

2020 MRF Grant Awardees

The Melanoma Research Foundation (MRF) is committed to advancing research across the spectrum of melanoma- from prevention through diagnosis, staging and treatment. In 2020 (thus far), the MRF has awarded 19 research grants encompassing not only cutaneous melanoma, but also the rare melanoma types. Additional details of the 2020 grant awardees are noted below.

Cutaneous Melanoma Team Award



MRF Breakthrough Consortium Young Investigator Team Award to Advance the Field of Translational Immuno-Oncology (*generously funded through a grant by BMS*)



Principal Investigator: **Diwakar Davar, MD**

Mentor: Hassane Zarour, MD
University of Pittsburgh

Co-PI: Meghan Mooradian, MD; Massachusetts General Hospital
Mentor: Ryan Sullivan, MD

Co-PI: Julie Stein, MD; Johns Hopkins University
Mentor: Janis Taube, MD, MSc

Proposal Title

Integrative Analysis of Prognostic Factors to Neoadjuvant Nivolumab/ CMP-001 in Stage III B/C/D Melanoma

Description

Patients with lymph-node positive melanoma have a high risk of recurrence despite curative surgery. While adjuvant therapy given *after* surgery improves RFS and OS, ~25% of patients particularly those with bulky lymph-node disease, progress prior to commencing adjuvant therapy. Neoadjuvant immunotherapy with anti-PD-1 produces pathologic responses in 25-30% of patients and is well tolerated. While combinations of anti-PD-1 with anti-CTLA-4 produce even greater pathological response rates, this combination is



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associated with considerable side effects in >50% of treated patients. Combinations that improve upon the benefit seen with anti-PD-1 with minimal additional side effects are desirable.

Based upon the successes of anti-PD-1/CMP-001 in advanced melanoma, we launched a clinical trial studying CMP/nivo in high-risk resectable melanoma with promising results. In 20 treated patients, we have shown that the neoadjuvant CMP/nivo produces pathologic responses in approximately 70% of patients. The combination is well tolerated with low incidence of adverse events. Patients who experience major pathologic response have prolonged RFS. In this context, we propose a tri-institutional collaboration to analyze immunophenotypic, histopathologic and ctDNA biomarkers of response to this therapeutic modality.

Established Investigator Awards



Principal Investigator: Linda Malkas, PhD
Beckman Research Institute of the City of Hope

Proposal Title
Novel Target for Melanoma Therapeutic Development

Description

Melanoma is one of the fastest growing malignancies and accounts for 5.5% of all new cancer cases in the United States. Treatment options and prognosis of melanoma patients depend on the risk stratification. Survival is excellent in low risk groups and localized diseases often require simple surgery only. In fact, a very thin melanoma may be removed entirely during the biopsy and require no further treatment. In contrast, the metastatic melanoma is very difficult to treat. The current standard of care uses aggressive multi-regimen treatment, which could cause severe side effect. The 5-year survival rate for patients with metastatic melanoma is less than 25%. There is a significant unmet medical need for new therapies to improve the treatment outcomes of this aggressive cancer phenotype.

Proliferating cell nuclear antigen (PCNA) is a protein that helps regulate DNA synthesis and repair. It is an attractive molecular target to develop a drug to treat melanoma, because melanoma cancer cells depends on PCNA for growth and survival. While studying this protein, we discovered a cancer-associated isoform of PCNA (caPCNA) that is present in a broad range of cancer cells and tumor tissues (including melanoma), but not present in otherwise healthy cells. We tested a series of drugs designed by computer modeling and medicinal chemistry to target caPCNA and identified AOH1996, a potent inhibitor that selectively melanoma cells but causes no significant toxicity to a broad range of normal cells. The pharmacologic and therapeutic properties of AOH1996 are extremely favorable in animal studies. When orally given to mice, AOH1996 suppresses the growth of a broad range tumor types without causing any observable side effects, including weight loss.

Based on our communication with the US Food and Drug Administration (FDA), we are confident that we will readily meet the FDA's regulatory requirement for a new investigational drug (IND) filing. The information derived from this proposal will inform the design and implementation of the expected clinical trials. Specifically, our proposal will determine the effective dose range for clinical trials. It will also validate

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biomarker(s) in tumor cells that will enable us to select melanoma patients who are likely to respond to AOH1996 treatment. Based on its favorable therapeutic properties seen so far in our animal studies, AOH1996 is likely to lead to a novel class of drug and significantly improve treatment options and outcomes of patients with metastatic melanoma.



Principal Investigator: Thorsten Mempel, MD, PhD
Massachusetts General Hospital

Proposal Title

Converting Regulatory into Proinflammatory Anti-Tumor Effector T Cells

Description

The majority of cancer patients do not yet benefit from immunotherapy, including from immune checkpoint therapies that invigorate the patients' own immune systems to fight their tumors. In many cases the underlying reason is that tumors are not recognized strongly enough by the patients' immune systems and consequently, are only poorly infiltrated by anti-tumor effector T cells that could otherwise reject the tumor. In addition, so-called regulatory T cells (Treg) actively limit the anti-tumor activity of those effector T cells that manage to enter the tumor tissue. One approach to address this situation has been to deplete Treg. However, effective depletion of these cells may cause autoimmune disease, because Treg also prevent our immune system from turning against our healthy tissues.

We have discovered a method to selectively reprogram immunosuppressive Treg in tumor tissue, but not those in healthy tissues, and convert them from immuno-suppressive pro-tumor into inflammation-causing anti-tumor effector cells. Thereby, we are able to sensitize otherwise treatment-resistant mouse tumors to immune checkpoint therapy and cause their rejection. This finding suggests a potential new strategy to successfully treat many of those cancer patients who currently do not respond to immunotherapy. However, in order to develop this method for human therapy we will need to understand 1) why only Treg in tumor tissue are reprogrammed, 2) through what mechanism Treg are induced to produce inflammatory cytokines, and 3) if human Treg can be reprogrammed the same way as mouse Tregs. We propose to address these questions in this project.

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Principal Investigator: **Jeffrey Ravetch, MD, PhD**
The Rockefeller University

Proposal Title

Defining the Mechanisms of Resistance to Anti-CTLA4 Antibodies in the TME

Description

Over the past decade, harnessing the power of a patient's own immune system for the treatment of cancer has been a major medical breakthrough. By using drugs to block inhibitory signals on immune cells, these medicines help "release the brakes" allowing them to kill cancer cells. One of these drugs is an antibody directed against a protein called CTLA-4. So transformative to the care of patients with melanoma and other cancers, the investigators who initially described such pathways were recently awarded the Nobel Prize. While these therapies have been lifesaving for many, they still fail to benefit the majority of patients receiving them. The reason for this lack of activity in some remains poorly understood. We recently uncovered a mechanism of how this may happen, in that cancers develop another "checkpoint" preventing the activity of anti-CTLA-4 antibodies at the tumor site. This checkpoint, called FcyRIIB, becomes increased in tumors and limits the ability of anti-CTLA-4 antibodies to deplete an important cell type contributing to the suppression of anti-cancer immunity. These studies will investigate this pathway in pre-clinical models and patient specimens, with the goal of using this knowledge to translate improved anti-CTLA-4 antibodies into the clinic.

Career Development Awards



Principal Investigator: **Lawrence Kwong, PhD**
The University of Texas M.D. Anderson Cancer Center

Proposal Title

CXCL9 as an Immune Anti-Melanoma Therapy in Combination with BRAF Inhibition

Description

A major obstacle to even the best melanoma therapies is that in the majority of cases, the tumor never completely goes away. Even if a little bit remains, called the minimal residual disease, the tumor can eventually start growing again and be drug-resistant. Very little is known about how and why these particular cells manage to survive, so we have taken a comprehensive approach using mouse modeling, human

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patient samples, and sophisticated genetic analyses to identify what goes on in melanoma residual disease after BRAF inhibition (“BRAFi”). We discovered that a functionally critical immune response to BRAFi starts off strong, but then rapidly recedes, leaving behind the residual tumor cells that somehow evaded or suppressed the immune response. We computationally identified a protein, CXCL9, that decreases at the same time as the immune response and that is predicted to regulate it. Given its known function, we speculate that this “chemokine” primarily recruit T cells into the tumor to aid rejection of the cancer, and that loss of its expression in the tumor over time contributes to the tumor evading the subsequently decreased immune response. We therefore hypothesized that when CXCL9 is forced into the tumors, it would sustain the anti-cancer immune response to further attack the residual cells. Indeed, in a pilot study using our mouse models, we found that injecting CXCL9 into a mouse tumor undergoing BRAFi resulted in the majority of tumors being completely eradicated, and they did not regrow when therapy was stopped. In this proposal, we further explore CXCL9 therapeutically and mechanistically. First, we will develop a new method of CXCL9 delivery to tumors that should increase its stability: by encapsulating the CXCL9 in small “nanoparticles”, these will protect the protein from degradation long-term, while slowly releasing it into the tumor. This also simplifies the treatment, as these nanoparticles could theoretically be delivered once a week instead of needing daily administration. Second, we will ask which immune cells are recruited to the tumor by CXCL9, and then determine which of the immune cells are most important for carrying out the anti-tumor activity by systematically ablating them from the tumor. This knowledge will help future refinements of CXCL9 as an immunotherapy. The long-term goal of this proposal is to establish CXCL9 as a potential clinical therapy in combination with BRAFi, as a way to target minimal residual disease and prevent tumor relapse in patients.



Principal Investigator: Zachary Schug, PhD
The Wistar Institute

Proposal Title

Elucidating Metabolic Changes that Occur in Melanoma Brain Metastases

Description

Melanoma is the third most common malignancy to metastasize to the brain. It is estimated that at least 50% of patients with stage IV melanoma will develop brain metastases during the course of disease. There is now abundant evidence that some of the most common treatment options for non-resectable melanoma brain metastases, such as radiotherapy and targeted therapies, fail to confer complete responses in patients and offer little to no benefit for survival. A common reason for the failure of radiotherapy and anti-cancer drugs in patients with melanoma brain metastases is due to presence of therapy resistant cancer cells within the tumor. One of the driving forces that creates these resistant cell populations in the tumor is the constant state of stress that melanoma cells are exposed to in the tumor microenvironment. Melanoma cells must adapt to cope and survive these harsh and inhospitable conditions in the tumor. The consequence of this is the emergence of melanoma cells that are more aggressive and more resistant to treatment. In our proposal, we describe a metabolic pathway that supports cancer cell survival during these episodes of stress in the tumor. Indeed, the enzymes we propose to target are involved in supporting melanoma tumor growth and promoting the transition to a more aggressive and resistant state during stress. We propose that targeting these enzymes will help prevent metastasis to the brain and help to treat patients with existing melanoma brain metastases. Since melanoma brain metastases are currently associated with dismal survival rates, our studies have the potential to address a significant unmet clinical need. We expect

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the proposed studies to advance the translation of our findings to the clinic and help reduce melanoma brain metastasis disparities.



Principal Investigator: Shruthy Suresh, PhD
Memorial Sloan Kettering Cancer Center

Proposal Title

Identification of Metastatic Modulators through Zebrafish Modeling

Description

Melanomas arise from pigmented cells called melanocytes, typically in the skin. Melanomas can spread to distal parts of the body, through a process called metastasis. Metastasis is the primary cause of mortality in all cancers; melanomas have the highest propensity to metastasize to the brain, contributing to the poor prognosis. Although significant progress has been made in melanocyte biology, the factors influencing metastasis still remain largely unknown. The major cause of melanoma is due to ultra-violet radiation exposure, which causes a large number of mutations in melanocytes. Large-scale sequencing efforts have identified frequently occurring DNA mutations in melanoma, but this approach fails to distinguish between passenger mutations and mutations that actually drive the disease. The role of neighboring cells such as adipocytes or immune cells adds further complexity to understanding factors driving metastasis. For example, the White lab recently uncovered a novel role for adipocytes in driving melanoma. Thus, animal models with an intact immune system that faithfully recapitulate human melanoma are crucial to identify mechanisms regulating metastasis. Here, we propose to utilize the zebrafish to study melanoma. Zebrafish are easy to breed in large numbers and form melanomas histologically and genetically similar to human melanomas. The optically transparent zebrafish casper, developed in the White lab, allows for easy visualization of melanoma by fluorescence imaging. For example, we can image cancer cells at the single-cell level and track its fate within the animal. We collaborated with the Adams lab to at the Sanger Center to obtain data from the AVAST-M clinical trial, the largest adjuvant study in high-risk primary melanoma. In this study, 466 patients underwent sequencing of the primary tumor to generate high quality sequencing data. Extensive clinical details were collected such as pathological details on the primary tumors and importantly, whether the patient did or did not ultimately metastasize. We used this powerful dataset to ask whether the expression of certain genes might predict metastasis in general, or more specifically to the brain, which has led us to a list of 60 exciting candidate genes. Additionally, the White lab has developed a method called Transgene Electroporation in Adult Zebrafish (TEAZ) to model melanoma. In TEAZ, mutations are induced in melanocytes, similar to what occurs in human melanomas, using powerful CRISPR-Cas9 based genome editing, which results in aggressive melanoma. In this study, we propose to use TEAZ and CRISPR-Cas9 to delete candidate genes in zebrafish and monitor metastasis by fluorescence imaging. We will also assess if there are specific factors driving metastasis to the brain, which remains the most aggressive subtype of melanoma. We anticipate that this study will help identify new regulators of metastasis and pave the way for novel therapeutic targets in melanoma.

Medical Student Awards

Principal Investigator: Samantha Black (UT Southwestern Medical School)

Mentor: Keith Argenbright, MD



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Proposal Title: Improving Melanoma Screening Education for Primary Care Providers Serving Patients of Skin of Color

**Looney Legacy Foundation Medical Student Award*

Principal Investigator: **Umair Khan** (Eastern Virginia Medical School)

Mentor: Jerry Chipuk, PhD

Proposal Title: The Mitochondrial Unfolded Protein Response Predicts the Immune Landscape During Melanoma

**Looney Legacy Foundation Medical Student Award*

Principal Investigator: **Alexander Mathew** (University of Virginia School of Medicine)

Mentor: Richard Price, PhD

Proposal Title: Leveraging Focused Ultrasound to Sensitize Refractory Melanoma to Immunotherapy

**Randy Lomax Memorial Medical Student Award*

Principal Investigator: **Breanna Nguyen** (University of Pittsburgh School of Medicine)

Mentor: Daniel Kaplan, MD, PhD

Proposal Title: Examining the role of TGF β activating Integrins B6 and B8 in melanoma

**Michael Atkins, MD Medical Student Award*

Principal Investigator: **Brennan Olson** (Oregon Health and Science University)

Mentor: Daniel Marks, PhD

Proposal Title: The Neuroendocrine Role of Lipocalin 2 in Melanoma Cachexia

Principal Investigator: **Victoria Orfaly** (Oregon Health and Science University)

Mentor: Sancy Leachman, MD, PhD

Proposal Title: Applying Cognitive Theory of Multimedia Learning to Melanoma Prevention Education in High School Adolescents

Principal Investigator: **Megan Trager** (Columbia University Vagelos College of Physicians & Surgeons)

Mentor: Larisa Geskin, MD; Yvonne Saenger, MD

Proposal Title: Image-Based Deep Learning to Predict Melanoma Recurrence

Principal Investigator: **Sarah Wang** (University of Virginia School of Medicine)

Mentor: Andrew Dudley, PhD

Proposal Title: Mechanisms of perivascular dispersal by brain-resident melanoma cells

**Christopher Westdyk Medical Student Award*

Principal Investigator: **Kevin Yang** (University of Alabama, Birmingham)

Mentor: Nabiha Yusuf, PhD

Proposal Title: Therapeutic intervention of melanoma



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Principal Investigator: **Angela Zaladonis** (Lewis Katz School of Medicine at Temple University)

Mentor: Jeffrey Farma, MD

Proposal Title: Immunization Effect in Patients with Multiple Primary Melanomas

Uveal Melanoma **Medical Student Awards**



Principal Investigator: **Usman Baqai** (Sidney Kimmel Medical College at Thomas Jefferson University)

Mentor: Andrew Aplin, PhD

Proposal Title: BAP1 Dependent Kinome in Uveal Melanoma

Mucosal and Acral Melanoma **Medical Student Awards**

Principal Investigator: **Jez Lim Marston** (Weill Cornell Medicine)

Mentor: Douglas Nixon, MD, PhD

Proposal Title: Human Endogenous Retrovirus Expression Profiles in Acral Melanoma

**Silverstein Family Medical Student Award*