Melanoma Research Alliance

Building on the Momentum:
Charting the Course

Highlights of the Melanoma Research Alliance
Fourth Annual Scientific Retreat
March 1-2, 2012 // Washington, DC

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Melanoma Research Alliance

Building on the Momentum

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This is a time of unprecedented hope and promise for melanoma patients and those at risk. Recent scientific and clinical advances have converged to provide better options for patients while expanding research opportunities for scientists to drive forward the next generation of tools and treatments. Discussions of cutting-edge melanoma research results and key policy issues were held on March 1-2, 2012, in Washington, DC, at the Melanoma Research Alliance (MRA) Fourth Annual Scientific Retreat.

As the largest private funder of melanoma research, MRA is leading the field in finding and supporting the most promising research projects designed to accelerate scientific discovery and translation. A key component of MRA's unique research program, which emphasizes collaboration within and across sectors, the annual MRA retreat is an important forum for exchanging ideas, bringing together more than 220 thought leaders from academia, industry, government, business, and philanthropy to share latest findings and forge new partnerships in pursuit of better outcomes for patients. MRA-funded investigators, including early career scientists, established investigators, and interdisciplinary teams, reported on the progress of their work. This report summarizes the meeting highlights, underscoring the momentum that has occurred due to recent research breakthroughs and opportunities for charting a new course in the fight against melanoma.

Melanoma, a cancer of pigment-producing melanocytes, most often arises in the skin, but may also originate in the eye, mucous membranes, brain, and spinal cord. Melanoma is the deadliest of all skin cancers because of its ability

These breakthroughs underscore remarkable progress that has been unfolding in the five years since the founding of the Melanoma Research Alliance (MRA).

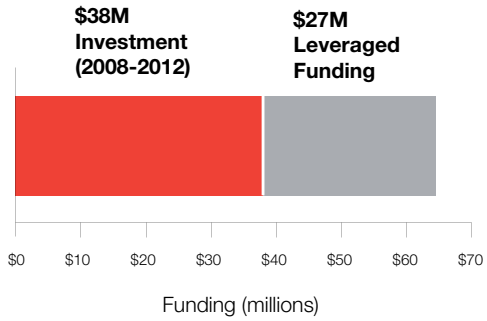
to spread widely to other organs and tissues in the body. More than 132,000 new cases are reported each year worldwide, and the incidence is growing. In the United States alone, melanoma incidence has tripled over the past three decades and now represents the fifth most common cancer in men and the seventh most common in women. More than 76,250 new cases and more than 9,180 deaths are expected in the United States in 2012. Alarmingly, melanoma is the second most frequently diagnosed cancer in U.S. young adults.

If caught early, melanoma can be successfully treated by surgery. In contrast, those diagnosed with widespread metastatic disease (Stage IV) have a median survival of less than one year. Recent advances in research have ushered in a new era in the fight against metastatic melanoma with two new treatments coming onto the market in 2011. Ipilimumab, an immunotherapy that boosts the immune system's ability to attack the cancer, was the first treatment shown to help late stage melanoma patients live longer. A second agent, vemurafenib, can extend survival for the approximately 50 percent of melanoma patients whose tumors carry the BRAF(V600E) mutation.

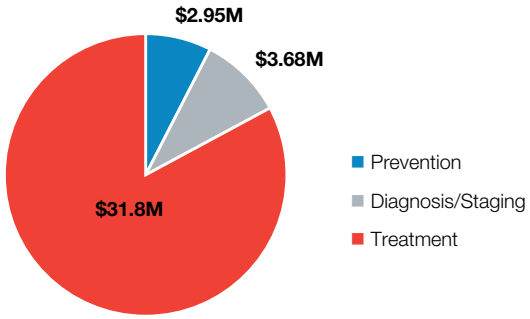
Melanoma Research Alliance's Fourth Annual Scientific Retreat

These breakthroughs underscore remarkable progress that has been unfolding in the five years since the founding of the Melanoma Research Alliance (MRA) by Debra and Leon Black, under the auspices of the Milken Institute. As the largest private sponsor of melanoma research, MRA has awarded more than $38 million in funding to 97 innovative, translational research programs led by 134 Principal Investigators at 65 institutions in 10 countries. MRA awardees are pursuing innovative, translational studies to benefit patients and those at risk of melanoma. While the newly approved treatments provide new hope, they alone will not cure most patients. Much more needs to be done until melanoma is effectively addressed. MRA-funded research is accelerating significant advances in the biological understanding of melanoma and the development of new and better preventative, diagnostic, and treatment approaches. MRA is focused on building on the momentum that has recently been achieved, continuing to create exciting opportunities for pivotal research in the laboratory and clinic that will bring new treatments to melanoma patients.

MRA-FUNDED RESEARCH WINS ADDITIONAL FUNDING, 2008-2012



MRA-FUNDED RESEARCH BY SCIENCE AREA, 2008-2012 (TOTAL = $38.4M)



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Therapeutic Drug Combinations and Resistance Mechanisms

A major thrust of ongoing research is to uncover additional drug targets and identify resistance mechanisms in order to develop combination therapies.

Last year, the first molecularly targeted drug for melanoma came on the market. This drug, vemurafenib, is used to treat melanomas that express the BRAF(V600E) mutation that is found in approximately half of patients. Agents that target additional key nodes on cell signaling pathways known to fuel melanoma are in clinical testing. But both clinical and preclinical results suggest that such targeted agents may not be curative for most melanoma patients because of drug resistance. Consequently, a major thrust of ongoing research is to uncover additional drug targets and identify resistance mechanisms in order to develop combination therapies that have better effectiveness than single agents. To date, MRA has invested approximately $8.5 million in this area.

Combining BRAF inhibitors with MEK inhibitors

BRAF, an initial node on the MAPK pathway, is frequently mutated in melanoma patients and is the target of vemurafenib and other BRAF inhibitors currently being tested. Why patients ultimately develop resistance to these inhibitors is a question that Christine Pratilas of Memorial Sloan-Kettering Cancer Center has been trying to answer. Her analysis of tumor cell lines found that V600 mutant BRAF signaling is associated with low levels of RAS-GTP. Such low levels are maintained by negative feedback, which is released by vemurafenib and other BRAF inhibitors. Treatment with these inhibitors results in an increase in RAS-GTP and subsequent rebounding of downstream ERK signaling, which

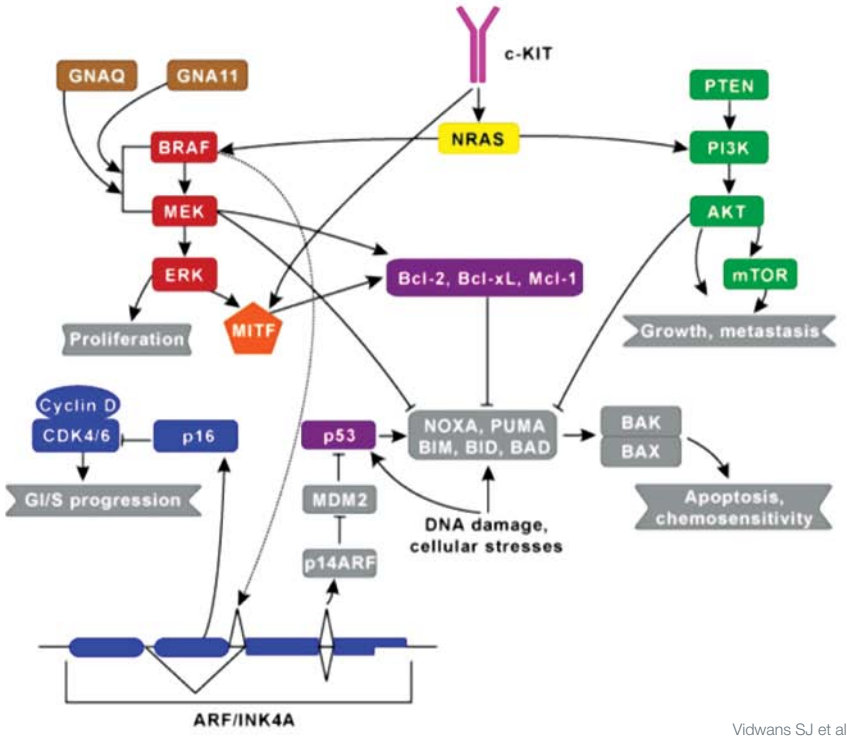
"We underestimate the frequency of co-mutational events that affect MEK inhibition."

David Solit, Memorial Sloan-Kettering Cancer Center

allows the melanoma tumors to subsequently grow anew. Her preclinical studies in tumor cell lines and mouse xenograft models also suggest that BRAF inhibition will be more effective if it is combined with inhibition of MEK.

The research of David Solit, Memorial Sloan-Kettering Cancer Center, also supports the benefit of combining BRAF inhibition with MEK inhibition. He found that BRAF mutant melanoma cell lines harbored a range of additional mutations that affect downstream signaling of MEK. "We underestimate the frequency of co-mutational events that affect MEK inhibition," he pointed out. Solit's lab found that some BRAF mutant melanomas also exhibit inactivation of the tumor suppressor genes PTEN and RB-1, allowing melanoma cell growth through pathways independent of BRAF and representing a mechanism of BRAF inhibitor resistance. He suggested that one goal is for patients to be tested for PTEN and RB1 status, but there currently is a lack of a credentialed assay. Solit also discovered a truncated form of the BRAF protein as another mechanism of BRAF inhibitor resistance observed in cell lines and patient samples. Cells with this short form of BRAF are still sensitive to MEK inhibitors, further supporting the rationale to combine BRAF and MEK inhibitors. This combination, in fact, is currently being tested in trials and is showing promising clinical activity.

CELL SIGNALING PATHWAYS INVOLVED IN MELANOMA



Vidwans SJ et al. PLoS ONE 2011;6:e18257

David Dankort of McGill University

Expression of BRAF(V600E) must be accompanied by other genetic alterations to induce melanoma, including the silencing of PTEN.

Targeting BRAF together with PI3K

Approximately 50 percent of BRAF mutant melanomas also show PTEN silencing and a smaller percentage express a mutated or amplified form of AKT, a protein kinase acting downstream of PTEN and PI3K. Using genetically engineered mouse models, Martin McMahon of the University of California, San Francisco found that oncogenic BRAF cooperates with either PTEN silencing or mutation of PIK3CA in melanomagenesis. As expected, pharmacological blockade of class 1 PI3'-kinases inhibited both BRAF mutant/PTEN null and BRAF mutant/PIK3CA mutant melanoma tumor cell growth. However, quite surprisingly, whereas single agent AKT inhibition strikingly inhibited the growth of BRAF mutant/PIK3CA mutant melanomas, there was no statistically significant effect on BRAF mutant/PTEN null melanomas, the most relevant clinical subset. Nevertheless, McMahon concedes that AKT might still have an important role in fostering melanoma that was not revealed by these particular experimental conditions. Compared to using either agent alone, MEK and PI3K inhibitors combined resulted in a "strikingly greater decrease" in ribosomal protein S6, a marker of cell proliferation. "We suspect that these pathways are cooperating in the regulation of key components needed for protein synthesis and thereby cell proliferation," McMahon said.

Expression of BRAF(V600E) must be accompanied by other genetic alterations to induce melanoma, including the silencing of PTEN. David Dankort of McGill University is generating innovative genetically engineered mouse models that replicate human melanoma development to study pivotal pathways in melanoma development and progression. Dankort reported on the mouse model he developed to detect downstream effectors of PTEN that might make good candidate drug targets in melanoma patients with both BRAF and PTEN alterations. The BRAF mutant mice were genetically engineered such that the researchers could knock out each potential PTEN effector gene by painting an activating chemical on the animals' skin. The goal not only is to identify PTEN effector genes involved in melanoma progression, but also is to determine when they are relevant on the progression timeline and "focusing on those that are druggable," Dankort said.

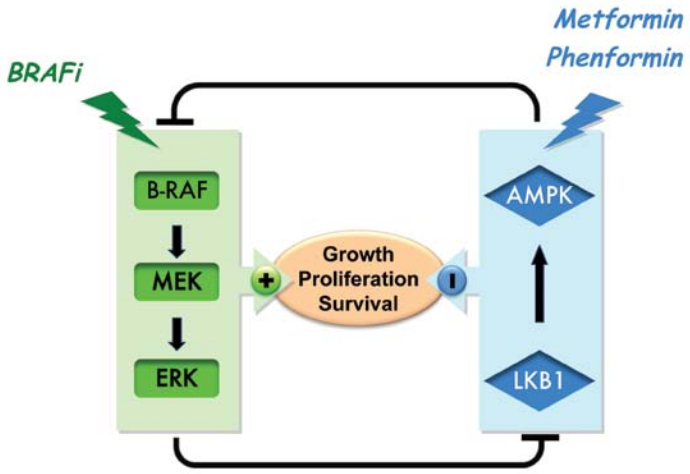
Combining targeted drug therapy with immunotherapy

As clinical studies to combine the immunotherapy ipilimumab with the targeted agent vemurafenib move forward, researchers strive to understand the mechanisms underlying the relationship between the immune system and cell signaling pathways driving melanoma. Using the BRAF mutant/PTEN null mouse model developed by Dankort and McMahon, Christian Blank of The Netherlands Cancer Institute found that vemurafenib impairs immune cell infiltration into the tumor, which was not restored with ipilimumab administration in his experimental system. He pointed out that unlike standard chemotherapy, vemurafenib is not toxic to immune cells, but instead might make tumors less immunogenic. However, studies conducted by other researchers show an increase in T cell infiltration into tumors after patients are treated with vemurafenib. It is clear that more research is needed to understand interactions between immunotherapies and targeted therapies in order to determine the best clinical applications for patients.

"These results suggest that targeting of both AMPK and BRAF signaling pathways is a promising therapeutic strategy for the treatment of malignant melanoma."

Bin Zheng, Columbia University

RATIONALE FOR COMBINING BRAF INIHIBTION WITH METFORMIN/PHENFORMIN



Courtesy of Bin Zheng

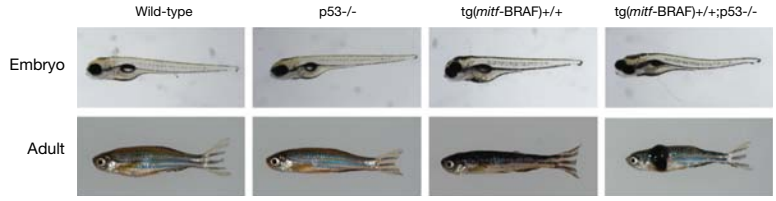
Investigating LKB1-AMPK signaling

Several years ago there was a serendipitous finding that diabetic patients taking the drug metformin had a lower incidence of cancer. Metformin works by activating the kinase AMPK, which is a key element of cell metabolism and energy balance. LKB1 lies upstream and directly activates AMPK and has been implicated as a tumor suppressor in several cancer types. Bin Zheng of Columbia University is investigating this pathway in melanoma and found that oncogenic BRAF negatively regulates LKB1-AMPK signaling. This finding led to the idea that metformin, or its analog phenformin, could have synergistic effects with BRAF inhibitors. This was confirmed when the researchers tested a combination of a BRAF inhibitor with phenformin in melanoma cell line and mouse xenograft studies. Interestingly, metformin is much less potent than phenformin in these melanoma models, probably due to the low expression level of a transporter that is required for the action of metformin. No adverse effects were seen in the animals' glucose metabolism. "These results suggest that targeting of both AMPK and BRAF signaling pathways is a promising therapeutic strategy for the treatment of malignant melanoma," Zheng said. He continues to test the drug combination in animal models.

Raya Leibowitz-Amit of Sheba Medical Center and Levi Garraway of Dana-Farber Cancer Institute

ZEBRAFISH BRAF MELANOMA MODEL

Transgenic zebrafish expressing BRAF(V600E) under the control of the promoter of the melanocyte-specific gene *mitf* develop pigmentation abnormalities and melanoma when crossed with p53–/– fish



"The path to durable control of melanoma will be enabled by expanded knowledge of melanoma dependencies and the ability to overcome resistance."

Levi Garraway, Dana-Farber Cancer Institute

Testing neural crest genes as targets for therapy

Leonard Zon of Children's Hospital Boston discussed the role of neural crest genes in the promotion of melanoma, which may represent new drug targets. His laboratory has generated several genetically engineered melanoma zebrafish models with BRAF and NRAS mutations as well as mutations affecting pigmentation. Using the BRAF(V600E): p53 model, his laboratory found that early neural crest genes were upregulated in the fish that developed melanoma. The neural crest gives rise to melanocytes and other cells during embryogenesis. One of these upregulated genes, called crestin, was shown to be expressed in cells in the BRAF(V600E):p53 fish and this seems to fix these cells in a stem-cell like phenotypic state. Many of the same markers were also found in human melanoma samples. A chemical screen to determine agents that inhibited transcription process of these genes implicated the arthritis drug leflunomide, suggesting BRAF inhibition plus leflunomide might represent a promising combination therapy. In a mouse xenograft model, this combination decreased tumor volume more than either agent alone. Based on this work, a clinical trial of this drug combination for melanoma patients is being launched.

Formulating an action plan towards durable control of melanoma

Levi Garraway, Dana-Farber Cancer Institute, summarized research activities that are working towards durable control of melanoma through better understanding of molecular melanoma drivers and drug resistance mechanisms. To date, genes such as BRAF, NRAS, PTEN and ERBB4 have been implicated in cutaneous melanoma; KIT in acral melanoma; and GNAQ/GNA11 and BAP1 in ocular melanoma. Some of these have already been extensively characterized and developed therapeutically. To identify additional melanoma drivers, comprehensive cancer genome characterization remains a powerful platform. A recent whole genome sequencing study of melanoma tumors carried out in collaboration with Lynda Chin's lab revealed many gene rearrangements and additional mutations associated with melanoma. One of the more common genetic aberrations discovered involves the PREX2 gene, which was mutated in 14 percent

Tumors are able to continually evolve strategies for survival, which hampers the long-term effectiveness of therapies that target just one specific driver of the cancer.

WHAT THIS MEANS FOR PATIENTS

Tumors are able to continually evolve strategies for survival, which hampers the long-term effectiveness of therapies that target just one specific driver of the cancer. For example, the new targeted treatment for BRAF mutant melanoma, vemurafenib, has shown dramatic responses in patients. However, eventually, most patients experience a relapse and progression of their disease due to the development of drug resistance. To overcome this problem and develop additional treatment approaches, researchers are trying to find out why this occurs in order to develop the most effective drug combinations for melanoma patients. The forefront of this research is focused on BRAF inhibitor resistance in order to build on this therapeutic platform. Studies are underway to test different drug combinations, and promising clinical results are emerging. Hundreds of genetic alterations have been revealed in melanoma, and the challenge is to identify those that are truly responsible for driving the melanoma and not simply genetic mistakes of little consequence. In addition, a critical area of study is the interaction between the immune system and these genetic events in order to design regimens combining immunotherapies with molecularly targeted agents. As a proof of principle for such an approach, a clinical trial of vemurafenib and ipilimumab is now underway. Multiple treatment approaches, particularly combination therapies, will be required to significantly improve the outcomes for patients with metastatic melanoma.

of the melanoma samples examined and promoted tumor progression in vivo. PREX2 activates the RAC1 GTP-binding protein downstream of PI3K and also interacts with PTEN. A separate study that utilized genome-scale rescue screens for resistance to MAP kinase pathway inhibitors revealed 169 candidate genes linked to the development of resistance. Validated genes include several that affect transcription, apoptosis, chromatin remodeling, protein phosphorylation, and RNA or DNA binding. Additional systematic functional studies that show great promise include the use of a technique called RNA interference. Such an approach has been successful in leukemia, for example. “The path to durable control of melanoma will be enabled by expanded knowledge of melanoma dependencies and the ability to overcome resistance. But there is still a lot of more work to do to understand what blend of cellular processes is most relevant in human tumors,” said Garraway.

Melanoma Research Alliance

Early Detection of Melanoma

Given that melanoma is highly curable with surgery when caught early, researchers are working to develop innovative systems that aid early detection.

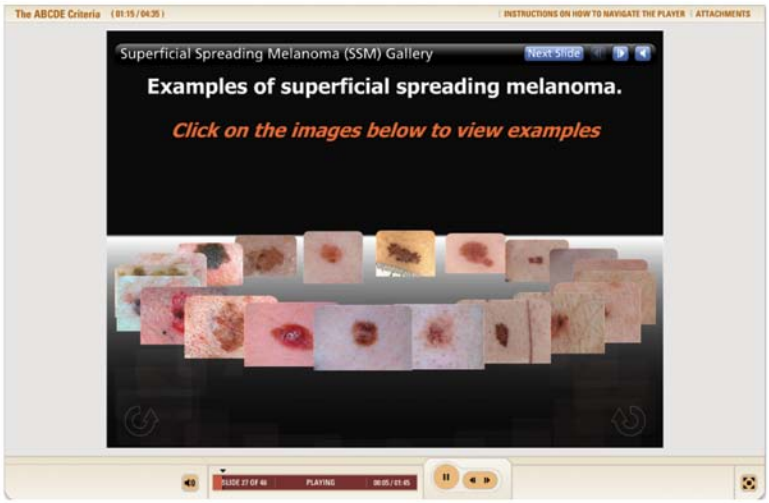
Early detection has the potential to significantly reduce deaths from melanoma. Given that melanoma is highly curable with surgery when caught early, researchers are working to develop innovative systems that aid early detection. These include devices to monitor suspicious moles over time and to distinguish benign from cancerous skin lesions. While routine skin screening is not currently practiced in the U.S., there is emerging knowledge about the effectiveness of screening that might inform such policies. At the same time, educational programs are being developed to expand the knowledge base among health care professionals to recognize melanoma in their patients. To date, MRA has awarded $1.2 million to accelerate initiatives in early detection of melanoma.

Training primary care physicians to detect melanoma

Most individuals do not perform skin self-exams, and the dermatologic workforce may not be sufficient to detect the increasing numbers of melanoma cases in the U.S. Therefore, primary care physicians have the potential to play an important role in early melanoma detection. In order to equip primary care physicians with the skills to participate in melanoma detection for their patients, Martin Weinstock of Brown University and his colleagues developed and tested a Web-based curriculum. The program, called INFORMED, is a self-paced, interactive module that takes less than two hours to complete and includes frequent self-assessments. Pilot testing found that it improved diagnostic

Alexander Lesokhin, Memorial Sloan-Kettering Cancer Center and Ellen Davis after the Young Investigator Breakfast. Dr. Lesokhin was the recipient of the 2011 Ellen and Gary Davis Foundation-MRA Young Investigator Award.

SCREEN SHOT OF INFORMED PROGRAM



Courtesy of Martin Weinstock, the INFORMED team, and skinsight.com

"This program can improve skills in distinguishing melanoma from benign skin spots and, therefore, has the potential to lead to earlier detection of melanoma without ballooning the cost of health care."

Martin Weinstock, Brown University

accuracy and management decisions that were sustained six months after program completion, as well as self-reported confidence and skills by the participating physicians. "This program can improve skills in distinguishing melanoma from benign skin spots and, therefore, has the potential to lead to earlier detection of melanoma without ballooning the cost of health care," Weinstock said. Weinstock suggested conducting larger clinical trials to evaluate the effectiveness of INFORMED in reducing mortality from melanoma.

Screening the German population for melanoma

In 2008, the German government implemented population-wide skin cancer screening after a successful pilot study in Schleswig-Holstein as described by Alexander Katalinic of the University of Lubeck. The pilot program involved more than 360,000 people aged 20 years or older, who were screened by whole body examination. Seventy-three percent of exams were performed by general practitioners with referrals to dermatologists if suspicious lesions were found. The remaining 27 percent of the participants were directly seen by a dermatologist. The population-based participation rate was 20 percent, and the average age was 50 years. More than 3,000 new skin cancers were diagnosed, including 585 melanomas. Findings now reveal that melanoma mortality was cut in half in the geographic region that initially participated in a pilot program that began in 2003. This decrease in melanoma mortality for both men and women was significantly greater than what occurred in other areas of Germany that did not have the screening program. This study has several implications for considering screening programs in the U.S. and elsewhere. Screening has the ability to improve prognosis by detecting melanoma at earlier stages. "Currently this is the best data to show the benefits of skin cancer screening on a population-based level," said Katalinic.

"The single most sensitive marker of melanoma is a changing lesion."

Allan Halpern, Memorial Sloan-Kettering Cancer Center

Developing innovative skin monitoring

Allan Halpern of Memorial Sloan-Kettering Cancer Center stressed that "the single most sensitive marker of melanoma is a changing lesion." Total body photography can detect changes in skin lesions, but most dermatologists do not employ it because it is expensive, laborious, and currently limited to two-dimensional images. To make total body photography more user-friendly, Halpern and his colleagues, working with Canfield Scientific on an Academic-Industry Partnership Award sponsored by MRA, are developing a three-dimensional imaging system with automated image processing and annotation that should be ready for clinical testing in 2012. "With this system, the patient can step into a booth and have total body photography within one millisecond," Halpern said. He and his collaborators are also laying the groundwork for computer analyses that would automate detection of suspicious lesions using this platform.

WHAT THIS MEANS FOR PATIENTS

The earlier melanoma is detected, the more likely surgical intervention will be curative. To improve detection, researchers are pursuing a number of avenues, including developing educational curricula for primary care physicians and systems for photographing and cataloging pictures of moles to monitor skin changes over time. Early detection is hampered by the fact that most people do not check their skin regularly. In addition, primary care physicians generally do not have the training or incentives to perform skin cancer exams on their patients. To address this latter gap, researchers developed a user-friendly web-based educational curriculum for primary care practitioners, which may be used as a platform for broader screening efforts.

Germany instituted a population-wide skin cancer screening program that dramatically reduced melanoma mortality, providing the best evidence to date on this topic. Detecting changes in moles is a critical hallmark of melanoma detection, and devices are being developed by a number of research groups and companies to aid dermatologists in this regard. For example, a public-private partnership is facilitating the development of a three-dimensional total body photography system that should be ready for clinical testing this year. All of these efforts have the potential to aid the ability of individuals, medical providers, and government to improve the early detection of melanoma and, thus, significantly impact outcomes for this deadly skin cancer.

Melanoma Research Alliance

Melanoma Vaccines

Much research has focused on how the tumor itself may be driving the suppression of immune responses to cancer.

Therapeutic cancer vaccines work by boosting the immune system's response against cancer through the administration of tumor specific antigens in a manner that promotes immune recognition. Although some melanoma patients respond favorably to experimental vaccines, this approach has not been effective in the vast majority of patients so far. In fact, only 3 percent clinical response rates have been seen in patients with Stage IV melanoma treated with vaccines. A major focus of melanoma research, consequently, is on understanding at the basic biology level why these treatments are effective for some patients, as well as why they are not effective for so many others. Researchers also continue to develop innovative vaccine formulations, including testing different peptides, developing DNA vaccines, designing better adjuvants, and combining vaccines with other immunotherapies. MRA has awarded approximately $3.3 million to improve melanoma vaccines.

Countering immune suppression

Much research has focused on how the tumor itself may be driving the suppression of immune responses to cancer. However, the research of Thomas Gajewski, University of Chicago, is revealing host-driven factors as

"We need to uncouple the CD8+ response from the immune suppression response."

Thomas Gajewski, University of Chicago

well. These mechanisms may have to be countered for tumor vaccines or other immunotherapies to be maximally effective. CD8+ T cells play a critical role in destroying tumor cells. However, Gajewski's studies in mice found that melanoma tumors invaded by the greatest number of these cells also had the greatest expression of key immune regulatory inhibitors, such as CTLA-4, PD-1, and IDO, as well as tumor suppressor cells (Tregs) and dysfunctional (anergic) T cells. In mice and tumors removed from patients vaccinated against melanoma antigens, Gajewski found that CD8+ cells give off signals that attract Tregs and lead to the expression of immune suppressing agents. "We need to uncouple the CD8+ response from the immune suppression response," he stressed. Significant tumor shrinkage was observed after depleting Tregs and reversing T cell anergy in mice with melanoma, or by interfering with PD-1. Gajewski and his collaborators are currently trying to target Tregs in clinical studies, including combining anti-CD25 antibody with a melanoma vaccine. Additional research revealed that the transcription factor EGR2 is implicated in T cell anergy. EGR2 regulates a small set of genes that mediate dysfunction of anti-tumor T cells. Disabling EGR2 or the genes it affects might lead to improved T cell responses and tumor control.

(from left to right) Willem Overwijk, University of Texas M.D. Anderson Cancer Center; Paul Chapman, Memorial Sloan-Kettering Cancer Center; Aaron Mackey, University of Virginia; and, Craig Slingluff, University of Virginia

Improving vaccines with better adjuvants

Melanoma vaccines often fail, not only due to short-lived T cell responses, but also due to poor homing of CD8+ cells to tumor sites, according to Willem Overwijk, University of Texas M.D. Anderson Cancer Center. One cause of this poor T cell trafficking to the tumor is the oil-based incomplete Freund's adjuvant (IFA), which is commonly used in vaccines. IFA fosters long-term presence of antigen at the vaccine site (antigen overload), which acts as a sink for T cells and "distracts" and "exhausts" them, Overwijk said. Testing a gp100 short peptide vaccine in a water-based preparation that lacked IFA resulted in more T cells at tumor sites and better anti-tumor immunity in mice. However, they still required additional adjuvants to work, and Overwijk's group specifically tested anti-CD40 antibody + imiquimod + IL-2. Non-self antigens may also serve as effective adjuvants to water-based vaccines. Overwijk noted that although other adjuvants besides IFA exist, they often are not made available to researchers for clinical testing, which delays translation of findings to patients. Overwijk plans to determine the optimal duration of antigen presentation by testing timed release formulations in hydrogels or designer nanoparticles.

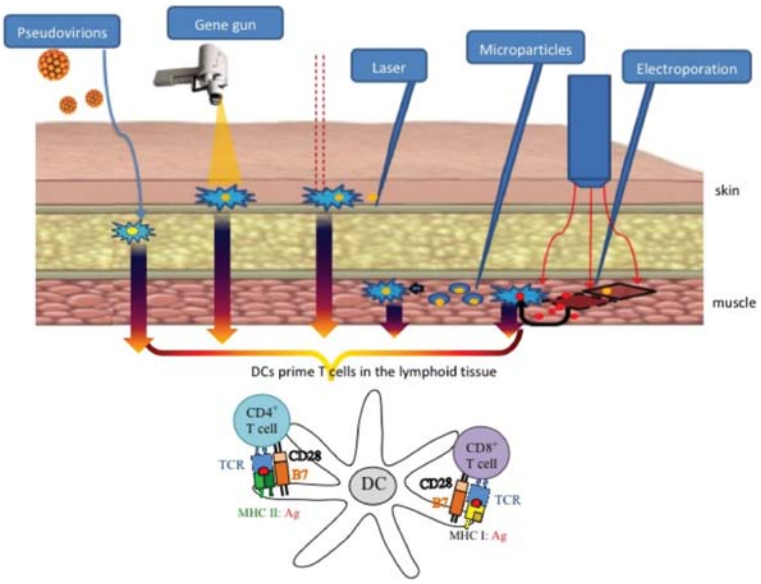
Utilizing long peptides

Craig Slingluff of the University of Virginia and his collaborators at M.D. Anderson Cancer Center aim to improve melanoma vaccines by testing the use of long (30 amino acid) peptides and better adjuvants. A clinical trial is being planned to test long peptides with agonists (activators) for toll-like receptors (TLR) 3 (polyICLC, Hiltonol), 7 and 8 (resiquimod, 3M) as vaccine adjuvants. Studies in mice by University of Virginia collaborators Rebecca Obeng and Victor Engelhard have found 10-fold higher T cell activation with long peptides compared to short peptides. This increased activity is likely due to enhanced antigen processing and presentation by dendritic cells, which is thought to drive T cell responses to tumor cells, he said. Other preclinical work by Willem Overwijk found that TLR agonists make more effective adjuvants than incomplete Freund's adjuvant alone.

DNA vaccines have emerged as an attractive approach for generating antigen-specific immunity due to their simplicity, stability, and safety.

DELIVERY OF DNA VACCINES

Several routes of administration currently used for HPV DNA vaccines, which focus on enhancing antigen uptake by dendritic cells (DCs), leading to priming of T cells for an enhanced immune response.



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TLRs play a role in the innate immune system. In addition to assessing immune parameters in serum samples, Slingluff and his colleagues will be biopsying the vaccine site to assess the immune response there.

Focusing on dendritic cells

Nina Bhardwaj of New York University School of Medicine aims to improve melanoma vaccines by enhancing endogenous dendritic cell maturation so that there is greater presentation of tumor antigens to T cells. Two approaches to accomplish this are being tested: 1) in vivo targeting with TLR agonists and 2) ex vivo prepared dendritic cell (DC) vaccines. In early phase clinical trials, Bhardwaj is testing the tumor antigen NY-ESO-1 vaccine with TLR agonist poly-ICLC versus IFA in high risk resected melanoma patients. Poly-IC is a TLR3 receptor and MDA5 agonist and is essential for DC maturation. In a phase I/II trial, both vaccine formulations are well tolerated, with early evidence that high titer antibodies against NY-ESO-1 are being elicited. Additional immune monitoring is ongoing. Another FDA-approved phase two trial is planned to systemically enhance endogenous DC maturation. Poly-ICLC matured DC will be used an adjuvant for NY-ESO-1 and Melan-A/MART-1 long peptide vaccination compared to Montanide in melanoma patients who are in complete clinical remission but at high risk of disease recurrence.

Scientists are identifying how the interactions between the tumor cells and the immune system can help or hamper a successful immune response.

WHAT THIS MEANS FOR PATIENTS

Therapeutic melanoma vaccines, which work to stimulate the proliferation and activity of tumor cell-killing immune cells, have thus far had limited clinical success in the setting of advanced melanoma. However, some studies have shown that they hold promise. As an example, the first therapeutic cancer vaccine was FDA-approved in 2010 for metastatic prostate cancer (Provenge). Therefore, continuing melanoma research efforts are aiming to reveal why vaccines are effective for some patients and not effective for so many others. Recent studies are finding that an ingredient commonly used in cancer vaccine formulations may hamper their effectiveness, and researchers are testing potential replacements to overcome this limitation. They are also designing ways to boost the ability of the tumor-killing T cells to recognize the tumor and home in on it more effectively to destroy it. In addition, scientists are identifying how the interactions between the tumor cells and the immune system can help or hamper a successful immune response. While melanoma is often recognized by the immune system and mounts a response against the cancer, it has many checks and balances that dampens this response and allows cancer to grow. A better understanding of these components will aid in the development of agents that target these factors alone along with tumor vaccines or other immunotherapies.

One way to improve the anti-tumor effects generated by DNA vaccines is to deliver DNA into dendritic cells to prime tumor-specific CD8+ T cells. DNA vaccines have emerged as an attractive approach for generating antigen-specific immunity due to their simplicity, stability, and safety, according to T.C. Wu of Johns Hopkins University. He used a gene gun to deliver DNA into mouse skin cells where it was taken up by dendritic cells that then moved into the lymphatic system. To bypass the need for antigen processing and presentation, Wu and his colleagues also genetically engineered an artificial DNA construct for presenting tumor antigenic peptide at the cell surface. This construct is comprised of the antigenic peptide linked to the ß2-microglobulin chain of MHC class I molecule and the Fc domain of IgG. In mice with melanoma, vaccination of this DNA vaccine encoding the antigenic peptide of the tyrosinase-related protein 2 (TRP2), a melanoma tumor-associated antigen was shown to boost the numbers of TRP2-specific CD8+ cells and increase survival of the vaccinated mice. In other studies, Wu showed that priming with a DNA vaccine followed by booster with intra-tumor injection of a vaccinia virus vaccine encoding the same antigens led to marked increase of antigen-specific CD8+ cells in tumors, leading to significant anti-tumor effects, and prolonged survival in a mouse model.

Melanoma Research Alliance

Novel Biomarkers for Staging and Therapeutics

Prognostic biomarkers are also needed to predict which tumors are likely to become metastatic, thereby requiring more aggressive treatment early on.

Cancer drug development is increasingly tied to molecular or immunologic subtypes. The increasing use of targeted therapies and immunotherapies for melanoma, to which only a portion of patients will respond favorably, makes it imperative to discern biomarkers that can predict response to therapy. Predictive markers may improve the effectiveness of therapies and increase safety while reducing unnecessary treatment, costs, and adverse events. Prognostic biomarkers are also needed to predict which tumors are likely to become metastatic, thereby requiring more aggressive treatment early on. Prognostic biomarkers anticipate the likely clinical outcome and are important particularly for early stage cancer in order to better stratify risk. The search for both therapeutic and prognostic biomarkers for melanoma is beginning to bear fruit. MRA has invested approximately $6.8 million in biomarker research.

"When we study cell lines we might miss mutations that cause metastasis."

J. William Harbour, Washington University

Identifying biomarkers in ocular melanomas

Although there have been great strides in the early detection of uveal (ocular) melanoma, there has not been an accompanying improvement in survival due to early micrometastatic disease, J. William Harbour of Washington University reported. "The tumors learn the trick that allows them to metastasize early on," he said. Uveal melanomas cluster into two groups: Class 1, which rarely metastasize, and Class 2 that frequently do. Harbour and his colleagues developed a 15-gene expression profile of tumors likely to metastasize that can be used for prognostic purposes in a clinical setting. Loss-of-function mutations in a gene called BAP1 were observed in at least 85 percent of Class 2 tumors, but were rare in Class 1 tumors, suggesting the role of BAP-1 as a tumor suppressor. The protein produced by this gene is a de-ubiquitinase, and the biochemical effects of its loss can be at least partly reversed by histone deacetylase (HDAC) inhibitors. In newly excised patient tumor samples, HDAC inhibitors induced differentiation and shifted Class 2 tumors to Class 1. Harbour and his colleagues are currently planning clinical trials to test the effects of HDAC inhibitors in uveal melanoma patients who have a BAP1 mutation. Harbour noted that BAP1 mutations are rarely seen in established melanoma cell lines. He found that they are lost after three to five in vitro culture passages of newly excised tumors, probably because they do not give a proliferative advantage. "So when we study cell lines we might miss mutations that cause metastasis," he pointed out.

Richard Carvajal of Memorial Sloan-Kettering Cancer Center

Richard Carvajal of Memorial Sloan-Kettering Cancer Center has also been searching for uveal melanoma biomarkers that predict response to treatment. GNAQ or GNA11 mutations are found in more than half of uveal melanomas, which activate several downstream signaling pathways in the PKC and MAPK pathway. PKC inhibitors were found to inhibit tumor cell growth in a mutation-dependent fashion, and a clinical trial testing PKC inhibition in uveal melanoma patients has been launched based on these data. PKC inhibitors may need to be combined with other treatments for ideal results in uveal melanomas with GNAQ or GNA11mutations, and preclinical evidence demonstrates that combined inhibition of PKC and AKT leads to greater cell death than PKC inhibition alone. In a clinical trial of a MEK inhibitor in metastatic uveal melanoma patients, preliminary results suggest a 20 percent response rate. Surprisingly, some patients without the more common exon 5 GNAQ or GNA11 mutations have responded; however, testing for exon 4 mutations has not yet been performed. Gene expression in patient biopsies identified three genes as potential pharmacodynamic biomarkers, and expression of JUN which is one of these genes may be linked to resistance to the MEK inhibitor.

Tremendous strides have been made in the molecular underpinning of melanoma and have the potential to improve the ability to enhance staging and better inform stage-specific outcomes.

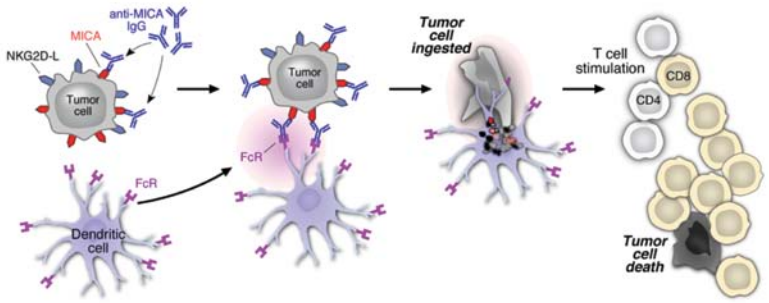
Characterizing predictive biomarkers for immunotherapy

Approximately 20 percent of patients with advanced metastatic melanoma benefit from ipilimumab, and an active area of research is focused on identifying biomarkers for predicting patients who will benefit from those who may not, including those who are at risk for serious adverse side effects. Jedd Wolchok of Memorial Sloan-Kettering Cancer Center and his colleagues assessed a number of different immune parameters in the blood samples of treated patients. Lymphocyte counts, ICOS expression, and NY-ESO-1 antibody expression have been previously reported as potential biomarkers. New evidence has associated myeloid-derived suppressor cells (MDSCs) with poor treatment response. MDSCs are populations of cells that have the ability to suppress T cell responses. In preliminary results, baseline expression of a subset of these MDSCs was shown to correlate with treatment response. In addition, protein array analysis of patient sera is starting to reveal other antigens that could serve as biomarkers predictive of response.

Glenn Dranoff and Kai Wucherpfennig of the Dana-Farber Cancer Institute are assessing biomarkers of successful patient response to vaccines and other immunotherapies. It was found that patients who respond to ipilimumab and GM-CSF melanoma vaccines produce antibodies to major histocompatibility chain related protein A (MICA), which is shed by tumor cells to help tumors avoid detection by the immune system. Dranoff and Wucherpfennig developed a method for isolating the cells that produce MICA antibodies from the millions of other immune cells generated by vaccinated patients, akin to “finding a needle in haystack,” noted Wucherpfennig. The group then generated a recombinant anti-MICA human monoclonal antibody. The goal of this research is to test the use of these antibodies in combination with other immunotherapies.

ANTI-MICA ANTIBODIES PROMOTE IN VIVO IMMUNIZATION AGAINST TUMOR CELLS

MICA is expressed on the surface of tumor cells in response to DNA damage and may be targeted with antibodies. Tumor cells are then internalized through receptors on dendritic cells, which in turn prime tumor-specific T-cell responses.



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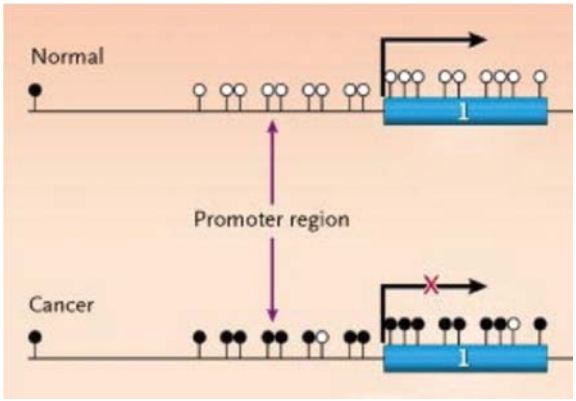
Monitoring serum miRNAs is potentially advantageous compared to tissue miRNAs, in that the former allow repetitive monitoring during disease progress, show reliable expression between individuals, and are more stable.

Integrating molecular markers for melanoma staging

Conventional melanoma staging has focused primarily on the histology of the primary tumor and, in the case of metastatic disease, on anatomic location and extent. Tremendous strides have been made in the molecular underpinning of melanoma and have the potential to improve the ability to enhance staging and better inform stage-specific outcomes. There is a need to improve management of early stage melanoma, for which prognosis is generally favorable albeit heterogeneous. Jeffrey Gershenwald, University of Texas M.D. Anderson Cancer Center, is leading an international team of investigators to catalog and validate molecular prognostic biomarkers and integrate the results into a contemporary American Joint Committee on Cancer (AJCC)-based staging system. To this end, a multi-center annotated database of several thousand Stage I-Stage IIIA (microscopic lymph node metastasis) patients treated in the contemporary era will be developed and used to analyze existing and putative clinicopathological prognostic factors. From a cohort of 500 patients, primary tumor samples will be interrogated at the DNA and protein level, and from a 200-patient subset of these, at the RNA level. In addition to interrogating resources from the team of investigators, results from the ongoing NIH TCGA melanoma effort will also hopefully be integrated into this project. “This will be a tremendous opportunity to inform ‘next gen’ melanoma staging systems and prognostic and predictive models,” said Gershenwald.

DNA METHYLATION IN CANCER

Depiction of hypermethylation in a cancer cell compared with a normal cell. Methylation (black circles) of the promoter region causes transcriptional silencing (red X) of a gene (blue).



Other studies comparing the methylation status of melanomas that differed with respect to metastatic capacity revealed additional aberrantly methylated genes associated with the metastatic phenotype.

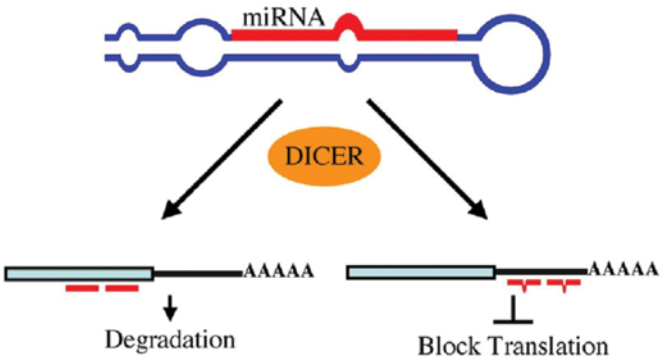
Implicating epigenetic factors

Li Zhou of the Henry Ford Health System discussed serum microRNAs (miRNAs) as prognostic and predictive biomarkers. miRNAs regulate gene expression post-transcriptionally and their dysregulation is thought to play a role in a variety of cancers and other diseases. Monitoring serum miRNAs is potentially advantageous compared to tissue miRNAs, in that the former allow repetitive monitoring during disease progress, show reliable expression between individuals, and are more stable. A comparison of serum miRNA expression profiles in melanoma patients to that of healthy subjects revealed 18 miRNAs with differential expression and 11 with changed detectable frequencies. Zhou also identified three stably expressed miRNAs that could serve as an internal normalizer for serum miRNA quantification, which would enable consistent analysis between labs. “These studies provide a strong base for us to further dissect serum miRNA biomarkers for the staging, prognosis, and therapeutic monitoring of melanoma,” Zhou concluded.

In melanoma cell lines and tumor samples, Raya Leibowitz-Amit at the Sheba Medical Center and her group found a cluster of down-regulated miRNAs located within a specific region of chromosome 14. This region is known to be important in cell development and differentiation. This differential expression was observed between normal melanocytes, benign nevi, and melanoma, and could partly be reversed by epigenetic modifications. Two of these miRNAs (mir-376a and mir-376c) target IGF1R, a growth factor receptor known to play a role in melanoma. In fact, stable expression of these two miRNAs in melanoma cells led to a decrease in IFG1R protein expression and to decreased proliferation and migration of melanoma cell lines, suggesting that aberrant expression of these miRNAs in melanoma takes part in the pathogenesis of this disease.

POST-TRANSCRIPTIONAL REGULATION BY MICRO-RNAS

Some miRNAs can bind to mRNA targets exactly and induce the RNAi/ degradation pathway (shown left). miRNAs also bind to targets imperfectly and block translation (shown right).



Courtesy of Raya Leibowitz-Amit

In addition to miRNAs, DNA methylation is another known epigenetic mechanism for gene regulation, and studies have linked aberrant methylation in melanoma.

WHAT THIS MEANS FOR PATIENTS

A major area of research is to identify markers in blood or tumor samples that predict which patients will benefit from different treatments. For example, last year the drug vemurafenib was approved for those patients whose tumors express the BRAF(V600E) mutation as detected by a diagnostic test. Patients whose tumors do not express this mutation are unlikely to respond to vemurafenib and in fact may be harmed. In addition to gene mutations as biomarkers like BRAF, researchers are also looking at how genes are regulated by factors that "silence" them and prevent making proteins that normally suppress tumor formation, growth, or metastasis. Such silencing mechanisms can be detected and serve as potential biomarkers for prognosis or treatment response prediction. Identifying biomarkers for immunotherapies will also be important to stratify patients for these treatments, and investigators have found several biomarkers that might predict response to the new melanoma immunotherapy ipilimumab (anti-CTLA-4). Another type of biomarker, called a prognostic biomarker, predicts which tumors are more aggressive, thereby requiring greater monitoring and early treatment. This will allow clinicians to identify the ~10 percent of early stage melanoma patients who are at high risk for recurrence and metastasis. Researchers are launching efforts to identify these markers to improve the staging of melanoma with the goal of improving clinical management of this disease.

In addition to miRNAs, DNA methylation is another known epigenetic mechanism for gene regulation, and studies have linked aberrant methylation in melanoma. Remco van Doorn of Leiden University Medical Center compared benign nevi to primary melanoma tumors. He found excessive methylation of genes involved in cell growth and differentiation in the tumors, including homeobox genes such as HOXA9, which are known to be hypermethylated in breast, colon, and ovarian cancers. One of the genes whose promoter was frequently excessively methylated was MAPK13 (13). When the researchers chemically demethylated melanoma cell lines, expression of the potentially tumor suppressive MAPK13 gene was restored. Other studies comparing the methylation status of melanomas that differed with respect to metastatic capacity revealed additional aberrantly methylated genes associated with the metastatic phenotype. Van Doorn plans to analyze this further to see if such aberrant methylation might be used as diagnostic and prognostic biomarkers.

SPECIAL SESSION: DEVELOPMENT OF MELANOMA BIOMARKERS FOR DIAGNOSTICS AND TREATMENT DECISIONS

While industry is focused on determining the safety and efficacy of an agent, academic investigators have great motivation and expertise to undertake investigator-initiated biomarker-based studies, and these types of academic-industrial collaborations should be supported and encouraged.

Both prognostic and treatment-specific biomarkers hold great promise for improving the care of cancer patients. The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) are encouraging drug developers to prospectively identify predictive markers and co-develop them as companion diagnostics.

As proof of principle, just last year, two new drugs and their companion diagnostics were contemporaneously approved by the FDA. One of these, vemurafenib, was approved for BRAF-mutant melanoma along with its companion diagnostic test. Yet, there remain numerous scientific, technical, regulatory, political, economic, and financial challenges to their development. A panel discussion led by Lynda Chin of the M.D. Anderson Cancer Center and Gideon Bollag of Plexxikon, Inc., and including representatives from academia, industry, and regulatory bodies, explored the pathways and current barriers to biomarker development in cancer therapy. Scientific and technical considerations include both analytic and clinical validation.

The desire for sufficient quantity and quality of the most appropriate samples is often a limiting factor, but investigators should avoid using "samples of convenience." Protocol harmonization and the use of proficiency panels can help to ensure consistency and accuracy of results. Validation is more complex when measuring immune-based parameters versus molecular-based factors (e.g., immune suppressive molecules such as PD-L1 vs. genetic mutations such as BRAF). Biomarker identification and validation should ideally begin pre-clinically. In the design of clinical trials, both academia and industry should attempt to integrate biopsy collection into the protocol. While industry is focused on determining the safety and efficacy of an agent, academic investigators have great motivation and expertise to undertake investigator-initiated biomarker-based studies, and these types of academic-industrial collaborations should be supported and encouraged.

Additional challenges in the development of prognostic biomarkers include the need to monitor large cohorts of patients over long periods to assess clinical correlations. To overcome this, surrogate markers can play an important role. In addition to these scientific and technical issues, important economic, financial, and regulatory considerations also impact the development of biomarkers. For example, diagnostic and therapeutic expertise often resides in different organizations. Academia, industry, and government must work together to address all of these issues in order to deliver on the great opportunities that now exist in cancer research to develop more effective tools and personalized treatments for patients.

SPECIAL SESSION: YOUNG INVESTIGATORS

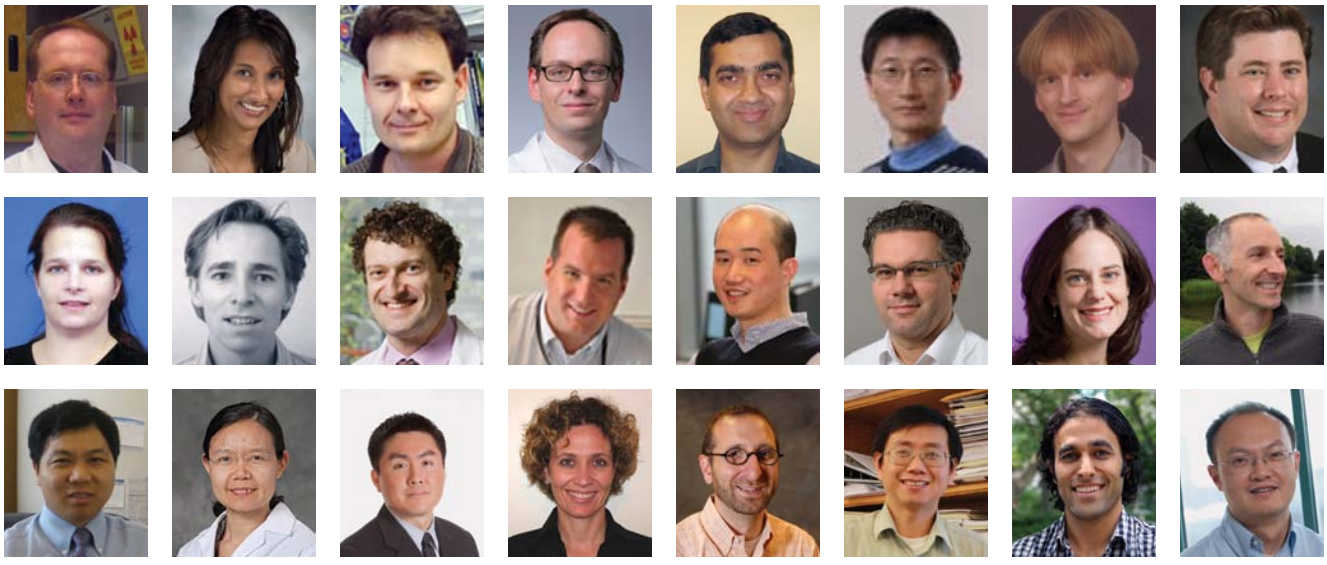
"In order to get anything done you have to attract talent to any field, and the first thing that the Melanoma Research Alliance has done is attract many of the best and brightest scientists in the world to the field of melanoma research."

Michael Milken, Milken Institute

The next generation of clinical advances for melanoma will only be possible through investments in early career investigators. Support for young scientists has never been more important. Research funding through the National Institutes of Health (NIH) has become threatened in recent years, leaving young investigators especially vulnerable. In 2006, only 1 percent of NIH funding was granted to young investigators. To fill this gap and to attract the best and brightest into a career in melanoma research, the MRA Young Investigator Award program supports early career scientists with innovative ideas.

To date, MRA has supported 24 Young Investigators at 15 institutions in four countries with a total of $4.5 million in research funding. To highlight these promising investigators and the MRA program, a special Young Investigators Breakfast was held as part of the 4th Annual Scientific Retreat. MRA Young Investigators, mentors of young investigators, sponsors of Young Investigator Awards, MRA leadership, and industry representatives participated in a discussion led by MRA Board Member Michael Milken. The breakfast provided a unique opportunity for interchange and interactions to further the mission of the MRA and this important program.

MRA Young Investigators



Melanoma Research Alliance

Charting the Course

The interactions, discussions, and presentations held at the 2012 MRA Scientific Retreat made it evident that robust cross-sector and cross-disciplinary collaborations have been fostered by the MRA's activities.

This is a time of great hope and promise for melanoma patients and those at risk. Recent scientific and clinical advances in molecular biology and immunology have converged to provide greater options for patients and more research opportunities for scientists to drive the next generation of tools and treatments.

MRA has accelerated the momentum of melanoma research in this era of unprecedented scientific opportunity by supporting a strong international, cross-disciplinary group of biomedical researchers possessing the clinical and scientific expertise to explore, identify, and pursue innovative solutions to critical questions that will lead to better treatments and a cure for melanoma patients. Cutting-edge research results from MRA-funded programs in the areas of early detection and treatment were highlighted at the 2012 Scientific Retreat. Yet, no single organization, investigator, or research sector can defeat melanoma alone. MRA is dedicated to fostering partnerships between all those who share the mission of defeating melanoma. The interactions, discussions, and presentations held at the 2012 MRA Scientific Retreat made it evident that robust cross-sector and cross-disciplinary collaborations have been fostered by the MRA's activities. By working together, the field is charting an aggressive and ambitious new course toward the day when no one suffers or dies from melanoma.

ACKNOWLEDGMENTS

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MRA would also like to thank the scientists who presented at the retreat about their work 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: Bristol-Myers Squibb, Genentech, Celgene, Eli Lilly, Amgen, Life Technologies, National Pharmaceutical Council, SpaFinder Wellness, Biotechnology Industry Organization, AdvaMed Dx, Celldex, Pfizer CTI, Provectus, Caris Lifesciences, Illumina, Aduro, Bird's Nest Productions, and the Hazen Polsky Foundation. Lauren Leiman, MRA marketing and development director, guided partner engagement during the retreat.

FOR MORE INFORMATION, visit the MRA Web site at www.curemelanoma.org. The Web site contains additional information about the MRA research program and about past MRA Retreats.

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MEETING AGENDA

THURSDAY, MARCH 1ST

Opening Remarks
Wendy K.D. Selig, MRA President and Chief Executive Officer

Therapeutic drug combinations and resistance mechanisms
Chair: Levi Garraway, Dana-Farber Cancer Institute

David Solit, Memorial Sloan-Kettering Cancer Center, Studies on the mechanism(s) of de novo and acquired resistance to RAF inhibition

Martin McMahon, University of California, San Francisco, Targeting signaling pathways for therapy in a new mouse model of melanoma

Christine Pratilas, Memorial Sloan-Kettering Cancer Center, Feedback adaptation of RAF-MEK-ERK signaling in BRAF mutant melanomas

Bin Zheng, Columbia University, Targeting the LKB1-AMPK signaling pathway in malignant melanoma

Leonard Zon, Children's Hospital Boston, Neural crest stem cell programs as targets in melanoma

Christian Blank, Netherlands Cancer Institute, Development of combined molecular/immunotherapy regimens for human melanoma

David Dankort, McGill University, Targeting critical Pten/PI3K pathway targets in BrafV600E malignant melanoma

Levi Garraway, Dana-Farber Cancer Institute, Perspective

Lunch, Speaker:
Representative Brian Bilbray (R-CA)

Early melanoma detection and skin screening trials
Chair: Martin Weinstock, Rhode Island Hospital

Martin Weinstock, Rhode Island Hospital, Developing melanoma screening in primary care

Allan Halpern, Memorial Sloan-Kettering Cancer Center, Comprehensive diagnostic imaging system for melanoma detection

Alexander Katalinic, University of Lübeck, Results of the German skin cancer screening experience

Melanoma vaccines
Chair: Glenn Dranoff, Dana-Farber Cancer Institute

Tom Gajewski, University of Chicago, Multipeptide vaccination with or without IL-12 and Daclizumab

Willem Overwijk, MD Anderson Cancer Center, Entrapment and deletion of melanoma-specific T cells at vaccination sites

Craig Slingluff, University of Virginia, Combined immunotherapy of melanoma with long peptides and TLR agonists

Nina Bhardwaj, New York University, Modulating anti-tumor immunity with dendritic cells

T-C Wu, Johns Hopkins University, Treatment of melanoma combining cancer gene therapy and immunotherapy

Glenn Dranoff and Kai Wucherpfennig, Dana-Farber Cancer Institute, The isolation of human anti-MICA monoclonal antibodies

FRIDAY, MARCH 2ND

Young Investigators breakfast (by invitation only)

Novel biomarkers for staging and therapeutics
Chair: Jeffrey Gershenwald, MD Anderson Cancer Center

Jeffrey Gershenwald, MD Anderson Cancer Center, Clinicopathologic and molecular staging and prognosis in early-stage melanoma

Li Zhou, Henry Ford Health System, Circulating microRNAs as diagnosis and staging biomarkers for melanoma

Raya Leibowitz-Amit, Sheba Medical Center, miRNA down-regulation in melanoma– Diagnostic and therapeutic implications

Remco Van Doorn, Leiden University Medical Center, Epigenomic analysis of melanoma metastatic behavior

Richard Caravajak, Memorial Sloan-Kettering Cancer Center, Development of targeted therapies for Gq/11 mutant melanomas

William Harbour, Washington University St. Louis, Targeting the Bap1 tumor suppressor gene in a mouse model of melanoma

Jedd Wolchok, Memorial Sloan-Kettering Cancer Center, Immunologic signatures of response to Ipilimumab

Panel discussion:
Development of melanoma biomarkers for diagnostics and standard-of-care, Co-chairs: Lynda Chin, MD Anderson Cancer Center and Gideon Bollag, Plexxikon

Panelists:
- Barbara Conley, National Cancer Institute
- Steve Usdin, BioCentury
- Patricia Keegan, U.S. Food and Drug Administration
- Kiran Patel, GlaxoSmithKline
- Jedd Wolchok, Memorial Sloan-Kettering Cancer Center

Closing remarks:
Suzanne Topalian, MRA Chief Science Officer