MELANOMA RESEARCH ALLIANCE

The State of Melanoma Research:
A Call to Action

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I. Introduction

Melanoma, which accounts for only 4 percent of all skin cancers, is the deadliest, responsible for 80 percent of all skin cancer-related deaths. Patients diagnosed with later stage, or metastatic melanoma, have less than a 15 percent chance of surviving five years after diagnosis. And this feared killer is rapidly increasing in incidence both in the United States and globally, thanks to an incompletely understood combination of genetic and environmental risk factors.

Over the past 35 years the rate of death from melanoma has remained the same, despite substantial research and a host of initially promising therapeutic interventions. Indeed, the melanoma therapy literature is heavily sprinkled with references to "some" or "moderate" success, much of which refers to tumor regression but not to an increase in survival. It is increasingly clear that the paucity of truly efficacious therapies, especially for later stage melanomas, is directly related to the sheer complexity of the group of diseases based on molecular alterations that are classified together under the term "melanoma." This is not to say that there are not effective treatments: In fact, almost every melanoma treatment tested to date works for some patients and not for others, reinforcing the underlying complexity of the disease from individual to individual and offering hope that better understanding could lead to better treatment. The challenge is two-fold: understanding the pathobiology of the form of melanoma in the presenting patient and identifying and implementing efficacious treatments that address that pathology. In other words, both ends of the melanoma spectrum (early diagnosis and treatment) must be brought together.

Recent advances in understanding both the risk factors and the molecular pathways that lead to melanoma suggest that new and more effective diagnostic, treatment, and prevention modalities may be relatively near —but not near enough for those who are currently living with or soon to be diagnosed with the disease, or for their families and friends.

To that end, the Milken Institute and *FasterCures,* drawing on the experience and expertise of leaders from the Prostate Cancer Foundation, jointly convened a world-class, cross-disciplinary group of expert biomedical researchers possessing clinical and scientific expertise to develop a new melanoma research agenda, one that will provide innovative research solutions, better treatments and—ultimately—a cure for melanoma. The Melanoma Research Alliance (MRA), a new organization formed under the auspices of the Milken Institute, with the generous support of Debra and Leon Black, intends to support ambitious and innovative projects from both individual scientists and research teams to develop novel diagnostic and therapeutic avenues relevant to pathways governing the behavior and clinical outcome of melanoma.

The first gathering of the MRA on November 15-16, 2007, in Washington DC, identified the crucial scientific and clinical questions that need to be addressed in order to transform the field of melanoma detection and treatment and to begin to map out concrete ways to effect that transformation.

This paper briefly describes discussions from the meeting about current limitations in melanoma basic and clinical science, and it summarizes the potential opportunities for the MRA to drive breakthroughs in the diagnosis, treatment, and prevention of this deadly disease.

II. Surgical Treatment, Diagnosis and Prognosis, and Prevention

The primary and most effective treatment of melanoma, at least in the early stages, is surgical resection. Indeed, if every melanoma could be recognized at the earliest possible stage and removed completely, we could realize a dramatic decrease in melanoma-related mortality. But the fact is that this may be an unattainable goal, at least without dramatic improvements in patient awareness, detection technologies, and implementation of those technologies in the clinical setting. Underlying this problem are significant issues that need to be addressed, providing several potential opportunities for the MRA to make a rapid difference in the clinical management of melanoma.

Staging

Current melanoma staging, based on the traditional four-stage model, is clearly inadequate to the task of describing melanoma's complexity, much less prognosing its outcomes. Although successful outcomes from surgical intervention generally align with the current staging system, i.e., the earlier the stage the more effective the surgery, the current staging is a blunt instrument at best. For example, what appears to be Stage II melanoma is in fact already metastatic in 20 percent of patients, indicating more extensive follow-up treatment including chemotherapy. Although there has been some success using sentinel lymph node biopsy to identify these patients and subsequent removal of the lymph nodes, the fact remains that much of the other 80 percent are being treated beyond what they require. Better diagnostic tools, including imaging that can detect small metastases, are required.

In addition, the current staging paradigm fails to take into account newer, though still incomplete, molecular insights into the pathogenesis of melanoma. Is it possible to identify subsets of melanoma with molecular "omics" tools, i.e., genomics, proteomics, metabolomics, etc., that have direct bearing on the prognosis—and thus treatment choice—of each patient's particular version of the disease? Underlying this question is the more fundamental one of whether or not melanoma dynamically evolves as it develops, i.e., is early-stage metastatic disease the same as late-stage metastatic disease?

The answer to this question, which requires significant molecular research across disease progression in many patients, has significant implications for developing effective treatments and using them optimally, as well as for early diagnosis.

Imaging

There are two immediate needs for improved imaging in melanoma: detection of primary lesions and detection of metastases. Dermoscopy, a technique that increases a physican's ability to distinguish suspicious moles from other pigmental skin lesions, is the current gold standard for primary melanoma screening. However, because melanoma is the only cancer for which screening is not currently recommended, dermoscopy is significantly underutilized, under-reimbursed, and not widely available. Relying on patient or general practitioner self-screening by simple visual inspection, which is by far the most-followed methodology, is highly inefficient, and it results in diagnoses that often fall into later stage disease where successful interventions are increasingly rare. The development of more robust and easy-to-use screening tests, for both general practitioners and patient self-examination, is an urgent requirement.

There are several recent and significant advances in positron emission tomography (PET) imaging technologies that can lead to earlier discovery of metastatic cancer. PET technology sensitivity is advancing quickly (including the use of hand-held devices), raising the possibility of finding increasingly small metastatic lesions early and increasing the possibility of successful surgical intervention. Furthermore, this technology can be applied successfully following either treatment response or disease progression. Perhaps the greater limitation is not the technology itself, but the molecular imaging agents used for PET imaging of melanoma. Although newer agents that are more specific for melanoma are possible, this requires an increased understanding of the molecular signature(s) of the disease so that even more effective imaging agents can be designed. Other emerging technologies include infrared visualization of cellular disorganization (a hallmark of cancer cells) and sophisticated new "laser-confocal" microscopy, but these technologies are still far from regular clinical use.

Late-Stage Surgery

Although the common wisdom is that late-stage surgical intervention in melanoma is futile, there is some evidence that surgical debulking of metastatic lesions, in combination with other treatments (immunotherapy, chemotherapy) may improve survival rates. This observation has some parallels with what has been found in late-stage ovarian cancer. However, this has not been rigorously tested, so the potential beneficial effect on survival cannot be quantified accurately.

Potential Opportunities for the MRA: Surgery, Staging, and Imaging

1. *Develop a more accurate, molecularly-based, staging system for melanoma (also see "Early Molecular Diagnosis" and "Treatment of Melanoma").*
2. *Perform an evidence-based study on the validity of melanoma screening.*
3. *Develop simplified screening tests (e.g., "paint-on" imaging agents) and protocols.*
4. *Develop more effective PET agents for metastatic screening and treatment evaluation.*
5. *Underwrite a controlled trial to determine if late-stage surgical intervention significantly increases survival.*

Early Molecular Diagnosis, Prognosis, and Prevention

As described previously, there is a significant challenge in diagnosing and staging primary melanoma. The current system, based on visual clues and histology, is not adequate, particularly in defining the extent of metastatic potential, resulting in either over treatment or under treatment of patients (with suboptimal therapies), with mixed results. It is clear that patients need to be stratified into more clinically meaningful stages, which is inextricably tied to a better molecular understanding of melanoma and thus better molecular diagnostics. In addition, the need for a melanoma-specific reliable and reproducible biomarker along the lines of the prostate specific antigen is still the "holy grail" for melanoma researchers, who find themselves very early in the quest.

The fact that multiple therapies have resulted in some positive response in a subset of patients underlines the biological complexity of the disease from patient to patient. Though vast, this complexity is not infinite, and the convergence of new "omics" tools and raw computer power suggests that it can be addressed.

Two recent advances, in particular, need to be applied in a systematic way to melanoma in order to uncover the pathobiology and to identify clinically meaningful molecular markers and targets. First, the rapid decrease in cost and increase in speed of DNA sequencing suggest that melanoma should have its own "genome project" in order to uncover the series of genetic changes that drive the aberrant molecular pathways that underlie disease development and progression (some of which are just beginning to be understood—see "Targeted Therapies").

Although this approach may be compromised by the complex evolutionary history of melanoma and thus by the sheer number of samples that have to be analyzed across the various stages, it is not an intractable problem.

The second advance—the possibility of extracting biomolecules from archived paraffin-embedded samples, as demonstrated by research at the Broad Institute of MIT and Harvard—makes the various large collections of well-annotated patient samples at several different academic biomedical institutions accessible to new genomic and post-genomic technologies. In addition, there are literally hundreds of melanoma cell lines available to researchers, although how well these lines reflect the *in vivo* disease state remains an open question. By matching molecular data extracted from these repositories to the clinical outcomes associated with the samples, it should be possible to identify meaningful diagnostic and prognostic markers, as well as new targets for developing effective drugs. Furthermore, as the discovery of robust prognostic indicators without having a matching therapy is essentially not clinically useful; this kind of knowledge may uncover information about what current treatments can be effective for individual patients and why.

Very early diagnosis of melanoma, whether through improvements in imaging or molecular measurement, or both, would be the most effective tool for preventing later-stage disease, but it would be even better to prevent the disease from forming at all. To that end, there is a paucity of systematic information about behavioral prevention techniques that could be effective. These include a deeper understanding of sun exposure's risks and benefits, as well as the role of exercise and nutrition.

Several recent studies suggest that the widespread use of sunscreen and limiting sun exposure is a two-edged preventative sword. Sunscreen use can compromise the long-known benefits of sun exposure to vitamin D metabolism for some patients, although the relative risk of "good" sun exposure to melanoma is not understood and needs to be more systematically investigated before altering recommendations and further confusing the public. This would require not only

identifying those who are at greater risk from a lack of sunlight than from melanoma development (most likely with relevant molecular markers) but also a deeper understanding of the role of vitamin D biology and its variation in different human subgroups.

In addition, the correlative benefits of exercise and nutrition in staving off melanoma need to be further evaluated. Recent studies in mice suggest that the beneficial effects of diet and exercise are mediated through a healthier immune system, which could be crucial in preventing early melanoma development. Specific dietary factors that have been identified as playing a potential anti-cancer role include Omega 3 and 6 oils, resveratrol, e.g., from red wine, and vitamin D supplementation. These findings, though suggestive, need further validation in both human and animal models.

Potential Opportunities for the MRA: Diagnosis, Prognosis, and Prevention

1. *Underwrite a Human Melanoma Genome Project to categorize the genetic changes in the development and progression of melanoma.*
2. *Support a centralized large-scale effort to extract and map molecular data from melanoma cell lines and paraffin-embedded samples to clinical outcomes, in order to identify relevant markers (and potential molecular drug targets) of disease and to optimize the use of current and emerging new therapies.*
3. *Determine the benefits vs. risk of limiting sun exposure and develop new guidelines that take into account the relative risk of different populations as determined by correlating molecular markers.*
4. *Develop a systematic study of the role of exercise and nutrition in preventing melanoma development and progression, including focused studies on identified nutrients such as omega 3/6 oils, resveratrol, and vitamin D.*

III. Treatment of Melanoma: Chemo-, Immuno-, and Targeted Therapies

The past 30-plus years of melanoma therapy are characterized by multiple failures and a few successes for small groups of patients or individuals. The successes hint tantalizingly at the potential for treating melanoma effectively, but this requires understanding why those various therapies "worked" in a few patients and not for others, thus underlining the complexity of the disease and the need for a more systematic understanding of the molecular underpinnings of melanoma.

Chemotherapy

As in all chemotherapeutic approaches to cancer, the goal of melanoma chemotherapy is to poison the cancer without killing the patient in the process. Chemotherapeutic approaches to melanoma have been largely disappointing, with five-year survival rates ranging from 3 to 14 percent. Why some patients respond when the majority of them do not remains a mystery. The most promising uses of chemotherapy (including agents such a temozolomide, thalidomide, carboplatin, and paclitaxel) appear to be in combination with emerging targeted therapies, although these have not been studied extensively. In general, chemotherapeutic approaches, even in combination, are unlikely to be as promising as newer immune-based or targeted approaches.

Immunotherapy

There are currently three main approaches to harnessing the patient's immune system to attack melanoma: non-specific immunostimulation, active immunization (cancer vaccines), and passive transfer of activated immune cells. All have demonstrated some level of success against melanoma at various stages in different patients, although the specific correlates of those successes are not well understood.

Non-specific immune stimulation through high-dose cytokines such as interleukin-2 and interferon have resulted in impressive responses in a small minority of patients, although this kind of approach carries with it serious side-effects (the equivalent of immune "chemotherapy"). A more recent approach involves administering antibodies against the T-cell surface inhibitory molecule CTLA-4, which can result in immune responses against melanoma in a subset of patients, although the side effects of this approach are increased autoimmunity against normal body tissues (indicating that the anti-CTLA-4 approach is indeed affecting immune response but with high levels of risk). Although these approaches can work for a small set of patients, why

they do so is not understood, but their efficacy appears to be correlated with a high level of pro-inflammatory cytokines.

The use of cancer vaccines that prime the immune response against specific melanoma markers has also demonstrated mixed, limited success (about three percent at best), including such vaccines as GM-CSF or GVAX. However, the use of these vaccines may be optimized in some kind of combinatorial approach, e.g., with anti- CTLA-4 or more targeted treatments. This requires a more systematic approach that is informed by an understanding of the baseline immune response of the patient as well as a better grasp of the molecular correlates that define who will or will not respond positively to therapy. There is also preliminary evidence that melanoma "stem-like" cells may play a crucial role in the efficacy of vaccine approaches, which needs further validation and characterization.

Finally, recent advances in passive transfer of activated autologous immune cells (or using T cells as a "drug") have demonstrated significant potential in late-stage metastatic melanoma. In essence, this involves identifying and growing tumor-infiltrating T lymphocytes *ex vivo* from melanoma patients, using a combination of chemotherapy and radiation to deplete the natural lymphocytes from the patient that would compete for cytokines, etc., and transferring back the anti-melanoma T cells. Dramatic reduction of even large melanoma lesions have been seen in over half of the patients treated with this regimen. This approach has been further enhanced recently by the ability to genetically engineer T cells from the patient with the specific receptors that can target melanoma, eliminating the need to identify the specific "natural" melanoma cells from the patient.

This highly effective approach to immunotherapy is not easy, cheap, or accessible. In essence, a "new drug" in the form of targeted T cells needs to be produced for each patient, along with the infection risks inherent in bone marrow replacement. This capability is also limited to two research centers at this time. However, it has been the only approach to date that appears to have high levels of success in metastatic melanoma, and it needs to be further validated and expanded.

Targeted Therapies

Genes and proteins, working in complex molecular pathways, are ultimately responsible for the initiation, survival, growth, and metastasis of melanoma. Identifying which of these are causal and which are correlative has proven difficult, but the fact remains that many, if not most, of the critical alterations in most forms of melanoma are at least partially understood. For example, alterations in the MAPK, mTOR, and STAT3 signaling pathways have been implicated in 70 to 80 percent of all melanomas. Furthermore, there are several late-development-stage or recently marketed drugs that specifically target these pathways. Access to these drugs for testing, especially in combination, is considered a major obstacle as a result of unwillingness of pharmaceutical companies to have their promising compounds tested in this manner outside the company; it is not, however, a scientific issue.

The poor survival rate in melanoma is paradoxically a positive attribute in establishing small proof-of-concept trials (phase 0) for testing these drugs, as survival time is the key metric in determining their efficacy. Such trials would need to include pre- and post-treatment biopsies, molecular assessment of mutation subtypes, and enhanced imaging techniques to effectively understand both response and lack of response to these compounds, but (as described previously) these tools are now available. The fact that 20 to 30 percent of melanomas do not have alterations in these pathways underlines the need for additional work to completely understand mechanistic contributions to melanoma. This work has to include analysis of immune responses, the microenvironment of the tumors, and melanoma cell lineage, i.e., a more "systems biology-based" approach that is capable of handling multiple types of data to derive valid knowledge about disease biology. It also requires that a new generation of melanoma researchers, particularly those who carry expertise in both clinical and laboratory settings, be identified, mentored, and resourced adequately.

Opportunities for the MRA: Immunotherapy and Targeted Therapies

1. *Identify the immune correlates in patients that benefit from non-specific and vaccine approaches in order to more precisely target these therapies.*
2. *Explore the potential of combinatorial immunotherapies, e.g., vaccines and non-specific immune stimulation.*
3. *Develop a more complete characterization of the biology and significance of melanoma "stem-like" cells in disease development and efficacy of vaccine (and other) approaches.*
4. *Expand the use of passive targeted T-cell transfer and find ways to drive down the costs and risks associated with this approach.*
5. *Provide access to marketed and late-stage development drugs that target the MAPK, mTOR, and STAT3 pathways for testing individually and in combination.*
6. *Develop a series of phase 0 trials to test the efficacy of these compounds in melanoma and to derive useful molecular information for further testing and discovery.*
7. *Incorporate a robust "systems approach" to drive further understanding of disease and to identify new opportunities for targeted therapy discovery and development.*
8. *Build a scholarship and mentoring program for young investigators doing clinical trial-based research and provide resources to do these rigorously in an academic setting.*

IV. Moving Ahead: Building a Foundation for the MRA

As stated by Mike Milken in his opening remarks at the MRA launch meeting, the goal of every participant there—and of the MRA—is the elimination of melanoma as a cause of suffering and death. The list of opportunities raised at the meeting to realize this goal is a good start, but it is neither complete nor absolute. The MRA will continue to solicit additional ideas and directions from the entire melanoma research and clinical communities. But it will also take decisive and quick action to ensure that the best of these are pursued rapidly and completely so that everyone who now works on melanoma will soon be, in the words of one participant, "free to pursue other areas of work," and that melanoma patients will no longer hear their diagnosis as a death sentence.

In response to the scientific issues and opportunities described, the MRA has decided on the following immediate actions:

1. *A Scientific Advisory Board was established at the end of 2007 to help guide the MRA in which promising opportunities to pursue.*
2. *Proposals for research that will have a transformative impact on the opportunities identified were solicited in December 2007. Funding decisions will be made in spring/summer 2008.*
3. *The MRA will cast a wide net to capture the most transformative ideas, i.e., making sure that "the right people are at the table."*
4. *The MRA will continue to seek and draw on international resources and talent, recognizing that melanoma is a global issue.*
5. *The MRA will continue to develop tools, such as those employed by the Alzheimer's Forum, that allow it to function as an open, collaborative, and multidisciplinary body that shares resources and expertise aimed at the common goal of eliminating the burden of melanoma.*
6. *Future MRA meetings will include biopharmaceutical and regulatory leaders who will play a crucial role in ensuring rapid translation of findings to clinical practice.*

To learn more about the latest progress of the Melanoma Research Alliance, apply for a grant, and to find out how you can help, go to www.melanomaresearchalliance.org.

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