biosciences, Celldex Therapeutics, Cynthia Hazen Polsky, Eli Lilly, EMD Serono, Genentech, Holland & Knight, Immunocore, Incyte, Johnson & Johnson, Merck, National Pharmaceutical Council, Novartis, OncoSec, PhRMA, Provectus, and Royalty Pharma.

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

Below L-R: Patrick Hwu, Jeff Rowbottom, Debra Black, Leon Black, Emily Ashkin, Francis Collins, Richard Ressler

Melanoma Research Alliance

Seventh Annual Scientific Retreat

February 25-27, 2015 Washington, DC

AGENDA

Mayflower Renaissance Hotel, 1127 Connecticut Avenue NW

Wednesday, February 25th

4:00-8:00 pm *Registration open.....Grand Ballroom Promenade*

6:30-8:30 pm **Welcome Reception:** "Fighting melanoma on all fronts".....**East/State Room**

Thursday, February 26th

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

7:00-8:15 am General Breakfast.....East/State Room
7:00-8:15 am Young Investigators Breakfast (by invitation only).....Chinese Room
"So you want to develop a treatment for melanoma?
Stories from the front lines"

8:30-8:45 am **Opening Remarks.....Grand Ballroom**
Wendy Selig, MRA President & Chief Executive Officer
Louise Perkins, MRA Chief Science Officer

8:45-9:10 am **Lecture: Improving survival for patients with melanoma: all hands on deck**:
Lynn Schuchter, University of Pennsylvania

9:10-10:45 am **Session: Discovery and integration of novel targets into melanoma therapy**
Chair: Marcus Bosenberg

9:10-9:35 Targeting CDK4/6 in melanoma: Andrew Aplin, Thomas Jefferson University

9:35-9:55 Blockade of a novel CTLA-4 pathway as a new approach in melanoma therapy: Kok-Fai Kong, La Jolla Institute for Allergy and Immunology

9:55-10:20 Downregulation of the ubiquitin ligase RNF125 underlies resistance of melanoma cells to BRAF inhibitors via JAK1 and EGFR deregulation: Ze'ev Ronai, Sanford-Burnham Medical Research Institute

10:20-10:45 Modeling the role of epigenetics in melanoma: Marcus Bosenberg, Yale University

10:45-11:05 am *BREAK*

11:05 am-12:25 pm **Session: Melanoma biology, prevention, and early detection**
Chair: Glenn Merlino

11:05-11:10 Recap of recent policy achievements: Wendy Selig, MRA

Melanoma Research Alliance

Seventh Annual Scientific Retreat

February 25-27, 2015 Washington, DC

AGENDA

Mayflower Renaissance Hotel, 1127 Connecticut Avenue NW

Thursday, February 26th (cont.)

11:10-11:35	Modeling initiation, progression and treatment of human melanoma in the mouse: Glenn Merlino, U.S. National Cancer Institute
11:35-12:00	Interaction of UVR and melanoma driver genes: Richard Marais, Cancer Research UK Manchester Institute
12:00-12:25	Melanoma prevention and diagnosis: an update: Allan Halpern, Memorial Sloan Kettering Cancer Center
12:30-1:30 pm	**Lunch and Speaker.....East/State Room** Francis Collins, Director, National Institutes of Health
1:45-2:10 pm	**Lecture: Adjuvant therapy of melanoma: challenges and potential inroads.....Grand Ballroom** John Kirkwood, University of Pittsburgh
2:10-4:05 pm	**Session: Accelerating early biomarkers of resistance and treatment response** Chair: Marisol Soengas
2:10-2:35	Single cell technologies for understanding immune-cell tumor cell interactions: James Heath, California Institute of Technology
2:35-3:00	Cancer genomes and immunotherapy efficacy: Timothy Chan, Memorial Sloan Kettering Cancer Center
3:00-3:20 pm	*BREAK*
3:20-3:40	New modalities for measuring response to immune checkpoint blockade: Evan Lipson, Johns Hopkins University
3:40-4:05	Imaging and therapeutic targeting of lymphangiogenesis in melanoma metastasis: Marisol Soengas, Spanish National Cancer Research Center
4:05-4:30pm	**Lecture: The future of translational melanoma research: a provocative overview:** Antoni Ribas, University of California, Los Angeles
4:30-4:45 pm	**Closing Remarks:** Wendy Selig
6:30-10:00 pm	**Reception and Dinner..... Teddy & The Bully Bar** Dress: Casual 1200 19th St. NW, (202) 872-8700 6:30-7:30 Reception; 7:30 Dinner

Melanoma Research Alliance

Seventh Annual Scientific Retreat

February 25-27, 2015 Washington, DC

AGENDA

Mayflower Renaissance Hotel, 1127 Connecticut Avenue NW

Friday, February 27th

6:30-10:00 am	*Registration open.....Grand Ballroom Promenade*
7:00-8:30 am	General Breakfast.....East/State Room
7:00-8:30 am	Industry Roundtable Breakfast (by invitation only).....Colonial Room "Post-approval optimization of new melanoma drugs"
8:50-9:00 am	**Opening Remarks:** Louise Perkins, MRA Chief Science Officer.....**Grand Ballroom**
9:00-9:25 am	**Lecture: Addressing difficult to treat metastatic disease:** Caroline Robert, Institute Gustave Roussy
9:25-11:15 am	**Session: Advancing combination therapy approaches** Chair: Jeffrey Weber
9:25-9:45	PI3K and BRAF inhibitor combination therapy: Tara Gangadhar, University of Pennsylvania
9:45-10:10	Understanding responses to therapy and rationale for combination strategies: Jennifer Wargo, MD Anderson Cancer Center
10:10-10:30	*BREAK*
10:30-10:50	Augmenting adoptive T cell therapy with IL-2 and IL-15: Mark Rubinstein, Medical University of South Carolina
10:50-11:15	Pre-clinical and clinical assessment of checkpoint protein inhibition with adoptive cell therapy using tumor infiltrating lymphocytes: Jeffrey Weber, Moffitt Cancer Center
11:15-11:40 am	**Lecture: The future of immune checkpoint blockade**: James Allison, MD Anderson Cancer Center
11:40 am-11:45 pm	**Closing Remarks:** Jeffrey Rowbottom, MRA Board Member
12:00-1:00 pm	General Lunch.....East/State Room

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"Curing melanoma will change the future for thousands who won't have to suffer from this disease."
Lisa Simms
FasterCures


"Curing melanoma will be the major step towards curing many other cancers."
Jim Heath
CalTech


"Research and clinical trials saved my life. It allowed me to never give up hope!"
Kelly O'Donnell Ware
Kelly's Dream


"Curing melanoma will bring us closer to finding cures for other cancers."
Rachel Gazzerro, Logan Kastner, Lauren Leiman, Jennifer Engel
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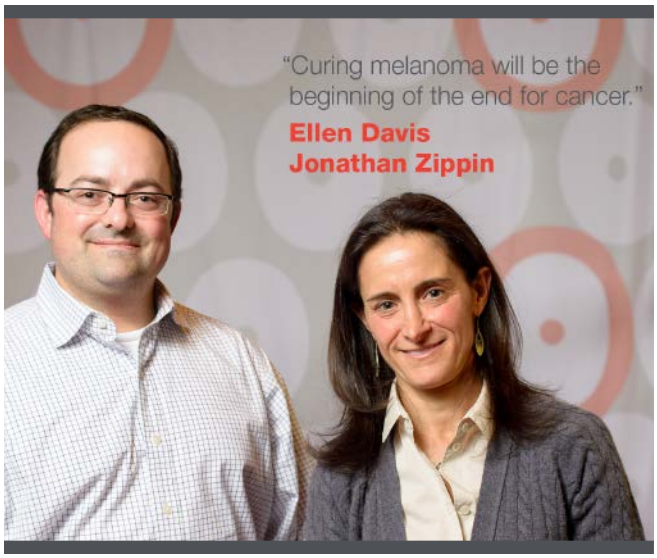
"Curing melanoma will be the beginning of the end for cancer."
Ellen Davis
Jonathan Zippin


"Curing melanoma will only be possible if we keep up the momentum and work together as we have already."
Louise Perkins
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