The Melanoma Research Foundation (MRF) was started by and for patients in 1996. Two years later our very first research grants were awarded. Over the past thirteen years the MRF has provided millions of dollars in funding for basic science research designed to unravel the puzzle that is melanoma. The MRF’s grants have helped scientists increase their understanding of how this disease works. As a result, new therapeutic approaches are being developed every day. On March 25th, 2011, a new drug was approved by the FDA for the treatment of metastatic melanoma — the first new drug to receive approval in thirteen years! After many frustrating years, scientific research is finally resulting in new and better therapies. The work must continue, however. In that spirit, we are pleased to announce the following grants, made possible through the generous support of our donors.
**FIRST YEAR CAREER DEVELOPMENT AWARDS**

**Two-year Grants: $90,000**

**Dr. Cynthia Cooper, Washington State University**

*Balancing melanophore number in Danio rerio zebrafish*

**Cosmopolitan Practice Safe Sun Research Grant**

Black pigment cells, or melanocytes, produce pigments that determine hair, skin and eye color in humans. Most critically, melanocytes initiate the tanning response, an event functioning to protect our skin cells from DNA-damaging ultraviolet light. Changes in the genetic properties and function of melanocytes are thought to lead to melanoma, a cancer of melanocytes that leads to the largest percentage of skin cancer-related deaths. In their advanced stages, melanoma cells have lost many features characteristic of normal melanocytes, suggested by their ability to cross skin boundaries, move throughout the body and set up new tumors in distant locations. The model organism, Danio rerio zebrafish, has very similar cells (called melanophores) which we study to identify new genes that participate in the development of melanocytes and help them to retain their normal features and function. We hope these studies will provide new information regarding genes that could function to prevent the development of melanoma and provide new treatment options.

**Dr. Kosaku Iwatsubo, UMDNJ New Jersey Medical School**

*Epac1 as a target for treating melanoma*

In honor of participants in Miles for Melanoma of New Jersey

This proposal aims to define a potentially new molecular target for melanoma therapy by determining the role of exchange protein directly activated by cAMP-1 (Epac1). Our preliminary data demonstrated that stimulation of Epac1 accelerates, but inhibition of Epac1 suppresses, proliferation and cell motility (migration) of melanoma cells. The underlying mechanism of these Epac1’s effects involves modification of inter-cellular communication among melanoma cells, and between melanoma cells and vessel-making cells (endothelial cells). This intracellular communication leads to tumor progression, and the resultant metastasis. Our project will clarify the molecular mechanism in Epac1-dependent melanoma progression and metastasis, and in addition, will demonstrate that inhibition of Epac1 could be a novel strategy for treating this life-threatening disease.

**Dr. Jim (Jianxun) Song, The Pennsylvania State University College of Medicine**

*Impact of iPS cell-derived highly reactive T lymphocytes on melanoma*

In memory of Andrea Sheridan and Steve Casey, and in honor of participants in Miles for Melanoma of Delaware and Tracy Welge

Adoptive cell transfer (ACT) of tumor-specific T killer cells (CTLs) is a promising treatment for a variety of malignancies. CTLs can recognize malignant tumors by T cell receptors (TCR) and play a cytotoxic role within the immune system. In addition, CTLs can secret cytokines to directly or indirectly kill/suppress tumor cells. It is known that less-differentiated, central-memory-like (termed highly reactive) CTLs are the optimal population for ACT-based immunotherapy. However, due to difficulties in obtaining such CTLs from patients, there is an urgent need to find a new approach to generate highly reactive tumor-specific CTLs for successful ACT-based therapies. Our long-term goal is to elicit efficient immune responses to tumors and facilitate the development and application of vaccines and immunotherapies that can be used to successfully prevent and treat cancer in humans. Our objective for this application is to develop a novel approach to generate highly reactive CTLs derived from induced pluripotent stem (iPS) cells, and to determine their therapeutic potential in the treatment of cancer.

Our central hypothesis for this proposed research is that iPS cells that are transduced with genes of tumor-specific TCR and stimulated with in vitro Notch signaling can differentiate into large numbers of highly reactive CTLs, which have therapeutic potential in the treatment of melanomas. The rationale for this proposed research is that, once it is known how to generate highly reactive antigen-specific CTLs derived from iPS cells, there is potential to elicit efficient anti-tumor immunity by ACT of iPS-derived CTLs, resulting in new and innovative approaches to the prevention and treatment of cancer. We plan to test our central hypothesis and accomplish the objective of this application by pursuing the following two specific aims: 1. Generate highly reactive melanoma-specific CTLs derived from iPS cells. We will generate large numbers of highly reactive melanoma-specific CTLs derived from iPS cells. 2. Characterize highly reactive melanoma-specific CTLs derived from iPS cells. We will characterize highly reactive melanoma-specific CTLs derived from human iPS cells and use a murine model to determine their therapeutic potential in the treatment of melanomas. The work proposed in these two specific aims is expected to have an important positive impact, because the iPS cell-derived immune cells are highly likely to be used in preventive and therapeutic interventions for cancer in addition to fundamentally advancing the fields of T cell biology. These studies will provide a solid foundation for further development of highly reactive immune cells derived from iPS cells, and ultimately for generating patient- and/or melanoma-specific therapies.
Dr. Qin Yan, Yale University

*Roles of epigenetic regulator JARID1B in metastatic melanoma*

*In memory of Paul Mikaulauskas, Nate Bloom, Gloria Wennerstrand, and Denny Neely, and in honor of the members of the 2010 Krokdiloes, Tigertones, and Whiffenpoofs*

Melanoma is a common disease that is frequently lethal. About 69,000 new cases and 8,700 melanoma-related deaths will occur in the US in 2011. Early metastases are characteristic of melanoma and distant spread of disease is associated with a median survival of about 8 months. In part, this is because melanoma is one of the most chemotherapy-resistant forms of cancer. Therefore it is critical to identify and validate new drug targets and develop alternative therapies to overcome metastasis. Successful eradication of any tumor depends on the elimination of the subsets of cells that drive tumor formation, relapse, and metastasis that have been called cancer stem cells. It has been shown recently that a histone demethylase JARID1B marks a subset of melanoma cells that are potential melanoma stem cells. The laboratory of co-investigator Dr. Marcus Bosenberg has recently generated a human-relevant Braf/Pten mouse melanoma model and identified a uniformly tumorigenic subset of mouse melanoma cells. Based on these findings, we hypothesize that loss of JARID1B represses formation of melanoma stem cells, which are essential for melanoma development and progression. To this end, we will combine our Jarid1b knockout mouse model with the Braf/Pten melanoma prone mouse model to determine the effects of Jarid1b loss in melanoma. We expect that Jarid1b loss suppresses melanoma progression by decreasing the number of melanoma stem cells. The results from these studies could provide strong rationale for anti-melanoma therapies targeting JARID1B, an enzyme that could be inhibited by small molecule inhibitors.

Dr. Ali Jazirehi, The Regents of the University of California

*Molecular determinants of apoptosis resistance in melanoma clinical immunotherapy*

*In memory of Aaron Anchor, Herbert Bates, Jr., and Tom Triphahn, and in honor of Neil Gaines and participants in the Dermatology Interest Group Association fundraising effort*

This career development award will support the conduct of a comprehensive analysis of tumor cells derived from patients with metastatic skin cancer (melanoma) after receiving billions of their own white blood cells genetically engineered to specifically recognize and efficiently kill their own melanoma cells. These scientific aims will help us better understand why some patients’ melanoma cancer cells can be killed, and others not. A well known mechanism of tumor evasion is the loss of their recognition units so that they are not detected by the immune system. Also, it may be due to changes in the patterns of their genes. To this end, we try to understand the inherent and/or acquired mechanisms adopted by tumor cells that render them unresponsive to an effective immunotherapy. Also, we try to potentially identify/design novel approaches that specifically target the problem areas in the tumor cells in hopes of making this kind of cancer treatment (immunotherapy) more effective.

Dr. Eva Hernando, NYU School of Medicine

*Study of the role of microRNAs in melanoma brain tropism*

*In memory of Peggy Spiegler, Kevin Brue, Douglas Grant Gillespie, and Thomas W. Barner*

Background: One of the most devastating complications of melanoma is spread to the brain after which most patients survive less than 6 months. Because the prognosis for these patients is so poor, they are excluded from clinical trials of new drugs because their inclusion might make the drug appear less effective. MicroRNAs (miRNAs) can simultaneously regulate several genes, thus they represent a potential molecular mechanism capable of modulating a complex biologic process such as spread of melanoma to the brain (B-Met).

Objective/Hypothesis: It is our hypothesis that altered miRNAs play an important role in facilitating the escape of melanoma cells from the primary tumor in the skin to the blood stream, through the circulation, and into the brain.

Study design: We have identified a subset of miRNAs whose levels are different in B-Met compared to melanoma metastases in other organs. The focus of this project will be to further investigate if those candidate miRNAs control B-Met development. In order for melanoma cells to escape from the skin and travel to the brain, certain cellular processes are required such as migration, adhesion, and invasion. We will determine if alteration of specific miRNAs can in turn affect these processes. We will initially perform these experiments using cells in vitro and then will further investigate a smaller subset of miRNAs in a mouse model. Results from these studies will increase our understanding of why melanoma cells are attracted to the brain and how we can therapeutically interfere with melanoma B-Met development and growth.
Dr. Minjung Kim, H. Lee Moffitt Cancer Center and Research Institute

Understanding molecular mechanisms for the role of NEDD9 in melanoma progression

In memory of Amanda Carter-Horn, Leonard E. Warren, Edward A. Merullo, Jan Wright Niles, and George A. Wilkins, and in honor of Hugh Allen’s USA Bike Ride for Melanoma Research

Metastasis is the cardinal and lethal feature of melanoma. Understanding the molecular mechanisms driving melanoma progression is imperative to developing molecularly targeted, rational therapeutic agents that can halt disease progression.

In a systematic comparison of primary and metastatic melanoma genomes developed in human patients and mouse models, we have identified a novel melanoma metastasis gene, called NEDD9. The goal of this project is to understand the molecular mechanisms underlying NEDD9 function in driving melanoma metastasis as a first step toward molecularly targeted therapy. To this end, we will identify “NEDD9 signatures” activated by NEDD9 and address its functional importance and prognostic value in melanoma progression. This study will lead to the identification of signaling components of NEDD9 that can be targeted to block melanoma progression. Considering the frequent up-regulation of NEDD9 expression in human melanoma patients, this study has prognostic and therapeutic importance, since the NEDD9 complex could be a strong candidate for metastatic melanoma intervention.

Dr. Roger Lo, UCLA David Geffen School of Medicine

Improving melanoma response to B-RafV600E targeting

In memory of Larry Poplawski, Harold Quade, and Jim Foy, and in honor of Full Spectrum Dermatology and Katie Brennan

Cutaneous melanoma ranks among the fastest rising human malignancies in annual incidence and is highly lethal when detected at advanced stages. The last 30 years have seen no treatment regimen for advanced melanoma that exceeds a 5-10% tumor response rate. Standard chemotherapy often targets fast dividing cells, in both the tumor as well as some normal tissues of the host patient, giving rise to unwanted side effects. Targeting a specific feature of cancer not present in the normal cells promises to reduce dramatically undesirable side effects.

A small molecule (PLX4032) targeting a common melanoma mutation, B-RAF(V600E), is showing unprecedented promise in an on-going clinical trial (80% of patients respond if their tumors harbor the BRAF(V600E) mutation) but meets a formidable challenge common to all targeted therapy, drug resistance and clinical relapse. This drug resistance can develop within months to years of drug initiation. We set forth three research goals, centered on this group of B-RAF(V600E)-positive melanomas. These aims are based on the premise that combination drug treatments would likely augment the success of targeted therapies such as PLX4032 and minimize drug resistance and clinical relapses. We will scan a “druggable” segment of the melanoma genome (so-called kinome) for genes whose functions are intimately linked with the growth promoting functions of B-RAF(V600E). Such functional “co-dependency” may present ideal combinatorial drug targets. Additionally, we will follow a set of experimental approaches (“integrated genomics”) that has led us to discover, in a subset of patients, a specific mechanism of melanoma resistance to PLX4032, which is akin to finding a needle in a haystack. Our goal here is to discover other mechanisms of acquired PLX4032 resistance, which is the first step in constructing a therapeutic strategy.

Thus, by studying B-RAF(V600E)-positive melanomas, we will build a rational knowledge base of codependent genetic networks and mechanisms of acquired resistance to B-RAF-targeted therapy. We hope this will rationally guide patient care or, at least, inspire clinical trials for in-human hypotheses.

The MRF research grant program is committed to advancing a national scientific agenda for melanoma research, coordinating with other leaders and funders, while funding research across the spectrum of melanoma – in prevention, diagnosis and treatment. The two-phased review process mirrors the National Institutes of Health (NIH) system and each application is peer-reviewed by no less than two experts in the field. This high quality review process ensures that only the best, most promising research is funded.
DONOR DESIGNATED AWARD FOR MUCOSAL MELANOMA
Two year grant: $100,000

Dr. Matthew VanBrocklin, Nevada Cancer Institute
Evaluating c-KIT in mucosal melanoma
In memory of Susan Fazio and Lenore Goldberg

Melanoma is one of the most rapidly increasing malignancies worldwide. Although it accounts for only 4% of all skin cancers with over 65,000 new cases diagnosed annually in the United States, it is responsible for over 77% of skin cancer deaths. If detected early, the disease is easily treated surgically; however, once the disease has metastasized it is largely refractory to current therapies and is associated with high mortality. The four most common forms of melanoma are Superficial spreading, Nodular, Lentigo maligna and Acral lentiginous. Mucosal melanomas are categorized as Acral lentiginous melanomas and affect all races with similar frequency. Nearly a third of all newly diagnosed cases possess regional spread, and despite aggressive surgical intervention, result in significant metastatic dissemination to other organs, especially the liver, lungs, brain and intestines, which is associated with poor prognosis.

As we enter the era of targeted therapy, it is vital to classify tumors on the basis of their driving genetic alterations so that appropriate therapeutic agents can be developed. While the majority of cutaneous melanomas possess activating mutations in BRAF, alterations in a vital cell surface receptor c-KIT have been identified as the most common event in mucosal melanomas. Therefore, therapeutic targeting of c-KIT has recently gained interest. Although several phase II clinical trials with an inhibitor of c-KIT in unselected melanoma patients proved disappointing, recent reports highlight several dramatic responses in patients diagnosed with mucosal melanomas that possessed c-KIT alterations. This has led to expanded clinical evaluation of c-KIT inhibitors in stratified patient cohorts. Despite increasing interest in targeting c-KIT in mucosal melanomas, very little is known regarding a role for c-KIT in promoting melanoma initiation and progression. To this end we will evaluate a role for c-KIT alterations in promoting mucosal melanomas in concert with other implicated cooperating genomic alterations in our novel preclinical model. We will assess multiple c-KIT directed agents and address potential mechanisms of resistance. Importantly, our studies will provide insight into which c-KIT alterations and cooperating events are responsive to various c-KIT inhibitors and identify factors leading to drug resistance in order to develop better therapeutic strategies for treating mucosal melanoma.

FIRST YEAR ESTABLISHED INVESTIGATOR AWARD
Two-year Grant: $180,000

Dr. Antoni Ribas, The Regents of the University of California
Understanding of CTLA4 blockade and its combination with BRAF inhibition
In honor of the participants in the Team M4M Marathon Training Program

The anti-CTLA4 antibody ipilimumab is the first treatment ever to demonstrate an improvement in survival in patients with metastatic melanoma. The effect of anti-CTLA4 antibodies is quite remarkable in a small subset of patients with durable tumor responses lasting years, but most patients do not respond. The work of many groups over the past 10 years has provided insight on how anti-CTLA4 antibodies impact on the human immune system, but this has not been enough to determine the major factors leading to durable tumor responses or to gain a good knowledge on how to increase the frequency of tumor responses.

We have been performing clinical trials with a similar anti-CTLA4 antibody, tremelimumab, with durable responses in a similar subset of patients as with the use of ipilimumab. We will conduct studies that focus on the immune cell/cancer cell interaction with the goal of advancing the knowledge on how anti-CTLA4 antibodies lead to durable tumor responses in some patients. The overall goal of this project is the study of how immune cells are attracted to tumors upon CTLA4 blockade and explore if the effects leading to a tumor response or progression are immune cell-intrinsic (lack of adequate activation, lack of tumor antigen specificity) or cancer cell-intrinsic (immune resistant oncogenic profile). In addition, we will test means to merge immunotherapy with the higher response rate achieved with novel targeted therapies. Such a combination may be able to broaden the benefits derived by the remarkably durable responses with tumor immunotherapy.

To test these hypotheses, we propose there specific study aims. The first one is focused on the characterization of tumor-infiltrating lymphocytes based on the analysis of already collected tumor biopsies in patient treated with anti-CTLA4 antibodies. The second aim focuses on the genetic characterization of tumors responding or resistant to anti-CTLA4 blockade to determine if certain cancer genes predict response or resistance. The third aim is based on the preclinical testing of combinations of immunotherapy with BRAF targeted therapy to analyze how best to combine the benefits of these two approaches for the future treatment of patients with metastatic melanoma.
SECOND YEAR ESTABLISHED INVESTIGATOR AWARDS
Two-year Grants: $180,000

Dr. Kelly McMasters, University of Louisville Research Foundation
Develop a prognostic scoring system in node-negative melanoma patients
In memory of Kent McCullough, Scarlet Lawrence Akins, Wolfgang Schlinkert, and Mandy Dean, and in honor of Ted Murphy and MelanomaGirl Foundation

Melanoma, the most lethal form of skin cancer, is currently the 5th most common cancer in American men and the 7th most common in American women, killing more than 8,000 Americans annually. The sentinel lymph node (SLN) is the first node that receives lymphatic drainage from the primary tumor—it is the first lymph node to which the melanoma will spread. SLN status is the strongest predictor of survival for early stage melanoma and often guides therapeutic decisions. Interferon alfa-2b (IFN) therapy is the only U.S. Food and Drug Administration (FDA)-approved adjuvant therapy for melanoma. It is generally recommended for patients with “high-risk” melanoma, predominantly those with spread of the melanoma to lymph nodes (stage III), but not for most patients who have no evidence of spread to lymph nodes (stage I and II). However, approximately 15% to 20% of patients with tumor-negative SLNs will develop recurrence and die of melanoma. Therefore, a critical unmet need exists to identify the truly high-risk stage I and II patients who may benefit from adjuvant IFN therapy. Our preliminary results indicate that the gene expression pattern in patients with tumor-negative SLN who are alive and without recurrence is quite different from those who have developed recurrence. We hypothesize that the gene expression pattern in the SLN will reveal evidence of exposure to melanoma cells, which will correlate with prognosis. This gene signature will be used, along with well-characterized clinical and pathologic prognostic factors, to create a prognostic model that defines low-, intermediate-, and high-risk subgroups of node-negative melanoma patients. We expect that this prognostic model will better define which patients may benefit from IFN therapy. The success of this project will not only further the goal to understand melanoma and its treatment but also increase the overall survival rate of mela
Dr. Sean Morrison, University of Michigan

The regulation of melanoma metastasis

In memory of Tricia Elaine Black, Deb Sandry, Nancy Fox, and Colleen DeMars, and in honor of Mike McAuliffe, Fred Hines’ Ride Across America, and participants in the Miles for Melanoma Marathon Program

The prediction, detection, and prevention of metastasis are among the most pressing clinical problems in melanoma. Yet we have little understanding of how metastasis is regulated in tumors because we have been unable to study the metastasis of melanomas obtained directly from patients, within the body. We have developed a new mouse assay that makes it possible to study metastasis by melanoma cells from patients with high sensitivity. We observe profound differences between patients in the extent to which their melanomas metastasize in these mice: melanomas from some patients metastasize widely while melanomas from other patients exhibit little or no detectable metastasis. These differences are reproducibly observed in multiple independent experiments, implying that differences among melanomas from different patients lead to differences in metastatic behavior. We hypothesize that genetic differences between tumors determine these differences. We will test this by genetically comparing tumors that exhibit extensive metastasis or no metastasis in mice. We will test whether changes in the expression of specific genes cause the observed differences in metastatic behavior. Using this approach we hope to identify new mechanisms that regulate the metastasis of human melanomas from patients. The discovery of genetic variants that predict which patients are most likely to metastasize, or by what routes, would change the treatment of melanoma.

Melanoma Research Foundation Breakthrough Consortium

MRF has pulled together some of the top melanoma researchers and clinicians in the world for the purpose of conducting clinical trials using combinations of the most promising drugs currently in development. Special support was provided for this effort in memory of Brenda B. MacDonald, Bill Walter, and James O. Robbins.

The following Universities, Institutions and Cancer Centers have been supported through the MRF Grant Program:

- Arizona Cancer Center
- Bloomsburg University
- Brigham and Women’s Hospital
- City of Hope National Medical Center
- Emory University
- George Washington University
- H. Lee Moffitt Cancer Center and Research Institute
- Harvard Medical School
- Indiana University
- John Hopkins University
- Memorial Sloan-Kettering Cancer Center
- Nevada Cancer Institute
- New York University School of Medicine
- Norris Cotton Cancer Center, Dartmouth College
- Ohio State University
- Pennsylvania State University College of Medicine
- Rutgers University
- Stanford University
- Thomas Jefferson University
- Translational Genomics Research Institute
- University of Arizona
- University of California-Los Angeles and San Francisco
- University of Colorado
- University of Louisville Research Foundation
- University of Maryland
- University of Medicine and Dentistry/Robert Wood Johnson Medical School
- University of Michigan
- University of North Carolina
- University of Pittsburgh
- University of Tennessee
- University of Texas-MD Anderson Cancer Center and Galveston
- University of Utah School of Medicine
- Washington State University
- Washington University – St. Louis
- Yale University
Adele Haimovic, NYU School of Medicine
Defining the melanoma anti-glycan antibody recurrence signature
In honor of Project Red Walrus

In the absence of effective therapy for advanced melanoma, the early identification of patients who are at high risk for the development of metastatic disease is critical. Reliable methods to non-invasively and accurately identify patients with localized disease who are at high risk of recurrence are still missing. The aim of this project is to determine if antibodies against cell-surface antigens, specifically glycans, can be used to improve our ability to determine the risk for development of recurrent disease. Glycans displayed on the surface of cancer cells are modified versions of those found on healthy cells. These abnormal glycans on tumor cells are immunogenic, and antibodies against these glycan antigens can be detected in patients’ blood. This project will examine the blood of patients with localized melanoma, some of whom experienced recurrence, to create a melanoma glycan “recurrence signature.” We will then validate this recurrence signature in an independent cohort of melanoma patients whose recurrence status we will be blinded to. This signature may be used in combination with clinicopathological data to improve stratification of patients, and to make an informed decision regarding who would likely benefit from systemic therapy after tumor resection.

Jason E. Hawkes, The University of Utah School of Medicine
GNAQ and GNA11 germ-line mutations as potential genetic biomarkers of increased melanoma risk in hereditary melanoma families
In memory of Staff Sgt. Jon Warrington and Brad Lanpher

Melanoma is the most serious form of skin cancer. It is the fifth and sixth most common cancer in men and women, respectively, and has an average lifetime risk of 1 in 75. While most melanoma cases are not hereditary, approximately 10% are familial. The majority of these hereditary melanoma cases do not carry a know genetic mutation. Our research is aimed at investigating the possible link between familial melanoma and hereditary changes in two human genes, GNAQ and GNA11. Previous studies have shown that mutations in these genes result in increased growth of melanocytes, the cells of the body that produce the pigment that colors our skin, hair, and eyes. Melanocytes are also the cells from which malignant melanomas originate. These findings suggest that hereditary alterations in GNAQ or GNA11 may represent an early step in the development of melanomas in families at high-risk for melanoma. Most importantly, the identification of genetic changes that positively correlate with familial melanoma may lead to a better understanding of the origin and development of this devastating cancer.

Diane Tseng, Stanford University School of Medicine
Genetic alterations in benign melanocytic neoplasms and invasive melanomas arising in the female genital tract
In memory of Robert Hansen, and in honor of Simple Serenity Spa and Wellness, LLC

Our understanding of melanoma has changed over the past several years: the mutations (or mistakes in the genetic code) that drive melanoma vary based upon where that melanoma develops on the body. For example, melanomas that arise on skin that has received chronic sun exposure have very different mutations than melanomas that arise in areas that have never had sun exposure. This latter group includes melanoma of the female reproductive tract, which has been relatively understudied as it is (thankfully) very rare. The goal of our study is to compare the mutations found in normal moles (or nevi) of the female reproductive tract to melanomas of the same anatomic area. Understanding the mutations found normally in moles in this area will help us better understand the melanomas, and may help identify targeted medications that can treat melanoma of the female reproductive tract.