2018 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 2018, the MRF awarded 20 research grants encompassing not only cutaneous melanoma, but also the rare melanoma types (e.g. uveal, mucosal, and pediatric). Further, MRF-supported research spanned scientists early in their career (e.g. medical students and post-doctoral fellows) as well as senior investigators. Additional details of the 2018 grant awardees are noted below.

Mucosal Melanoma
Career Development Award

Principal Investigator: Florian Karreth, PhD
H. Lee Moffitt Cancer & Research Institute

Mentor: Keiran Smalley, PhD

Proposal Title
Using the ESC-GEMM Approach to Study Mucosal Melanoma In Vivo

**Funded by the Cavan Foundation*

Description

Mucosal melanoma presents a significant challenge for oncologists. Compared to cutaneous melanoma, mucosal melanoma has a far lower survival rate and is more difficult to treat. The lack of efficient therapies is at least partly due to our incomplete knowledge of what goes awry in mucosal pigment cells, the precursors of mucosal melanoma. Thus, a better understanding of which gene mutations cause the formation of mucosal melanoma and what molecular changes are elicited by such mutations is needed to develop improved therapies. Here, we propose to apply a novel approach termed ESC-GEMM to quickly develop transgenic mice to study mucosal melanoma development. Studying mucosal melanoma in ESC-GEMM mouse models offers several advantages. First, we will be able to study the development and evolution of mucosal melanoma within its natural environment. This is important to determine the effects of mutations on tumor growth and to assess the response of tumors to targeted therapies. Second, the ESC-GEMM approach is highly versatile and allows us to quickly adapt it to study many putative cancer genes

2018 MRF Grant Awardees

Mucosal Melanoma
Career Development Award Cont'd
Florian Karreth, PhD
Using the ESC-GEMM Approach to Study Mucosal Melanoma In Vivo

in parallel. Third, the ESC-GEMM approach can generate experimental animals in as little as 2 months and thus dramatically accelerates the rate at which putative cancer genes can be analyzed. Fourth, the ESC-GEMM approach does not produce surplus mice that cannot be used for experiments and therefore significantly reduces the number of mice required for our studies. We will use the ESC-GEMM approach to study the function of the c-KIT gene, which is frequently overactive and/or mutated in human mucosal melanoma. We will test if c-KIT is able to promote the development of mucosal melanoma and compare tumor formation in the mucosa to that in normal skin. In addition, we will assess if mucosal melanomas with overexpressed normal or mutant c-KIT respond to an FDA-approved drug that inactivates c-KIT either alone or in combination with a drug that inhibits the MAPK signaling pathway downstream of c-KIT. Our ESC-GEMM mucosal melanoma model will not only help to better understand the role of c-KIT in mucosal melanoma development, but also be a powerful resource to interrogate the genetics of this melanoma subtype with the goal to design better treatment strategies.

Uveal Melanoma
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.

2018 MRF Grant Awardees

Uveal Melanoma
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.

Pediatric Melanoma
Medical Student Award

Principal Investigator: William Dufficy (University of Colorado)
Mentor: William Robinson, MD, PhD

2018 MRF Grant Awardees

Pediatric Melanoma
Medical Student Award Cont'd
William Dufficy

Proposal Title: Molecular and Clinical Profile of Melanoma in Pediatric Patients
Christy Findlay Memorial Award

Cutaneous Melanoma
Established Investigator Awards

Principal Investigator: Jonathan Chernoff, MD, PhD
The Research Institute of Fox Chase Cancer Center

Proposal Title
RAC1 Mutant Melanoma: Models and Therapeutics

Description

Many genes have recently been discovered that, when mutated, promote the development of malignant melanoma. Such discoveries are important, as they can point the way towards specific treatments. Recently, two new genes were discovered to cause melanoma in response to sun-damage: PREX2 and RAC1. We recently showed that melanoma cells with these mutations do not respond to drugs such as vemurafinib, even if the cells also have BRAF mutations, but do respond to inhibitors of a protein called Pak. We believe that such anti-Pak drugs could be useful specifically in patients who have the PREX2 or RAC1 mutation, but we lack good cell-based or animal-based models to test this idea. In the first aim of this proposal, we evaluate a cellular model of RAC1-driven melanoma, comparing its drug sensitivity to that of matched BRAF and NRAS-mutant cells. In addition, since melanoma cells are known to acquire resistance to "targeted" agents, we will use a new method to determine how these cells adapt to evade these drugs. In the second aim, we construct a new mouse model of melanoma by altering the RAC1 gene in melanocytes, which we expect will cause the mice to develop melanoma over the course of a few months. This animal model can then be used to evaluate the efficacy of anti-melanoma drugs such as Pak inhibitors and others.

Principal Investigator: Ivana de la Serna, PhD
University of Toledo Health Science Campus

Co-Investigators: Kam Yeung, PhD & Thomas Blomquist, MD, PhD

Proposal Title
Targeting BRD9 in Melanoma

2018 MRF Grant Awardees

Cutaneous Melanoma
Established Investigator Awards Cont'd

Ivana de la Serna, PhD

Targeting BRD9 in Melanoma

Description

Melanoma is the most serious type of skin cancer that can spread to other parts of the body, where it becomes difficult to treat and can be fatal. Over half of all melanomas have a mutation in a gene called BRAF that is required for melanoma to grow. Drugs that prevent BRAF from working have improved patient survival but are still not curative. Patients inevitably develop drug resistance, resulting in disease relapse. Resistance commonly occurs due to acquisition of additional genetic and epigenetic changes that allow tumor cells to survive even when BRAF has been inactivated. Epigenetics is a process by which genes are switched on and off by proteins that change the way the genetic material, DNA, is configured within the cell. We have identified the bromodomain protein, BRD9 as a novel epigenetic protein that is required for melanoma growth. Our studies show that BRD9 is highly expressed in patient derived melanoma samples and is associated with poorer patient survival. Drugs that prevent BRD9 from working, reduce melanoma growth and enhance the antitumor effect of drugs that inactivate BRAF. We also found that inactivation of BRD9 results in changes in the expression of genes required for cancer growth and drug resistance. The studies in this MRF application will determine if combining a drug that inactivates BRD9 with a drug that inactivates BRAF is more effective than a drug that inactivates only BRAF for treating melanoma with BRAF mutations. In order to understand the therapeutic effect of BRD9 inactivation, we will investigate how BRD9 switches genes on and off.

Principal Investigator: Rudolf Jaenisch, MD
Whitehead Institute for Biomedical Research

Proposal Title
In Vivo Model of Human Melanoma Using a Novel Neural Crest Chimera System

Description

The immune system acts as the body's defense mechanism against cancer by recognizing and attacking cancer cells. However, cancer cells have devised ways to thwart these protective mechanisms called "immune evasion" thus making it difficult for immunotherapies to be fully effective and to lead to complete cure. These mechanisms have only recently been recognized to involve suppression of immune responses by activating negative regulatory pathways (also called checkpoints) that are associated with immune homeostasis, or by adopting features that enable tumor cells to actively escape detection. Current therapeutic strategies are aimed at mobilizing the host's immune system to eliminate tumor cells by stimulation of the anti-tumor cell response of cytotoxic T cells and inhibition of tumor induced immune cell paralysis. Given that only a minority of patients respond to these therapies, we need to further understand

2018 MRF Grant Awardees

Cutaneous Melanoma
Established Investigator Awards Cont'd

Rudolf Jaenisch, MD

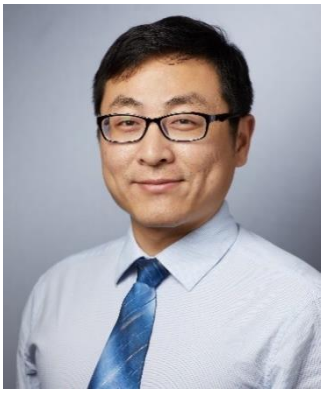
In Vivo Model of Human Melanoma Using a Novel Neural Crest Chimera System

the interaction between melanoma cells and the immune system. Conventional approaches to investigate human cancer are limited by the fact that only end stage tumor cells are transplanted into host animals that are immune deficient, which eliminates the possibility to investigate any anti-tumor immune reaction or immune evasion.

We propose to establish an experimental model system that allows the study of initiation, progression and manifestation of human melanoma in immune competent host animals. The approach is based on generating human-mouse neural crest (NC) chimeras. NC cells emerge from the neural tube at gastrulation and generate a wide variety of lineages including the entire pigment system, as well as the autonomous nervous system. Thus, the melanocyte cells that give rise to melanoma are derived from NC cells. We have shown that in utero injection of human NC cells into the gastrulating embryo generates postnatal chimeras with coat pigmentation derived from the human donor cells. More importantly, we showed that human neuroblastoma, a childhood tumor derived from the NC, develop in human–mouse NC chimeras when the donor NC cells express engineered neuroblastoma relevant oncogenes. Most relevant for this proposal, these tumors develop in immune-competent mice and are invaded by host cytotoxic CD8 T cells as well as T-Regs, which inhibit the cytotoxic action of the T cells. These results provide proof of principle that human-mouse NC chimeras allow the investigation of immune reaction and immune evasion of human tumor cells in an in vivo model system.

A major impediment to the accurate study of cancer progression and immune evasion is the lack of animal models representative of human disease. In this project we propose to generate human-mouse NC chimeras which carry melanoma relevant oncogenes in the donor NC cells. This platform will help understanding the ways in which melanoma cells are able to evade the immune system, allow identifying novel targets and testing novel strategies for immunotherapies.

Cutaneous Melanoma
Career Development Awards



Principal Investigator: Jian Cao, PhD
Yale University

Mentor: Qin Yan, PhD

Proposal Title
Targeting KDM5 Histone Demethylases to Boost Immune Response in Melanoma

**Funded by the Denver & Philadelphia Wings of Hope for Melanoma Gala Fund-A-Grant*

2018 MRF Grant Awardees

Cutaneous Melanoma
Career Development Awards Cont'd

Jian Cao, PhD

Targeting KDM5 Histone Demethylases to Boost Immune Response in Melanoma

Description

The goal of this research is to target KDM5s family proteins to enhance the response to immune checkpoint inhibition in melanoma. The recently developed immune checkpoint blockade therapies release the brakes in patients' immune cells and free these immune cells to attack tumor cells. However, most patients do not response because of lack of sufficient immune cells in tumors. Our earlier work has shown a connection between the KDM5 family proteins and cancer immune response. A combination of inhibitors of the KDM5 family proteins and immune checkpoint blockade therapies is like to press accelerator and release break simultaneously, leading to an enhanced anti-tumor immune response. This study will investigate the mechanism of anti-tumor immune response induced by KDM5 inhibition and evaluate the combination of KDM5 inhibition with immune checkpoint blockade therapies for treating melanoma. This combination will likely allow more melanoma patients to benefit from immunotherapies.

Principal Investigator: Michael Emmons, PhD
H. Lee Moffitt Cancer Center & Research Institute

Mentor: Kieran Smalley, PhD

Proposal Title
Targeting HDAC8 to Overcome the Acquisition of Drug Tolerance in Melanoma

**Funded by the NYC Wings of Hope for Melanoma Gala Fund-A-Grant*

Description

There has been great progress in increasing the treatment options for patients who have the skin cancer melanoma in the past decade. However, the melanoma will most likely reappear and be resistant to more treatment options. There are specific types of melanoma cells which allow this to occur. We are currently targeting a protein called HDAC8 which plays a role in the cells which are resistant to therapy. This protein becomes active when the cell is under stress and regulates cell pathways which encourage cell survival. It does this by making the protein c-Jun, which is involved in the production of genes involved in cell growth and migration, more active. In this proposal we will determine how HDAC8 can stop drugs, stress and the immune system from killing cancer cells. We believe HDAC8 binds to DNA binding proteins which are involved in the production of RNA including c-Jun and CREB. When HDAC8 binds to CREB it stops it from being active. On the other hand when HDAC8 binds to c-Jun it activates it. We will look at the genes which are expressed either more or less by HDAC8. We will also test to see if the expression of HDAC8 can be lowered in mice and if lowering the expression of HDAC8 allows cells to be more receptive to established therapies and therapies which activate the immune system. We expect HDAC8 to become active and allow for a cell to become resistant to therapy by inactivating CREB and activating c-Jun. This allows for the increased production of RNA and proteins at sites in the DNA where c-Jun binds. We also expect that

2018 MRF Grant Awardees

Cutaneous Melanoma
Career Development Awards Cont'd

Michael Emmons, PhD

Targeting HDAC8 to Overcome the Acquisition of Drug Tolerance in Melanoma

lowering the expression of HDAC8 will increase the response of patients to inhibitor therapy with melanoma and will increase the response of the immune system in fighting these cancers.

Principal Investigator: Gloria Sheynkman, PhD
Dana-Farber Cancer Institute

Mentor: Marc Vidal, PhD

Proposal Title
Network Rewiring in Melanoma due to Transcription Factor Isoform Switching

Funded by the DC Wings of Hope for Melanoma Gala

Description

The cancer genomics field has focused on how mutations in the genome change proteins to cause cells to progress into metastatic cancers. However, new molecular profiling technologies in the past years have shown that during cancer progression thousands of genes produce abnormal forms of their proteins through a mechanism called alternative splicing. This mechanism has been found to change the activities of many proteins, including transcription factors, molecules that act as the control center for the cell. However, very little is known about how these alternative splice-driven changes in TF activity lead to cancer. Therefore, we have developed several key technologies that allow for 1) sensitive detection of the presence of cancer-specific protein forms, and 2) profiling of the deregulated activities of these protein forms. This information can be used to understand new cancer mechanisms, as well as discover new precise targets for drugs or biomarkers to better diagnose cancer.

Cutaneous Melanoma
Medical Student Awards

Principal Investigator: Emily Cai (Stanford University Medical School)
Mentor: Kavita Sarin, MD, PhD
Proposal Title: Identification of genetic, clinical and environmental risk factors in patients with multiple primary melanomas
Frank C. Campbell, MD Memorial Award

Principal Investigator: Nathaniel Campbell (Weill Cornell Medical College)
Mentor: Richard White, MD, PhD & Joao Xavier, PhD
Proposal Title: Dissecting the Ecology of Melanoma Metastasis: Size and Number Trade-Offs in Circulating Tumor Cell Clusters

2018 MRF Grant Awardees

Cutaneous Melanoma

Medical Student Awards Cont'd

Nathaniel Campbell
The Craig P. Merkel and James K. Saunders Memorial Award

Principal Investigator: **Anita Gade** (New York Institute of Technology College of Osteopathic Medicine)
Mentor: Jonathan Zippin, MD, PhD
Proposal Title: Vitamin C as Novel Therapeutic for Melanoma
Christy Findlay Memorial Award

Principal Investigator: **Alec Gramann** (University of Massachusetts Medical School)
Mentor: Craig Ceol, PhD
Proposal Title: Examining BMP Signaling as a Regulator of Neural Crest Identity During Melanoma Initiation and Progression
Looney Legacy Foundation Medical Student Award

Principal Investigator: **Michael Lee** (University of Maryland)
Mentor: Tonya Webb, PhD
Proposal Title: Targeting the Host Immune System to Improve Viral Oncolytic Therapy
Looney Legacy Foundation Medical Student Award

Principal Investigator: **Steve Lu** (Johns Hopkins University School of Medicine)
Mentor: Janis Taube, MD
Proposal Title: Tumor-infiltrating myeloid cells as biomarkers for response to PD-(L)1 checkpoint blockade
Paul Massimini Memorial Award

Principal Investigator: **Yuzhong Jeff Meng** (Harvard Medical School)
Mentor: Rameen Beroukhim, MD, PhD
Proposal Title: Determinants of Response and Mechanisms of Resistance to Tumor-Infiltrating Lymphocyte Therapy for Metastatic Melanoma
Looney Legacy Foundation Medical Student Award

Principal Investigator: **Constance Shreckengost** (Emory University School of Medicine)
Mentor: Michael Lowe, MD
Proposal Title: Effects of Obesity on the Skin Stress Response and Treatment Outcomes in Melanoma
The Dieter Ernest Memorial Medical Student Award

Principal Investigator: **Khiem Tran, PhD** (University of Arizona, Tucson College of Medicine)
Mentor: Emanual Maverakis, MD
Proposal Title: The Role of Man1a1 in Immune Evasion During Progression of Melanoma

2018 MRF Grant Awardees

Cutaneous Melanoma

Medical Student Awards Cont'd

Khiem Tran, PhD
Looney Legacy Foundation Medical Student Award

Principal Investigator: **Todd Wechter** (Stony Brook University School of Medicine)
Mentor: Iman Osman, MD
Proposal Title: Targeting EZH2 in the Treatment of Non-Sun-Exposed Melanoma
Looney Legacy Foundation Medical Student Award