Department of Health and Human Services

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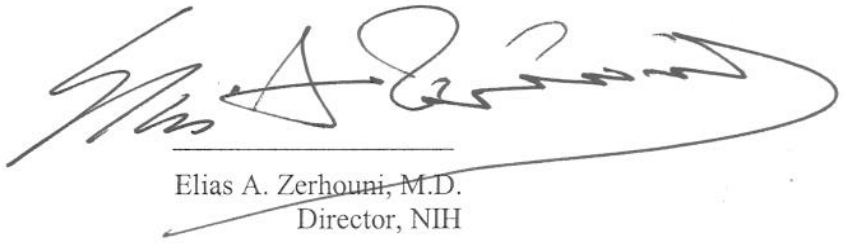
National Cancer Institute

Community-Oriented Strategic Action Plan for Melanoma Research



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Executive Summary

In Senate Report No. 109-287, the Committee on Appropriations requested that the National Cancer Institute (NCI) convene a panel of extramural and intramural scientists and consumers to identify the current shortfalls and promise of melanoma research and develop a 5-year strategic plan for melanoma research that recommends new directions and targets for future research. The report added that the plan "should also explore the role of new and innovative technologies including shared biospecimen repositories, identify and validate melanoma-specific targets to design effective therapy, and identify opportunities for facilitating translational research in this area."

This *Strategic Action Plan for Melanoma Research* is submitted in response to that request. A number of community-oriented action items to be implemented by government, academia, industry, the health care system, and the advocacy community, are suggested to address three over-arching transformational research opportunities. The panel also identified three cross-cutting, resource-building initiatives that could support efforts to address the three transformational research opportunities. These are briefly summarized in the tables below and described in greater detail in the following pages. This strategic plan was developed without regard to other competing interests.

Transformational Melanoma Research Opportunities		
Reduce Melanoma Mortality Through Prevention and Early Detection	**Streamline the Development of Personalized Melanoma Diagnosis and Treatment**	**Improve Melanoma Survival**
• Study the mechanisms by which ultraviolet radiation causes melanoma. • Investigate agents that have the potential of preventing melanoma. • Conduct large clinical trials to test the efficacy of early detection methods. • Conduct collaborative research to develop applications of imaging technology for early detection of melanoma. • Develop and deliver standardized messages and materials for public and professional education. • Create a melanoma group within the Early Detection Research Network.	• Develop model systems for discovery, validation, and preclinical testing of targets with demonstrated biological importance. • Develop a systems approach to studying complex melanoma biological systems. • Support "high-risk/high-gain" research. • Study the tumor microenvironment (e.g., stem cell biology, host-stroma interactions, inflammation, and immune regulatory cells).	• Improve investigators' access to new drugs and orphan drugs by streamlining the Cancer Therapy Evaluation Program and the Rapid Access to Intervention Development program. • Facilitate collaborative studies to test combinations of drugs from multiple sources using innovative research strategies by eliminating barriers to participation in such studies by pharmaceutical companies.

Cross-Cutting, Resource-Building Initiatives

Enhance Prevention, Early Detection, and Treatment Research

- Biomarkers should be developed that can help focus the application of new therapies on patients most likely to respond, and they should be tested and validated to serve as adjunct diagnostic methods. Therapeutic targets research should adopt a systems approach to studying the complexity of melanoma biological systems through comprehensive analysis of multiple targets that interact to sustain melanoma viability.

Promote Sharing of Melanoma Biospecimens, Cell Lines, Animal Models, and Research Data

- A variety of strategies should be used to standardize biospecimen and data collection procedures; encourage the creation of billing codes for collection of biospecimens; and make data, biospecimens, cell culture systems, and animal models accessible to melanoma researchers via a Web-based portal in collaboration with the NCI Cancer Biomedical Informatics Grid (caBIG) project.

Create a Critical Mass of Researchers in Melanoma

- A variety of mechanisms and strategies should be pursued to increase the number of scientists entering the field of melanoma research, including contracts to support a melanoma training program for young investigators, T32 grants to support collaborative training among multiple extramural institutions, facilities for cross-training of researchers and physicians, foundation grant programs, and mentoring programs.

Introduction

In its report on the fiscal year (FY) 2007 budget for the Department of Health and Human Services, the Senate Committee on Appropriations stated the following:

> Melanoma is the fastest growing cancer in the United States and worldwide. The etiology of the disease is not well understood, and the average life span of patients with advanced melanoma is less than 1 year. Nevertheless, there is a shortage of melanoma researchers and a lack of effective drugs and treatments. Therefore, the Committee strongly urges the NCI to convene a panel of consumers, extramural and intramural scientists to develop a 5-year strategic plan for melanoma research and submit it to the Committee by July 1, 2007. The strategic plan should identify the current shortfalls and promise of melanoma research and recommended new directions and targets for future research. The plan should also explore the role of new and innovative technologies including shared biospecimen repositories, identify and validate melanoma-specific targets to design effective therapy; and identify opportunities for facilitating translational research in this area. (Senate Report No. 109-287, pages 106-107)

The following report has been prepared by the National Cancer Institute (NCI), National Institutes of Health, Department of Health and Human Services in response to this request.

Background

To address the Senate's request for a melanoma research strategic plan, NCI renewed its ongoing dialogue with the Society for Melanoma and the Research Melanoma Research Foundation. In partnership with those groups, NCI had convened a Melanoma Focus Group in September 2005. During that meeting, participants reviewed a *Roadmap for New Opportunities in Melanoma Research* developed earlier in 2005 by the Society and the Foundation, identified several high-priority overarching research opportunities, and discussed the need for a community-oriented action plan for melanoma research.

In the summer and fall of 2006, NCI worked with the Society and the Foundation to plan for a meeting of melanoma researchers and advocates to update and prioritize melanoma research opportunities already identified and develop a strategic action plan for implementing those recommendations. During a meeting held in Bethesda, Maryland, February 27–March 1, 2007, representatives of the intramural and extramural melanoma research community, as well as the melanoma advocacy community,[1] identified several short- and long-term opportunities for focused, collaborative research aimed at reducing the incidence and mortality associated with a disease that is potentially preventable and curable. The strategic plan presented below resulted from these discussions, but it must be noted that it was not developed with regard to other competing budget priorities.

[1] Members of the expert panel are listed following the conclusion of this document.

Action Steps for Addressing Transformational Melanoma Research Opportunities

1. Reduce Melanoma Mortality Through Prevention and Early Detection

- Although ultraviolet radiation (UV) exposure is the major environmental risk factor for the development of melanoma, the mechanisms by which this exposure causes melanoma are not well understood; significant efforts should be applied to research in this area. Scientists should also develop methods for consistent measurement of UV exposure. The behavioral aspects of UV exposure should also be studied. This information is needed to develop effective educational interventions regarding sun safety.
- The melanoma research community should investigate agents that have the potential of preventing melanoma. Effective prevention could reduce melanoma mortality by 50 percent within 10 years.
- Large, multisite, population-based clinical trials (including collection of biospecimens in addition to clinical and family history data) are needed to test the efficacy of early detection methods. Lack of proof of the ability of early detection to reduce mortality has been a barrier to implementation of screening for melanoma. Another major barrier is the cost of general population screening; identification of high-risk individuals for screening could substantially improve the cost-benefit ratio.
- Collaborative research is needed to develop applications of imaging technology for early detection. Experts in the field of imaging are not widely familiar with melanoma, while some melanoma researchers do not have sufficient expertise in imaging or equipment to conduct imaging.
- Using consistent messages and materials, the public as well as health care providers must be educated about melanoma. Medical school curricula need to include instructions on skin examination.
- The melanoma research community should establish a formal working group within the Early Detection Research Network (EDRN), which currently does not include a melanoma-related collaborative group.

2. Streamline the Development of Personalized Melanoma Diagnosis and Treatment to Improve Diagnostic Accuracy, Disease Classification, and Prediction of Treatment Response

- Melanoma researchers need a panel of improved, more relevant model systems for therapeutic target discovery, validation, and preclinical testing. Priority should be given to targets with demonstrated biological importance (e.g., those associated with metastasis and tumor survival).
- Support is needed for "high-risk/high-gain" research proposals—that is, proposals that are likely to have a significant impact in improving melanoma outcomes if they are successful.

- The NCI melanoma research portfolio contains only a few studies on the melanoma tumor microenvironment, which includes important areas such as stem cell biology, host-stroma interactions, inflammation, and immune regulatory cells. A variety of research questions in these areas need to be addressed using organotypic models or *in vivo* models which mimic tumor-host interactions seen clinically.
- Investigators should be encouraged to incorporate molecular and functional imaging modalities into early detection, staging, and therapy monitoring trials.

3. Improve Survival from Advanced Melanoma

- Drug development efforts focusing on rare and understudied diseases such as melanoma face unique challenges. Addressing the rising incidence and unique biology of human melanoma will require a well-defined process to access and provide input to existing NCI drug development programs such as the Cancer Therapy Evaluation Program (CTEP) and the Rapid Access to Intervention Development (RAID) program. The procedures followed by CTEP for identifying new agents for evaluation and introducing them into clinical trials should be streamlined, and interactions between CTEP and RAID should be expedited. Currently, the Investigational Drug Steering Committee (IDSC) is designed to provide NCI with broad external scientific and clinical input for the design and prioritization of phase I and phase II trials with agents. IDSC membership has included principal investigators, representatives from the NCI Cooperative Groups, NCI staff members, and additional representatives as ad hoc members for consideration of specific agents.
- To facilitate rational clinical trials of therapies for advanced melanoma, researchers need improved access to new drugs and orphan drugs. Testing of combinations of drugs from multiple sources, including pharmaceutical companies and academia, will accelerate progress in melanoma research. This is currently hindered by legal liability and intellectual property issues. Regulatory support, and the additional funding required, should be provided to facilitate access to promising drugs for preclinical and clinical studies relevant to melanoma, even if their application is limited to this disease, in order to address legal and IP issues. Drug companies should be indemnified against the risks of allowing their drugs to be combined in innovative strategies to encourage participation in melanoma clinical trials.
- Lost-opportunity drugs should be identified, and funds should be devoted to production, validation, and quality control for drugs that private industry is unwilling or unable to develop due to the perception that the market is limited. This is particularly relevant when the investigational agent is not expected to have single agent activity, but could be essential as an adjuvant to a vaccine or supplement one of the important, existing immunologic approaches in melanoma.
- The melanoma research community needs dedicated support for the efficient study of scientific opportunities within timelines expected in the more common tumors. Funding for innovative new trials, especially those using agents from CTEP or prepared by the RAID program, should be increased. This can be accomplished by leveraging existing programs and creating partnerships.

- Biological discoveries in trials of patients with advanced disease may inform the research in premalignant and early-stage disease, as well as predict which patients will respond to immunologic therapies such as interleukin, interferon, T-cell antibodies, or other signaling pathways. The government has a unique opportunity to stimulate scientific research simultaneously with federally-supported treatment trials. Funding should be designated for bench-to-bedside translational research through those clinical trials that have the greatest potential to improve melanoma survival.
- A high-priority should be to enhance infrastructure that supports clinical trials in rare diseases. Rare diseases require a focused national accrual effort for early drug development trials in addition to large, randomized Phase III trials. Single-institution funding is not sufficient to coordinate a national infrastructure. Existing structures such as the NCI Cancer Trials Support Unit (CTSU) could provide regulatory coordination and access on a national scale for Phase II trials, allowing the pace of scientific inquiry to approach that of trials in common tumors.

Action Steps for Implementing Cross-Cutting, Resource-Building Initiatives

1. Enhance Prevention, Early Detection, and Treatment Research

- Melanoma researchers need biomarkers for prediction of aggressiveness and response that will focus the application of new therapies on patients most likely to respond. Comprehensive genetic/molecular definition of *in vitro* melanoma models, together with selected drug sensitivity and other functional studies, may enable robust preclinical identification of biomarkers linked to therapeutic response.
- Special attention should be given to testing and validating biomarkers that can serve as adjunctive diagnostic methods to identify ambiguous lesions with poor outcomes and small tumors with aggressive behavior.
- Research on therapeutic targets should adopt a systems approach to studying the complexity of melanoma biological systems through comprehensive analysis of multiple targets that interact to sustain melanoma viability.
- Accrual of significant numbers of patients into clinical trials should be facilitated and clinical trials based on continuous evaluation and curation of preclinical results prioritized.

2. Promote Sharing of Melanoma Biospecimens, Research Data, Cell Lines, and Animal Models

- Blood and tissue specimens with clinical annotations should be collected from melanoma research centers, as well as nonacademic hospitals, SEER registries, and large, high-quality commercial and public-sector pathology laboratories. Blood samples should provide germline DNA for the study of genetic susceptibility to melanoma, and tissue samples should be used to construct annotated tissue microarrays. These samples would be made available to researchers through a Web-based portal.

- Standardized research tools, including consent forms and transfer agreements for sharing tissue samples should be developed; resource and data sharing, including biospecimens should be coordinated; and legal issues should be addressed.
- Best practices and standardization for tissue sample collection and annotation to promote high-quality, harmonized collections should be developed.
- Hospitals should be offered technical assistance in developing blood and tissue sample collection procedures and addressing institutional review board (IRB) concerns.
- Mechanisms are needed to educate patients about their right to release their biospecimens for use in research and the importance of making these samples available to scientists for developing improved melanoma therapies.
- Policy changes may be needed to avoid state-by-state variations in the definition of biospecimen ownership and rules governing use of samples in research.
- Non-government members of the melanoma research community should encourage the creation of a mechanism to reimburse physicians for biospecimen collection at diagnosis. This mechanism should be accompanied by quality standards. One option could be new Current Procedural Terminology (CPT) codes to allow billing for specimens to be accessioned into a federally supported, research-based archive/bank.
- A Web-based portal for data sharing should be created, and aggregation of data would expedite data mining and triangulation. The NCI Cancer Biomedical Informatics Grid (caBIG) project should be explored to provide infrastructure for the proposed data portal.
- Preliminary steps in developing shared cell culture systems for use by melanoma researchers should include identifying experts in generating cell lines, creating lists of cells representative of certain tumors, and identifying large collections that are annotated to some degree.
- Preliminary steps in developing shared animal systems should include identifying experts who have developed animal models for melanoma research, ensuring that as many melanoma models as possible are added to the Mouse Models of Human Cancers Consortium (MMHCC) repository, conducting a comparison of models to determine which are most comparable to humans, exploring the potential of grafting models, and sharing tools used to build models.
- The lack of access to imaging resources to support melanoma research should be addressed by establishing centralized imaging facilities or creating a mechanism to support decentralized imaging through reimbursable fees.

3. Create a Critical Mass of Researchers in Melanoma

- The American Association for Cancer Research and the American Society of Clinical Oncology should be encouraged to increase their support for melanoma research and professional education.

- Collaborative efforts should be encouraged in the melanoma research community to coordinate resource sharing and encourage infrastructure building.
- A contract mechanism should be used to establish a national melanoma training program for junior investigators.
- Dermatologists should be engaged in melanoma education through collaborative efforts between the NCI and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.
- Foundations should be encouraged to provide pre- and postdoctoral training grants.
- Opportunities to obtain multidisciplinary training in melanoma should be increased for doctoral and post-doctoral scientists.
- Facilities for cross-training of researchers should be established. Training of scientists and physicians should overlap to encourage translational activities.
- Senior researchers should be encouraged to mentor new researchers through incentive programs.
- Grants using the T32 funding mechanism should be used to support collaborative training among multiple extramural institutions.

Current Infrastructure that Supports the Melanoma Research Agenda

This Strategic Plan is by no means an inclusive survey of research and resources needed to advance progress in melanoma research; rather, it is meant to stress the most obvious areas that could benefit from further research.

NCI continues to invest in melanoma research. Examples of programs that are relevant include:

- Four skin cancer-specific Specialized Programs of Research Excellence (SPOREs), which are identifying new biologic treatments for melanoma, identifying the genes that regulate the body's immune response to melanoma, and identifying markers of high-risk melanoma.
- The Cancer Therapy Evaluation Program (CTEP) which has established the Translational Research Initiative to fund correlative studies performed during the conduct of sponsored clinical trials of CTEP Investigational New Drug (IND) agents. CTEP staff provide expertise on translational review committees for studies involving investigational agents that may be of interest to melanoma researchers.
- Intramural research at NCI which is focusing on new methods of gene therapy that can alter immune cells for treatment of advanced melanoma. Additional research at NCI which has resulted in new risk prediction models, such as the risk assessment tool which help estimate the 5-year absolute risk of melanoma and identify at risk individuals.

- Collaborations between NCI and other Institutes and Centers at NIH are helping identify the molecular pathways that result in malignant transformation of melanocytes into melanoma cells and the spread of melanoma; this should facilitate the design of better methods for identifying the disease in its earliest stages as well as the design of better therapeutic interventions.
- The Mouse Models of Human Cancer Consortium (MMHCC), which is developing a collection of mouse models that mimic human skin cancers, including malignant melanoma.
- The Specimen Resource Locator, a database that helps researchers locate human specimens (e.g., tissue, serum, and DNA/RNA) for cancer research. It includes data on normal, benign, precancerous, and cancerous human tissue from a variety of organs, including skin.
- The Tumor Microarray Research Program (TARP), which has collected samples of melanoma and metastatic lesions to construct multitumor tissue microarrays for studying the expression of genes and proteins.
- The Clinical, Laboratory, and Epidemiologic Characterization of Individuals and Families at High Risk of Melanoma Study, which is determining how genetic and environmental factors contribute to melanoma development.
- The translational activities for melanoma in the SPOREs include the development of novel therapeutics (predominantly immunotherapies), characterization of risk and prognostic biomarkers, as well as the utilization of novel animal and cell culture models to test therapeutic or preventative agents.

The melanoma research community is committed to leveraging federal research support through partnerships with the private sector and the advocacy community to increase community-based collaborative efforts to address the research and resource priorities outlined in this strategic plan.

Members of the Expert Panel That Developed the Strategic Action Plan for Melanoma Research

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