Ocular Melanoma Grant Awardees

The Melanoma Research Foundation (MRF) is committed to advancing ocular melanoma research. To date, the MRF has funded 13 ocular melanoma grants totaling $1,562,250. Additional details of this research are noted below.

2018

Pilot Proposal
Principal Investigator: Walter Fast, PhD
University of Texas at Austin

Proposal Title
Innovative Approaches for GNAQ/11 Mutation Characterization and Therapeutic Targeting

**Made possible through the efforts of the MRF as well as the generosity of Jack Odell, John Dagres, and their supporters*

Description
A type of cancer found in the colored part the eye is called uveal melanoma. This particular type of cancer can often be treated successfully with surgery and radiation. However, if allowed to spread, the cancer is often deadly and there are very few effective treatment options. By building an understanding of how this cancer starts and spreads, new therapeutic treatments can be developed. Many cases of uveal melanoma appear to arise from harmful changes in one particular protein (a “G-protein”) that essentially turns on the circuits that lead to cancer growth. In this project, we are studying the changes in this G-protein to understand how they “turn on” this switch. We are also using this information to take the first steps in designing new drugs to stop these cancers. By knowing more information about the changes in the G-protein, we can design new drugs that seek out and turn off only the harmful proteins, and not the healthy versions. Although these efforts lie in the realm of basic research, they provide a foundation on which useful anti-cancer drugs can be built.

MRF
MELANOMA RESEARCH FOUNDATION

2018

Career Development Award
Principal Investigator: Alison Skalet, MD, PhD
Oregon Health & Science University

Mentor: Sancy Leachman, MD, PhD

Proposal Title
A Novel Peripheral Blood Biomarker for Early Diagnosis of Uveal Melanoma

Partially Funded by the Philadelphia Wings of Hope for Melanoma Gala Fund-A-Grant

Description
Uveal melanoma is an aggressive cancer of the eye. There is no cure for metastatic disease, and therefore it is always fatal. Predictive tests can identify patients with aggressive tumors but require tumor sampling which risks vision, and in small tumors is not always an option. Development of a blood-based test that can differentiate benign (non-cancerous) tumors from low grade or aggressive uveal melanoma is needed to improve survival. Our group has discovered a new tumor cell population in the blood of cancer patients, created when a tumor cell and a white blood cell fuse together. These cells, called circulating hybrid cells, can travel to distant sites, thereby spreading disease to other places in the body. In our earlier studies in pancreatic cancer patients we showed that the numbers of circulating hybrid cells can predict overall survival. Now, we have found circulating hybrid cells in the blood of patients with uveal melanoma.

For this grant application, we will evaluate levels of circulating hybrid cells in patients with benign tumors called choroidal nevi and compare the levels to those in patients with uveal melanoma, where we anticipate higher numbers. We will explore whether measuring circulating hybrid cell levels may be helpful in diagnosing small uveal melanomas when the diagnosis is not clear based upon existing methods. We will also measure levels of circulating hybrid cells in uveal melanoma patients over time to see if circulating hybrid cell levels decrease after the eye tumor is treated. We predict that the numbers of circulating hybrid cells decrease over time after treatment of the eye tumor, except in patients who have already had spread of their melanoma to another site in the body. If only a small number of cells have spread, traditional imaging testing cannot detect the disease spread. If successful, measuring circulating hybrid cell levels in patients may allow us to identify the patients with disease spread earlier, when there may be better options for treating the cancer. Finally, we will determine whether we can isolate circulating hybrid cells from the blood to perform the same testing that currently requires tumor biopsies. If successful, this project will be the first step in developing a minimal-risk “liquid biopsy” for uveal melanoma. This will impact treatment decisions, allow all patients to have the benefit of the newest predictive testing, and will open the door to repeated testing over time to detect disease spread earlier and monitor responses to treatment. We will be able to study the biology of disease progression and learn more about the cells involved in uveal melanoma—an important step in finding new treatments for this deadly cancer.

2017

Career Development Award
Principal Investigator: Alan Hunter Shain, PhD
The Regents of The University of California

Proposal Title
The genetic evolution of uveal melanoma

**With support from Ted & Joan Newton & the Live4Life Foundation in honor of Liz Reilly*

Description
Uveal melanoma is a type of melanoma that occurs in the eye as opposed to the most common presentations of melanoma, which occur on the skin. A diagnosis of uveal melanoma carries a poor prognosis, especially when these cancers are caught late. At this point, there are no effective treatment options to offer patients with late-stage uveal melanoma. A better understanding of how uveal melanoma is formed in the eye and how it spreads through the body could provide markers for early detection of these tumors and identify crucial steps of their development, which could be subject to future treatment. Several groups have sequenced primary uveal melanomas (i.e. tumors that are situated to the eye). However, few studies have focused on metastatic uveal melanomas (i.e. tumors that have spread to other anatomic sites) or precursors to uveal melanoma (i.e. benign tumors in the eye that pose little risk to the patient). We propose here to study the entire clinical spectrum of uveal melanoma from their earliest precursors all the way to their metastatic state. This has not been done, in part, because it is very challenging to acquire tissues from lesions in the earlier and later phases of uveal melanoma progression. To overcome this challenge, we have established a collaboration with physician-scientists affiliated with one of the world's largest ocular tumor banks who can provide these informative tissues. It is also technically challenging to sequence and analyze these types of samples. We have previously established a tissue processing, sequencing, and bioinformatic pipeline to analyze the progression of melanomas found on the skin, and we will repurpose this pipeline to analyze the progression of uveal melanomas for this grant. Overall, we are well-positioned to overcome the main challenges to execute this important work. In conclusion, completion of these studies will shed light on the progression of uveal melanoma, a poorly understood process, to guide future therapeutic studies and to also reveal biomarkers for disease progression.

2016

CURE OM Unite! Established Investigator Award
Principal Investigator: Andrew Aplin, PhD
Thomas Jefferson University

Proposal Title
Regulation of the response to targeted inhibitors in uveal melanoma

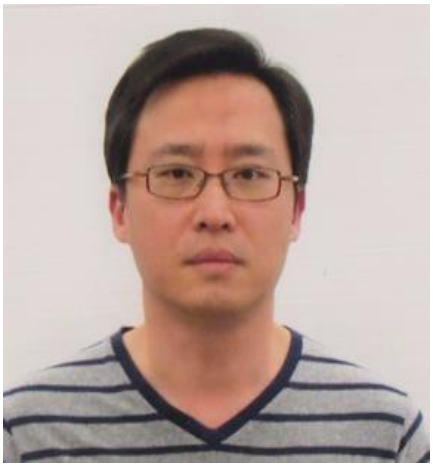
**With matching funds by Mark and Alison Weinzierl*

Description
Melanoma of the uveal tract (a region of the eye) is the most common ocular malignancy in adults and accounts for 5% of all melanomas. According to National Cancer Institute data, there are 4.3 new cases of uveal melanoma per 1,000,000 individuals in the U.S. per year. Very little is known about the initial causes and factors that contribute to progression in this disease. Approximately 2,000 adults are diagnosed every year.

Uveal melanomas are very aggressive cancers. Half of patients will develop metastasis within 15 years of diagnosis. Uveal melanomas typically metastasize to the liver and are invariably fatal. Despite recent breakthroughs in cutaneous melanoma, there are no U.S. Food and Drug-approved (FDA) targeted therapies for uveal melanoma. A glimmer of promise has been provided by targeted therapeutic agents known as MEK inhibitors, but additional therapeutic agents must be added to a MEK inhibitor regimen to enhance the response rates and provide more durable effects in patients.

This project will analyze ways in which the anti-tumor action of MEK inhibitors may be enhanced in uveal melanoma. At Thomas Jefferson University, we have access to unique uveal melanoma resources and a large patient population. Additionally, we are collaborating with others in the field to promote multi-institutional efforts. At the completion of our experiments, we expect to have identified resistance-promoting mechanisms to targeted inhibitors and provide the basis for the design of new therapeutic strategies for metastatic uveal melanoma.

2016



Career Development Award
CURE OM Junior Fellowship by Astra Zeneca
Principal Investigator: Jae Hyuk Yoo, PhD
University of Utah

Proposal Title
Mechanism of Metastasis in a Less Common Molecular Subset of Uveal Melanoma

Description
The major cause of death in uveal melanoma patients is the spread, or metastasis, of the cancer to other vital organs such as the liver. Although most patients do not show signs of metastasis at the time of diagnosis, eventually about 50% of patients will develop metastatic disease, which is almost invariably fatal. Recently, it has been shown that about 80% of uveal melanomas possess a mutation in one of two similar Gaq genes, known as GNAQ and GNA11. These mutations are known to drive the formation and growth of the uveal melanoma tumors. We have recently shown that the activation of a particular protein (known as ARF6) by these mutations controls all of the known signaling pathways that are involved in cancer formation and growth. However, the genes that control the spread of the cancer to other parts of the body are not known for either the cancers with these more common Gaq mutations or for the remaining 20% of uveal melanomas that do not have mutations in the Gaq genes. Given that metastasis of uveal melanoma is the primary cause of death, it is very important to identify the molecular basis for this the development of metastatic disease. In an earlier study, we showed that activation of ARF6 also controlled the metastasis of cutaneous melanoma. Our preliminary data for the present study suggest that activation of ARF6 by the binding of WNT5A to the cell surface receptor ROR2 enhances the molecular signaling pathways downstream and that ARF6 accomplishes this role by helping to move ROR2 from the cell surface to the inside of the cell. We have preliminary data suggesting that ARF6 not only promotes the internalization of ROR2 but also its localization to the nucleus of the cell where it functions in unknown ways possibly to promote uveal melanoma metastasis. Although we have preliminary data for all of these ARF6 functions, we need to confirm these results and try to better understand the mechanisms that govern these functions. Our experiments are designed to establish the role of ARF6 in uveal melanoma metastasis and begin to tease apart the mechanism underlying them. During the course of these experiments, we will be testing the function of ARF6 by reducing its expression levels and by inhibiting its activation using a small molecule compound that directly targets ARF6. If our experiments are successful and we show that ARF6 plays a critical role in uveal melanoma metastasis, we will have not only identified a novel molecule that could be targeted to reduce metastasis, but we will have generated a proof of concept for future drug development by showing the efficacy of inhibiting ARF6 activation using a small molecule compound. Such a compound could be used as a template for development of even more potent and specific compounds that could become drugs for the treatment or prevention of uveal melanoma metastatic disease.

2014

Established Investigator Award
Principal Investigator: John Sondek, PhD
University of North Carolina at Chapel Hill

Proposal Title
Fast Cycling GAQ GA11

Description
In approximately 85% of uveal melanomas, G-α-q or the closely related G-α-11 are mutated at either of two sites normally needed to terminate signaling by these G proteins. These sites are often referred to as “hotspots” because of their high frequency of mutation in uveal melanoma. Similarly, the mutated G proteins are described as “drivers” of cancer since their inability to shutoff promotes this disease.

In addition to these hotspots, extensive genomic studies of uveal melanomas highlight a spectrum of low-frequency mutations throughout the genes that encode G-α-q and G-α-11. Based on our knowledge of the structure and function of G proteins, we hypothesize that many of these low-frequency mutations might also contribute to uveal melanoma.

Medical Student Award
Principal Investigator: Matthew Field (University of Miami Miller School of Medicine)
Proposal Title: The role of BAP1 mutations in establishing a pro-metastatic immune microenvironment in uveal melanoma

2013

Career Development Award
Principal Investigator: Richard Carvajal, MD
Memorial Sloan-Kettering Cancer Center

Proposal Title
Overcoming Resistance to MEK Inhibition in Advanced Uveal Melanoma

Description
The development of metastasis from uveal melanoma (UM) is common and occurs in approximately 50% of patients with this diagnosis. No effective systemic therapy has been identified for these patients and outcomes are poor. We have demonstrated that inhibition of a pathway called the MAPK pathway at the level of MEK may be an effective therapy for UM. Selumetinib is a medication that inhibits MEK. We are currently leading a 16-center randomized trial of selumetinib versus temozolomide in patients with metastatic UM.

In addition to MEK inhibition alone, we have demonstrated that another pathway may influence this response in cells. Specifically, we have demonstrated that blocking both MEK and PI3K/AKT pathways together leads to greater antitumor effects than blocking one pathway alone. We are now planning to evaluate the efficacy of combined pathway inhibition in this disease through a clinical trial entitled, “A Randomized Two-Arm Phase II Study of Trametinib Alone and in Combination with GSK214795 in Patients with Advanced Uveal Melanoma” (NCI#9445; PI: Carvajal). Through this trial, we will test the hypothesis that concurrent treatment with a MEK inhibitor called trametinib and an AKT inhibitor called GSK214795 will result in better outcomes when compared with MEK inhibition alone. We will evaluate the downstream effects of these therapies by evaluating tumor biopsy samples. Through analyzing these biopsy samples, we will be able to explore what makes certain tumors more or less responsive to this therapy. In doing this, we will be able to further optimize treatment approaches enlisting combinations of drugs. This trial will be conducted through a partnership of organizations in the United States and Europe.

Finally, this application builds upon promising clinical and laboratory data and rigorously assesses whether combined pathway blockade will result in improved clinical outcomes when compared with MEK inhibition alone.

2013

Established Investigator Award
Principal Investigator: William Tansey, M.D.
Vanderbilt University Medical Center

Proposal Title
MYC as an invisible driver in metastatic uveal melanoma

Description
Uveal melanoma (UM) is the most common form of adult eye cancer and results from malignant transformation of melanocytes in the uvea (made up of the choroid, ciliary body, and iris of the eye). Although the eye tumor can be treated via targeted radiation or surgery, approximately half of all UM patients develop spread of the cancer beyond the eye (metastatic disease) which is almost always fatal. One of the key predictors of whether UM will spread beyond the eye is loss of BAP1 in the tumor cells. BAP1 is a molecule that is deleted or mutated in a staggering 84% of metastatic UM cases. Exactly how loss of BAP1 triggers the transition to UM metastasis is unknown and is arguably one of the most important questions that needs to be answered if this deadly disease can ever be treated effectively.

Our lab has produced data showing that BAP1 drives tumor spread by enhancing the activity of cellular molecules called MYC and HCF1. MYC is a cellular factor that is often increased in uveal melanoma cells through the increased activity of HCF-1.

The goal of this project is to understand how MYC, HCF-1, and BAP1 function to control gene expression to influence the spread of UM from the eye to other parts of the body. Using state-of-the art genetic and genomic approaches, we will interrogate how MYC and HCF-1 influence UM cells, and probe how loss of BAP1 alters these processes to promote the transition to a metastatic state. We will also directly test whether drugs that target MYC (i.e. inhibit or block MYC) can prevent or reverse the transition to metastatic disease. Until now, it is unclear what role MYC plays in the development of UM metastasis and this project has the potential to unlock an entirely new treatment.

2012

Established Investigator Award
Principal Investigator: Levi Garraway, MD
Dana-Farber Cancer Institute

Proposal Title
Dissecting therapeutic avenues in UM through genomic and functional studies

Description
Uveal melanoma (UM) is the most common ocular tumor in adults. Despite recent advances in the understanding of its molecular underpinnings, metastatic UM remains a deadly malignancy. Uveal melanoma tumors do not share the cancer-causing mutations in the BRAF gene that are common in melanomas arising in the skin. Thus, UM patients cannot benefit from the new targeted therapies known as RAF inhibitors that have proved so beneficial in the treatment of metastatic cutaneous melanomas.

Over 80% of UM tumors carry mutations in two genes: GNAQ and GNA11, and about 50% have inactivating alterations in a third gene (BAP1). Unfortunately, it has proved unclear how best to develop new medicines to target these mutations. As a result, there remains no effective treatment for metastatic uveal melanoma. Unfortunately, other than the GNAQ/11 mutations, little is known of the genomic alterations driving uveal melanoma. These challenges underscore the critical need to gain a fuller understanding of the genetic basis for uveal melanoma tumors and to identify new therapeutic options in this malignancy.

To address these unmet medical needs, the goals of this proposal are: i) to perform a comprehensive genome sequencing in >65 uveal melanoma tumors, and ii) to identify a spectrum of new potential drug targets in UM that may provide a basis for new drugs and drug combinations. Comprehensive genome sequencing data of UM tumor samples (spanning all known human genes) will be generated and analyzed at the Broad Institute. The goal is to define, for the first time, the full landscape of mutated genes in UM. Furthermore, the identification of new therapeutic targets will be undertaken.

Once completed, this project should provide decisive insights into the spectrum of UM genetic alterations, as well as possible new drug targets that could provide the basis for effective therapies in this lethal cancer type.

2012

Established Investigator Award
Principal Investigator: John Sondek, PhD
University of North Carolina at Chapel Hill

Proposal Title
Interdiction of signaling by G-alpha-q to treat ocular melanoma

Description
Uveal melanoma is the most prominent cancer of the inner eye, with approximately 1,500 new cases occurring each year. There are very few treatments for this cancer, and in 40-50% of cases it metastasizes to other parts of the body. Recent research has shown that malignancy is often caused by mutations that hyper-activate G protein signaling. G proteins are molecular “on” and “off” switches controlled by a large family of receptors embedded in the cell membrane. G proteins control a vast array of signaling cascades that regulate diverse cellular processes, including cell proliferation, migration, and death. Therefore, it is perhaps not surprising that approximately 50% of current drugs target G protein-mediated signaling. In the majority of uveal melanomas, a critical mutation is found in a particular G protein, G-α-q, which causes signaling to be continually “on”, resulting in cancer progression. Our long-term goal is to inhibit overactive G-α-q that causes ocular melanoma using small molecule inhibitors. To achieve this goal, we have designed a high-throughput assay to screen molecules that will prevent G-α-q from directly activating effectors that mediate downstream signaling. We intend to use this assay to screen large libraries of low molecular weight compounds for inhibitors of overactive G-α-q. Promising hits will be thoroughly tested to confirm inhibition of downstream signaling by G-α-q. We will test these small molecules in cell lines harboring mutated G-α-q to determine their efficacy in inhibiting cancer progression. This research will create and expand strategies to find and develop new drugs that can prevent and treat uveal melanomas.

Medical Student Award
Principal Investigator: Nisha V. Shah (University of Miami Miller School of Medicine)
Proposal Title: Treatment outcomes with bevacizumab and triamcinolone for posterior uveal melanoma in patients undergoing I-125 plaque brachytherapy

**In honor of participants in the Suncoast Miles for Melanoma*

2011

Established Investigator Award

Principal Investigator: J. William Harbour, MD
University of North Carolina at Chapel Hill

Proposal Title
Characterization of the BAP1 uveal melanoma metastasis suppressor gene

**In memory of Kerry Daveline, Mike Revers, Kathy Bowers, Patricia Schellhardt Malone, Tom Butler, and Jonnie Newcomer*

**Co-funded with the MRA*

Description
Metastasis, the spread of cancer cells to distant parts of the body, is the most common cause of death in patients with melanoma and most other cancers. Yet, our understanding of how cancer cells acquire the ability to metastasize remains very limited. Uveal melanoma (UM) is the most common primary cancer of the eye and the second most common form of melanoma. UMs are notoriously metastatic, resistant to conventional chemotherapy and often fatal. UMs that metastasize can be distinguished from those that do not by their distinct patterns of gene expression, and are classified into “class 1” tumors, which have a low risk of metastasis, and “class 2” tumors, which have a very high risk of metastasis. Almost all class 2 tumor cells lose one copy of chromosome 3, which has led to the widespread expectation that the remaining copy of chromosome 3 contains a mutated (disabled) gene that normally functions to prevent metastasis. Using state of the art genome sequencing techniques, we have identified the gene BAP1 that is located at chromosome 3p21 and is mutated in almost all class 2 tumors but not in class 1 tumors. BAP1 meets several of the major criteria expected for the chromosome 3 metastasis suppressor gene, but very little is known about the role of BAP1 in normal melanocyte biology and melanoma. Thus, the objectives of this research proposal are to study the effects of BAP1 mutation in melanoma cells using cell culture experiments and animal models. We expect to find that disabling BAP1 in UM cells increases their ability to metastasize. Further, we will identify the key proteins that interact with BAP1 in melanoma cells, which will provide clues as to which proteins to target therapeutically. Overall, the project is expected to lead to innovative new strategies for treating metastatic.