INTRODUCTION
The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas. In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine was assembled to evaluate the CDMRP’s two-tier review process and its coordination of research priorities with the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). As part of their final report, the committee recommended that each CDMRP program “… develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3–5 years into the future,” and that these strategic plans “should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives.”

In response to these recommendations, this document presents the current strategy for the CDMRP’s Melanoma Research Program (MRP). The MRP Strategic Plan identifies the high-impact research goals that are most important to its stakeholders while providing a framework that is adaptable to changes in the medical research environment. This plan has been formulated to provide greater clarity of the program’s goals over time to the public and other stakeholders. Funding for the MRP is Congressionally appropriated on an annual basis; therefore, there is no guarantee of future funding. The MRP Strategic Plan will be reviewed during the program’s annual Vision Setting meeting and updated as necessary.

MRP BACKGROUND AND OVERVIEW
The American Cancer Society estimates that 96,480 new melanoma cases will be diagnosed in 2019, with about 7,230 people expected to die from their disease. 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 since active duty Service members spend prolonged periods outside, especially during deployment. Recent studies suggest that exposure to high levels of solar radiation in young adulthood is associated with a higher risk of melanoma mortality. Melanoma diagnoses are increasing among active duty Service members, with the greatest incidence rates in the U.S. Air Force, Navy, and Marines.

In response to the rising concerns about melanoma diagnoses, the U.S. Congress established the Melanoma Research Program (MRP) with an appropriation of $10 million (M).

VISION: Prevent melanoma initiation and progression

MISSION: Earlier intervention to enhance mission readiness for U.S. military personnel and to diminish the disease burden on Service members, Veterans, and the American public

FUNDING HISTORY
Melanoma and other skin cancers (MOSC) research has been funded by the CDMRP for a decade through the Peer Reviewed Cancer Research Program (PRCRP) (Figure 1).

From fiscal years 2009 through 2018 (FY09-FY18), the PRCRP invested $52.5M in melanoma research, representing 17% of total research dollars invested (Figure 2). The PRCRP funded a broad range of different research types from detection and diagnosis to treatment.
RESEARCH PORTFOLIO (PRCRP)
The MOSC portfolio within the PRCRP has been evaluated using the Cancer Care Spectrum (CCS), where studies are categorized according to anticipated long- or short-term clinical relevance. The CCS classifies projects into six major research areas (biology/etiology, prevention, detection and diagnosis, prognosis, treatment, and survivorship). This method analyzes a portfolio from basic research to more advanced research, with patient and clinical anticipated outcomes as the endpoint. Even the most basic biology/etiology studies should have a long-term goal that is relevant to patient care and impact. In Figure 3, the FY09-FY18 PRCRP investment CCS portfolio for MOSC focused heavily on the development of new treatments and testing of established therapies. The PRCRP portfolio also showed a strong investment in more basic studies, such as biology/etiology, as well as investment in new areas for melanoma detection and diagnosis.

RESEARCH ACCOMPLISHMENTS (PRCRP)
Multiple melanoma projects funded by the PRCRP have been successful and either have had their results translated toward clinical applicability or have contributed toward the advancement of understanding melanoma. Examples include the following:

- Mesenchymal stem cells loaded with oncolytic herpes simplex virus target metastatic brain lesions and significantly extend survival in mouse models of metastatic melanoma.
- Anti-RANKL antibody (denosumab) has a synergistic effect on the checkpoint inhibitors, anti-CTLA4 and anti-PD1, decreasing tumor growth and prolonging survival. The results of this project informed the development of a Phase II clinical trial in melanoma patients using anti-RANKL in combination with anti-PD1 immunotherapy.
- The histone methyltransferase DOT1L functions as a tumor suppressor and repairs ultraviolet (UV) radiation-induced DNA damage in melanocytes. Loss of DOT1L in combination with BRAF mutations makes melanocytes more susceptible to melanoma development.

STATE OF THE SCIENCE
A comprehensive review of the state of the science in melanoma research was published in 2016 after a broad evaluation of the field initiated by the Melanoma Research Foundation (MRF). Over the past decade, the field of melanoma research has expanded, growing rapidly and leading the way in treatment areas such as immunotherapy and kinase inhibitors. Understanding of melanomagenesis as
a multi-step process that initiates from normal melanocytes to the benign and dysplastic nevus, then to the development of primary melanoma, and finally to metastasis has been critical to clinical progress. Normal cellular processes are disrupted during melanoma pathogenesis. Initiation events pinned to UV radiation exposure have been the focus of mainstream prevention methods.

With cutaneous melanoma, UV radiation may be the direct culprit causing genetic mutations in the melanocytes of the skin. An individual’s genetic background, however, may influence outcomes.³

The genetic heritage of an individual will influence how well melanocytes may be able to defend against the mutations induced by UV radiation (e.g., tanning). Evidence, however, points to UV radiation-independent melanomagenesis due to the occurrence of melanomas in locations with no sun exposure. The development of these rare subtypes (acral, mucosal, and uveal) may be linked to types of melanin, not UV radiation. In a study funded by the PRCRP, Premi et al.⁴ showed that the type of melanin an individual produces may increase the possibility of DNA damage in melanocytes without UV radiation exposure. Chemiexcitation as the pathway toward melanoma pathogenesis represents a paradigm shift in understanding of this disease.⁵ Therefore, the process of melanomagenesis is complex and depends on genetic risk factors such as skin type, epigenetic expression, and other factors.

In their review of the state of melanoma research, Merlino et al.² found four major areas for the future of melanoma research. Under these research areas, both challenges and opportunities exist.

### PREVENTION

The role of prevention in skin cancer has been a signature of clinical care. Although the direct causative role of UV radiation has been more difficult to define in melanomagenesis, sunscreen and prevention remain the fulcrum of preventive care. It has been reported that, from 2005 through 2014, melanoma was the most frequent cancer diagnosis in the active duty Service member population.⁶ Genetics, epigenetics, and behavioral studies are all needed to further the field and successfully implement safe, effective, and behavioral-compliant prevention for cutaneous presented melanoma. Prevention of rare subtypes of melanoma is still in its infancy.

### DETECTION AND DIAGNOSIS

As the largest organ of the body, the skin presents a unique problem with monitoring for potential changes. Not all lesions are the same; some benign nevi will never develop into primary melanoma. Identification of precursor lesions in an easily scannable way is paramount to the long-term success of preventive care. An improvement on staging of melanoma would assist in treating this disease. Diagnostic accuracy throughout the stages of melanoma (Figure 4), with identifiable biomarkers that discriminate the difference between neoplasic and dysplastic nevi, etc., are imperative to improving patient treatment plans and outcomes. Clear phenotypic and genotypic stratification markers would inform both future research investigations and clinical choices. The current system (ABCDE [Asymmetry, Border, Color, Diameter, and Evolution])⁷ is a visual guide lacking any genetic or epigenetic information. Thus, the information gathered by the ABCDE offers only superficial data at best and is somewhat clinically archaic.

### DORMANCY AND EARLY METASTASIS

Tumor dormancy has been recognized by the cancer field for over 50 years. Current theories regarding the process of dormancy and “wakefulness” by metastatic cells depend on different causative events that are not mutually exclusive, but may act independently.⁸
These causative events are (1) angiogenic dormancy may influence the activity of the cancer cells through the vasculature or the interaction of the angiogenic characteristics of the cells and the microenvironment (including the vasculature and the stroma); (2) immuno-mediated dormancy regulates cancer cell growth through mechanisms that control immune response, including the balance of innate and adaptive immunity; and (3) cellular dormancy, where the melanoma cells are in a state of quiescence and are not actively proliferating. Each of these are interlinked and vary the response of the other two. Prevention of dormancy or stasis may increase the ability to reduce long-term recurrence due to metastatic lesions escaping the initial treatments.

**THERAPEUTICS**

The first use of an immune system agent to treat melanoma was IL2 therapy. The side effects were harsh and required in-patient care during treatment. While it showed some promise, it was not to be the long-term answer to melanoma treatment. Over the past decade, advances in the understanding of genetic drivers in melanoma development (Figure 4) opened up opportunities for experimental therapeutics. Specific mutations such as NRAS and BRAF were identified, along with epigenetic changes that cause benign to malignant changes. This progress led the way toward the development of new therapies beyond dacarbazine and IL2. Between 2010 and 2015, 10 new treatments were approved by the Food and Drug Administration (FDA) for patients with metastatic melanoma. Current FDA-approved monotherapies for melanoma include inhibition of CTLA-4, BRAK, MEK, and PD-1, as well as talimogene laherparepvec (TVEC). Crucial questions still remain, like what is the best treatment for each patient. Personalized medicine is still in its earliest stages for melanoma treatment. Acquired resistance is a prominent hurdle in treatment. Combination therapies, along with personalized medicine, offer a new avenue and hope for patients that have recurring melanoma or resistance to or non-response to treatment.²⁹

**RESEARCH FUNDING LANDSCAPE**

In 2019, the MRP held a Stakeholders meeting for the purpose of identifying the state of the science and acknowledging the gaps in research and patient care. The final outcome of that meeting is published online.¹⁰ Presenters from the PRCRP (Emilee Senkevitch, Ph.D.); National Cancer Institute (NCI) (Glen Merlino, Ph.D.); MRF (Ms. Kyleigh LiPira); Melanoma Research Alliance (MRA) (Mr. Michael Kaplan); AIM at Melanoma Foundation (Ms. Samantha Guild); and U.S. Navy (LCDR Karen Zeman) gave an overview of the state of research funding.
In brief, Drs. Senkevitch and Merlino summarized the highlights of investments by the PRCRP and NCI. In Figure 5, the FY09-FY18 PRCRP investment portfolio in melanoma studies is compared to the extramural investments by the NIH/NCI. In addition to comparing the PRCRP portfolio to the NIH/NCI investment, Figure 5 also shows non-Federal investment into melanoma research including MRF and MRA. AIM at Melanoma Foundation investment is not included but reviewed below.

During the Stakeholders Meeting, each representative of the different melanoma focused organizations briefed the participants on their goals and mission. The MRF’s scientific initiatives include the creation of resources, a focus on rare subtypes, and grant-making to support medical students, career development, established investigators, and team science. The MRA from 2007 through 2018 has awarded over $100M for scientific initiatives, including funding early and established investigators, team science, and pilot studies, as well as industrial partnerships. In addition, the MRA has special initiatives with the American Cancer Society. Awards for FY19-FY20 will focus on metastases. With the focus of a working group, the AIM at Melanoma Foundation has two major research initiatives: the International Melanoma Tissue Bank Consortium and the Melanoma International Collaboration for Adoptive Trials. LCDR Zeman offered a brief on melanoma incidence in the military (see the following section).

THE MILITARY AND MELANOMA

LCDR Karen Zeman briefed the participants on the incidence of melanoma in the military and issues with overall skin protection behavior and exposures (https://cdmrp.army.mil/mrp/pdfs/MRP%20stakeholder%20summary_2019.pdf). Cancer diagnoses increasingly impact mission readiness. From 2005 through 2014, melanoma was the most frequent cancer diagnosis in the active duty population.6 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 preventive care. Active duty Service members are also exposed to significant risk factors for melanoma, such as high rates of intense UV radiation 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.

STRATEGIC DIRECTION

The goal of the MRP is to prevent melanoma initiation and progression. The mission of the MRP is to support earlier intervention to enhance mission readiness for U.S. military personnel and to diminish the disease burden on Service members, Veterans, and the American public.

In FY19, the MRP challenged the research community to redefine the concept of prevention. The melanoma clinical, research, and patient communities traditionally view prevention as the use of sunscreen/blockers to protect the melanocyte from harmful UV radiation. While the traditional view of prevention is useful, the strategic direction of the MRP seeks to upend the definition and shift it to affect the entire disease process. As discussed above, melanomagenesis is a multi-step process. The new paradigm of prevention includes every step along the pathway toward melanomagenesis to stop the initiation of dysplasia, the progress to malignancy, and/or micro-metastases. The strategic direction of the MRP broadens the focus to prevention of the disease pathway (see Figure 4). To change the landscape, the research community must revolutionize the paradigm of prevention.

STRATEGIC GOALS AND PRIORITIES

The strategic goals and priorities set by the FY19 Stakeholders meeting and the FY19 Vision Setting meeting take into account the FY19 MRP challenge statement to the scientific community with a view toward the wider melanoma research landscape. In the short term, pushing the boundaries of the definition of prevention is a focal point of the MRP, but as the program grows and matures, the mid- and long-term goals reflect that development.
### Table 2: Strategic Blueprint

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<th>Short-Term</th>
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<tr>
<td>• Identification/validation of new clinical markers (prevention, metastasis, etc.)</td>
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<td>• Identification/validation of new therapeutic strategies (cure, prevent recurrence)</td>
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<tr>
<td>• Build upon established/new collaborations (i.e., team science, networks)</td>
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<tr>
<td>Mid-Term</td>
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<td>• Identify/stratify patient populations (personalized medicine)</td>
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<td>• Mechanistic understanding of immunotherapies</td>
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<td>• Lower the social barriers to early detection (i.e., telehealth networks, improved diagnostic tools, prevention through education)</td>
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<tr>
<td>Long-Term</td>
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<tr>
<td>• Reduce the number of patients who require treatment by improving prevention/early detection, with a focus on the military setting</td>
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<tr>
<td>• Affect changes in behavior (i.e., sunscreen use, decreased sunbed use)</td>
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<td>• Clinical markers to inform therapeutic direction (prevent recurrence)</td>
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### INVESTMENT STRATEGY

For its inaugural year, the MRP developed the FY19 Challenge Statement to announce the intentions of the program. With a defined programmatic focus on shifting the definition of prevention to an overarching goal, the MRP seeks research that will implement this vision. The MRP required all FY19 applications to address at least one of the following Focus Areas:

- **Precursor Lesions, Melanomagenesis, Host Factors, and the Tumor Microenvironment** (e.g., melanoma instigators, UV exposure, other instigators)
- **Melanoma Primary Tumor Evolution** (e.g., dormancy, heterogeneity, metabolism, epigenetic dysregulation, cell death)
- **Therapeutic Prevention** (e.g., interruption of disease progression, recurrence)
- **Minimal Residual Disease** (e.g., chemoprevention, micro-metastasis)
- **Rare Melanomas** (e.g., uveal, acral, leptomeningeal disease, pediatric, adolescent and young adult, mucosal)

The MRP developed an investment strategy to reflect the vision and mission of the program, as well as to answer the needs of the research and patient communities. During each Vision Setting meeting, the Programmatic Panel will reassess the investment strategy, research landscape, and gaps in patient care to adjust and modify the funding opportunities to be offered.

- Research focused on innovation:
  - Idea Award
  - Concept Award
- Research focused on multidisciplinary studies and/or translation to the clinical
  - Team Science Award
  - Translational Research Award

### MEASURING PROGRESS

To measure progress toward the strategic goals and priorities and the FY19 Challenge Statement, the MRP will evaluate the utility of the investment strategy and the award mechanisms. These assessments will include monitoring the outcomes of funded applications (publications, patents, and presentations). Review of all applications received with respect to the applicants’ responses to the FY19 Challenge Statement and how they impact the research approach, innovation, and other key elements of the project will be performed. In addition all awards will have their research evaluated at the time of award to determine their knowledge readiness level (KRL). At the end of each award’s period of performance, the KRL will be measured again, and any progress in the research project and the state of the science will be noted. This will give the MRP an understanding of the program’s impact and the relevance of the strategic goals and priorities toward the program’s vision and mission.

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<th>Table 3: Investment Metric Goals for the MRP</th>
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<td>50% Funded portfolio invested in innovative research for the development of new approaches throughout the research spectrum</td>
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<tr>
<td>50% Funded portfolio investment in more advanced studies, including multidisciplinary team science and translational research</td>
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REFERENCES


