

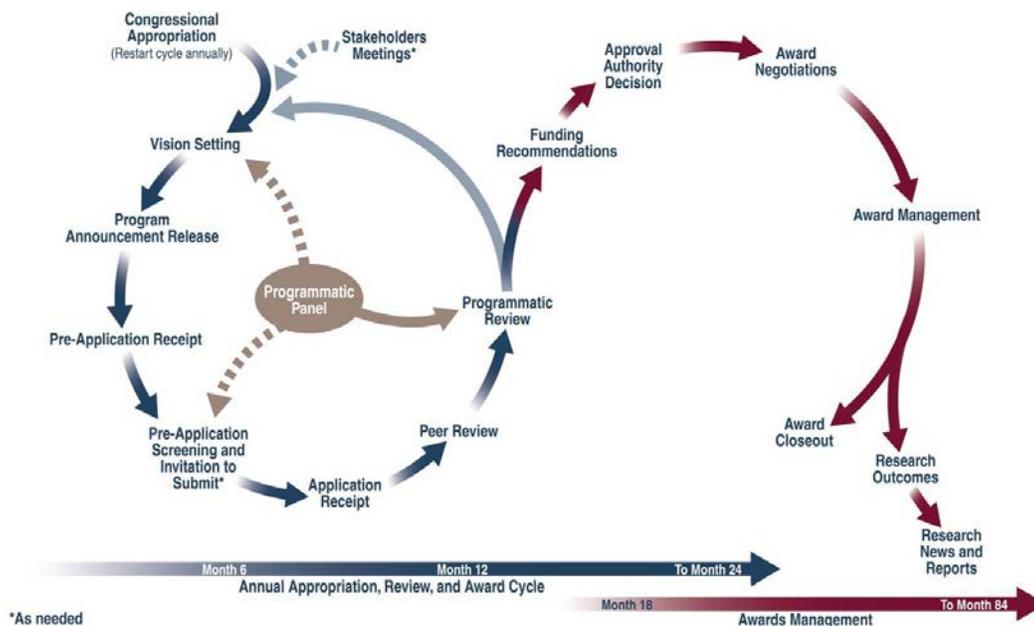
**FISCAL YEAR 2019
MELANOMA RESEARCH PROGRAM
STAKEHOLDERS MEETING
Summary
March 2019**

Background

The Defense Health Agency J9, Research and Development Directorate manages the Defense Health Program Research, Development, Test, and Evaluation appropriations, including funds for seven Congressionally-directed cancer research programs assigned to the United States Army Medical Research and Development Command Congressionally Directed Medical Research Programs (CDMRP) for management. Since its first appropriation of congressional funding in FY92, CDMRP has been responsible for managing more than \$14 billion (B) in appropriations. The CDMRP implements the investment of congressionally directed dollars provided to fund groundbreaking, high impact, meritorious research that targets critical knowledge and product gaps for military health. In addition, the CDMRP provides support for the management of core dollars (presidential budget) directed in both intramural and extramural military medical research portfolio areas.

The CDMRP uses a two-tier model¹ based on recommendations from the Institute of Medicine (now the National Academy of Medicine) to ensure that program’s research portfolio contains the most meritorious science and programmatically relevant research (Figure 1). The first tier, scientific peer review, is conducted by an external panel of scientists, clinicians, military members, and consumers (patient advocates). Each application is reviewed with respect to the criteria outlined in the program announcement and scored on scientific and technical merit. The second tier, programmatic review, includes experts in the field to assess applications based on peer-review summary statements to ensure a balanced portfolio that aligns with the Congressional language. Proposals that meet the program’s interest and goals are recommended for funding by the Programmatic Panel. Once approval is received by the Commanding General, awards are made in the form of 1- to 4-year grants.

Figure 1. CDMRP Annual Program Cycle



¹ Strategies for Managing the Breast Cancer Program: A Report to the U.S. Army Medical Research and Development Command, 1993

Introduction to the Melanoma Research Program

According to the National Cancer Institute, there were 91,270 new cases of melanoma diagnosed in the United States (U.S.) during 2018. Melanoma cases have been increasing steadily over the last 40 years. It is the fifth most common type of cancer in the United States, representing 5.3% of all new cancer diagnoses every year. Melanoma is of particular interest to the U.S. military because active duty Service members spend prolonged periods outside, especially during deployment. Among military personnel, the greatest incidence rates are in the Air Force, Navy, and the Marines.² Since 2009, the CDMRP has funded melanoma research through the Peer Reviewed Cancer Research Program (PRCRP). From fiscal year 2009 (FY09) through FY18,³ PRCRP invested \$52.5 million (M) in melanoma research. With the knowledge that melanoma is an increasing concern for active duty Service members and Veterans, the U.S. Congress encouraged the DoD to continue its investments in melanoma research and established the Melanoma Research Program (MRP) with an appropriation of \$10M (FY19 SAC-D Report 115-290 28 June 2018). With this new program, MRP will continue to invest in research focusing on the prevention, detection, diagnosis, and treatment of melanoma for the benefit of Service members, Veterans, their families, and the American public.

Meeting Objectives

Purpose

The Stakeholders meeting is a forum for an open dialogue among experts (clinicians, researchers, lay persons affected by melanoma, and active duty Service members) to identify critical issues facing melanoma research and patient treatment, as well as to acknowledge the underfunded, understudied areas of research and patient care in the field of melanoma.

Stakeholder Participants

Representatives from melanoma non-profit organizations, lay persons with the disease, academia, and Government institutions are invited to share broad perspectives on which initiatives have the greatest potential to propel the science forward, break down potential barriers in research and patient outcomes, address key knowledge or scientific gaps, and identify potential approaches for the treatment of melanoma.

Key Activities

- State of the Science Panel Discussion
- Point and CounterPoint Discussion
- Discussion of Strategic Blueprint to identify program goals and measures of success

² Zhu J, Enewold L, Zahm S, et al. 2011. Melanoma incidence rates among whites in the U.S. military. *Cancer Epidemiol Biomarkers Prev.* 20(2):318-323.

³ The awards recommended for funding by the FY18 PRCRP Programmatic Panel in the Melanoma and Other Skin Cancer topic area are under negotiation, which may result in a change in the PRCRP's total investment.

Outcomes

- A summary of capability gaps, refinement of the state of the science in melanoma, identification of potential challenges, and strategic blueprint for success.
- Input from the Stakeholders meeting will be used by the FY19 MRP Programmatic Panel to recommend the overall FY19 MRP goals, priorities, and Focus Areas.

FY19 MRP Stakeholders

Dr. Ravi Amaravadi	University of Pennsylvania
Dr. Andrew Aplin	Thomas Jefferson University
Dr. Richard Carvajal	Columbia University Medical Center
Dr. Clara Curiel	University of Arizona
Dr. Michael Davies	M.D. Anderson Cancer Center, University of Texas
Ms. Ellen Davis	Melanoma Research Alliance
Dr. Keith Flaherty	Massachusetts General Hospital
Dr. Sacha Gnjatic	Icahn School of Medicine at Mount Sinai
Ms. Samantha Guild	AIM At Melanoma Foundation
Dr. Hensin Tsao	Massachusetts General Hospital
Dr. Eva Hernando-Monge	New York University School of Medicine
Dr. Thomas Hornyak	VA Medical Center, Baltimore, Maryland
Mr. Michael Kaplan	Melanoma Research Alliance
Dr. Nikhil Khushalani	Moffitt Cancer Center
Dr. John Kirkwood	University of Pittsburgh Medical Center
Dr. Kyleigh Lipira	Melanoma Research Foundation
Dr. Jianrong Lu	University of Florida
Dr. Alison Martin	Melanoma Research Foundation
Dr. Glenn Merlino	National Cancer Institute
Dr. Kristen Mueller	Melanoma Research Alliance
Dr. Sapna Patel	M.D. Anderson Cancer Center, University of Texas
Dr. Ze'ev Ronai	Sanford Burnham Prebys Medical Discovery Institute
Mr. Steven Silverstein	Melanoma Research Foundation
Dr. Jeffrey Sosman	Northwestern University
CDR Heather Tracy	Naval Medical Center San Diego
Dr. Margaret Tucker	National Cancer Institute
Ms. Vicki Walker	Melanoma Research Foundation
Dr. M. Raza Zaidi	Temple University
LCDR Karen Zeman	Walter Reed National Military Medical Center
Dr. Kangmin Zhu	Uniformed Services University of the Health Sciences

FY19 MRP Programmatic Panel

FY19 Panel Member / Organization	Area(s) of Expertise
John Kirkwood, M.D. (Chair) University of Pittsburgh Medical Center	Immunobiology, Therapy, and Prevention
Ellen Davis Melanoma Research Alliance	Patient Advocate
Keith Flaherty, M.D. Harvard University, Massachusetts General Hospital	Development of Therapeutics, Targeted Therapies
Valerie Guild AIM at Melanoma	Patient Advocate
Sapna Patel, M.D. MD Anderson Cancer Center, University of Texas	Uveal Melanoma
Ze'ev Ronai, Ph.D. Sanford Burnham Prebys Medical Discovery Institute, La Jolla	Regulation of Cellular Function
Steven Silverstein Melanoma Research Foundation	Patient Advocate
CDR Heather Tracy, M.D. Naval Medical Center San Diego	Immunotherapy
Margaret Tucker, M.D. National Cancer Institute	Etiology, Familial Cancers, Genetics
Ashani Weeraratna, Ph.D. Wistar Institute	WNT Signaling, Molecular Mechanisms of Melanoma Metastasis
M. Raza Zaidi, Ph.D. Lewis Katz School of Medicine, Temple University	Molecular Mechanisms of UV Radiation-Induced Melanomagenesis
LCDR Karen Zeman, M.D. Walter Reed National Military Medical Center	Hematology/Oncology

Summary of State of Science Presentations

Presenter: Glen Merlino, Ph.D., National Cancer Institute

Dr. Merlino presented an overview of National Cancer Institute's (NCI) intramural melanoma research and extramural melanoma research funding. The extramural melanoma portfolio has remained relatively stable over the last 6 years, funding basic, translational, and applied research. Dr. Merlino presented high impact outcomes funded by NCI in the areas of immunotherapy, microbiome, the tumor microenvironment, and therapeutic advances. Within the NCI, Dr. Steven Rosenberg has been successful in treating melanoma using adoptive T cell transfer. Lastly, Dr. Merlino presented data on his pre-clinical mouse models for studying response to immune checkpoint inhibitors.

Presenter: Kyleigh LiPira, CEO, Melanoma Research Foundation

The Melanoma Research Foundation (MRF) is an advocacy organization that is focused on melanoma research, education, and advocacy. Ms. LiPira focused her presentation on MRF's research portfolio, which funds early career investigators (medical students, postdoctoral fellows, and research associates), established investigators, and collaborations. The majority of their funded research is in the area of treatment (66%), followed by diagnosis (19%) and prevention (15%). In 2010, the MRF launched the MRF Breakthrough Consortium, which established 20 centers of research excellence to support greater collaboration in melanoma translational research. In 2016, MRF convened melanoma experts to draft "The State of Melanoma: Challenges and Opportunities."⁴ With regards to rare melanoma subtypes, the Community United for Research and Education of Ocular Melanoma (CUREOM) was created in 2011 to promote awareness, education, and research for ocular melanoma.

Presenter: Michael Kaplan, Melanoma Research Alliance

The Melanoma Research Alliance (MRA) is a non-profit component of the Milken Institute which aims to accelerate research, advance cures, and prevent melanoma. MRA has grant mechanisms for young investigators, established investigators, "high risk, high reward" research, and team research. Their research portfolio is largely in the area of treatment (91.5%), followed by diagnosis (4.5%) and prevention (4.0%). The organization also focuses on funding rare melanoma subtypes (acral, uveal, and mucosal). Recently, MRA has supported special initiatives in the areas of checkpoint immunotherapy adverse events, metastases, and artificial intelligence. Mr. Kaplan ended his presentation with a discussion on gaps in melanoma research, which include prevention, epidemiological studies, treatment of brain metastases, neoadjuvants, and difficult to treat subtypes (failed therapies, rare melanomas, acquired resistance).

Presenter: Samantha Guild, AIM at Melanoma Foundation

Ms. Guild began her presentation by stating that AIM is different from other organizations, in that they build infrastructure rather than fund individual researchers. AIM designs, manages, and funds research initiatives that accelerate the development of effective therapies. To obtain this objective, AIM has initiated the International Melanoma Working Group (IMWG), the Melanoma International

⁴ Merlino G, Herlyn M, Fisher DE, et al. 2016. The state of melanoma: Challenges and opportunities. *Pigment Cell Melanoma Res.* 29(4): 404-416.

Collaboration for Adaptive Trials (MICAT), and the International Melanoma Tissue Bank Consortium (IMTBC). IMWG was established in 2006 and initiated MICAT and IMTBC. MICAT aims to establish a global clinical trial to bring melanoma therapeutics to market faster. IMTBC is the first collaborative melanoma tissue bank consortium and is comprised of six institutions. The consortium will provide fresh-frozen primary tissue samples and corresponding patient data for research. Scientists from anywhere in the world can apply to obtain tissue, and access is granted through a peer-review process.

Presenter: LCDR Karen Zeman, M.D., Melanoma in the Military

LCDR Zeman is an oncologist at Walter Reed National Military Medical Center. Cancer diagnoses increasingly impact mission readiness. From 2005 through 2014, melanoma was the most frequent cancer diagnosis in the active duty population.⁵ There are multiple reasons for an increased rate of melanoma, including inadequate sunscreen access, insufficient emphasis on sun protections, and prioritizing immediate safety concerns over preventative care. Active duty Service members are also exposed to significant risk factors for melanoma, such as high rates of intense UV exposure, exposure to chemicals associated with melanoma (polychlorinated biphenyls), and exposure to jet exhaust and ionizing radiation. As a result, they have higher rates of skin cancer compared to civilians, but report low rates of skin cancer awareness and dermatologic care.

⁵ Lee T, Williams V, and Clark L. 2016. Incident diagnoses of cancers in the active component and cancer-related deaths in the active and reserve components, U.S. Armed Forces, 2005-2014. *Medical Surveillance Monthly Report* 23(7): 23-31.

Summary of Point/Counterpoint Discussion

In late 2018, a State of the Science survey was sent out to over 200 melanoma scientists and advocates. These survey results were used to generate discussion in the form of point/counterpoint topics. Four main topics were discussed: basic research, immunotherapy, prevention and early detection, and resource development. Stakeholders commented on the advantages and disadvantages of MRP focusing on each of the topics for FY19. The panel members converged on the idea of focusing on one main theme and addressing it from all angles. The panel continued to express interest in funding ideas that have been historically underfunded, such a dormancy, prevention, and relapse.

Basic Research

- Program should balance between basic and translational research.
- Basic research should rely on clinical samples.
- Critical questions are related to prevention and diagnosis, to help patients before melanoma starts to develop.
- Identify the most important biological questions and address it from every angle.

Prevention and Early Detection

- Essential to develop early detection biomarkers.
- There is a knowledge gap in understanding how UV exposure actually causes melanocytes to develop into cancer.
- Technology applications for early detection to get to dermatologist earlier.

Immunotherapy

- Understanding of cell death and how it changes the tumor and microenvironment.
- Better understanding of alternative checkpoints.
- Better models for basic research to understand the immune system.
- Research into the endoplasmic reticulum stress response and autophagy are not well funded, with no drugs in the clinic to target these pathways.

Resource Development

- Department of Defense should promote collaborations between institutions.
- Leverage existing samples.
- Focus on what can be done to get tangible results in regards to the military.
- Databases can be pictures, not just tissue.
- Want to fund research into rare subtypes of melanoma.

Strategic Blueprint

Stakeholders were also tasked with drafting a strategic blueprint by identifying short-, mid-, and long-term goals for MRP. A number of potential themes were identified, including melanomagenesis, prevention and early detection, predictive markers, cell death, discovering new targets, metabolism, tumor microenvironment, toxicity of therapeutics, and predicting relapse. Stakeholders also suggested investing in technology development and infrastructure, utilizing biorepositories of tissues and clinical information, and leveraging DoD/VA databases. Potential measures of success for the MRP program include (1) increasing patient survival; (2) decreasing melanoma mortality for Service members; (3) increasing understanding of the disease; (4) supporting paradigm-changing research; (5) developing new treatments; (6) expanding the meaning of “prevention;” and (7) empowering the patient population.

Short Term
<ul style="list-style-type: none">• Identification/validation of new clinical markers (prevention, metastasis, etc.)• Identification/validation of new therapeutic strategies• Build upon established/new collaborations (i.e., team science, networks)• Liquid biopsy
Mid Term
<ul style="list-style-type: none">• Identify/stratify patient populations• Mechanistic understanding of immunotherapies• Lowering the social barriers to early detection (i.e., telehealth networks, improved diagnostic tools)
Long Term
<ul style="list-style-type: none">• Focus on the military setting• Affect changes in behavior (i.e., sunscreen use, decreased sunbed use)• Clinical markers to inform therapeutic direction• Reduce the number of patients who require treatment through improvement of prevention/early detection