CURE OM Research Recipients

In 2012, CURE OM began funding ocular melanoma specific research grants. Falling under the MRF’s general Research Grant Program, the research emphasizes both basic and clinical research projects that explore innovative approaches to understanding OM and its treatment. Proposals are submitted from around the world and undergo a rigorous peer-reviewed process by experts and leaders in the OM field. This helps us identify the most promising and impactful research to fund. In the first 2 years, we have secured over $800,000 specifically for OM research and have funded 4 different research recipients.

Dr. Richard Carvajal
Memorial Sloan-Kettering Cancer Center

Project Title:
Overcoming Resistance to MEK Inhibition in Advanced Uveal Melanoma

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 in preclinical models and we are leading a 16-center, investigator-initiated, Cancer Therapy Evaluation Program (CTEP)-sponsored randomized trial of selumetinib versus temozolomide in patients with metastatic UM (NCI#8443; PI: Carvajal), with promising activity observed thus far.

We have further demonstrated that activation of another pathway called the PI3K/AKT pathway may limit the efficacy of MEK inhibition, and that concurrent inhibition of both pathways leads to greater antitumor effects than inhibition of one pathway alone. We are now planning to clinically evaluate the efficacy of combined pathway inhibition in this disease and further investigate markers of sensitivity and resistance to this therapy. Using a CTEP-sponsored 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), 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 using serial tumor biopsy samples and explore mechanisms of sensitivity and resistance in order to further optimize combinatorial approaches to treating patients with this disease.

This trial will be conducted under the auspices of the International Rare Cancers Initiative (IRCI) Uveal Melanoma working group, a group established by the Cancer Research UK and the NCRN in the UK, the NCI in the US, and the EORTC to facilitate the design of and rapid accrual to clinical trials of treatments for rare cancers such as UM. We anticipate the participation on this trial of up to 10 centers in Europe and the UK, which will expand patient access to this promising therapy into the international arena and will facilitate the rapid completion of this study. The Multicenter Trials Core of the MSKCC Clinical Trials Office will function as the central operations center for this trial and will support all necessary international operations.
Thus, this application builds upon promising clinical and laboratory data generated by our group, rigorously assesses the hypothesis that combined pathway inhibition will result in improved clinical outcomes when compared with MEK inhibition alone, and uses serial tumor biopsies obtained from treated patients to assess mechanisms of sensitivity and resistance.

Dr. William Tansey  
Vanderbilt University Medical Center  

Project Title:  
MYC as an invisible driver in metastatic uveal melanoma

Uveal melanoma (UM) is the most common form of adult eye cancer and results from malignant transformation of melanocytes in the choroid, ciliary body, and iris of the eye. Although UM can be locally contained via targeted radiation or surgery, approximately half of all UM patients develop metastatic disease that cannot be treated and is invariably fatal, usually within a few months. One of the key determinants of whether UM will transition to the metastatic state is loss of BAP1, a chromatin-associated deubiquitylating enzyme that is deleted or mutated in a staggering 84% of metastatic UM cases, and whose knockdown in cell culture systems produces phenotypic and gene expression changes that are hallmarks of aggressive metastatic disease. 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.

Here, I present evidence that loss of BAP1 drives metastatic UM by unleashing the full tumorigenic potential of MYC, an oncoprotein transcription factor that is frequently overexpressed in UM. I argue that loss of BAP1 activates MYC by triggering the ubiquitin-mediated proteolysis of a chromatin regulator called HCF-1, which we have recently found binds to and suppresses the oncogenic activity of MYC. Realization of the BAP1–HCF-1–MYC nexus reconciles the known functions of MYC and its frequent upregulation in UM, and provides a molecular mechanism for how loss of BAP1 promotes tumor progression and metastasis. Importantly, this realization also leads to the unexpected prediction that small molecules designed to target MYC (e.g., JQ1) could have real value in treating metastatic UM.

The goal of this project is to understand how MYC, HCF-1, and BAP1 function to control gene expression programs directly relevant to metastatic UM. Using state-of-the-art genetic and genomic approaches, we will interrogate how MYC and HCF-1 sculpt transcriptional processes in UM cells, and probe how loss of BAP1 alters these processes to promote the transition to a metastatic state. We will also directly test our novel concept that MYC is a previously ‘invisible’ driver of metastatic UM, and ask whether drugs such as JQ1 that target MYC can prevent or reverse the transition to metastatic disease. Minimally, our work will expose the now opaque role of MYC overexpression in UM, as well as revealing the impact of BAP1 depletion on one of its major substrates (HCF-1). If our model is correct, however, results of these studies will transform understanding of the molecular processes that underly UM, and lead to new therapeutic strategies that delay or prevent metastatic UM death.
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 cancer-causing mutations in one of 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 new targets in UM that may provide a basis for new drugs and drug combinations.

Comprehensive genome sequencing data (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. The identification of new therapeutic targets will be undertaken by using an approach known as RNAi screening to identify new genes whose silencing enhances the anti-tumor effects of a novel therapeutic agent (AKT inhibitor) in GNAQ-mutant in UM cells. The AKT inhibitor will be used since the cellular pathway targeted by this drug has been shown to be activated in UM cells that contain GNAQ or GNA11 mutations.

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.

G proteins are molecular switches: they have “off” and “on” states. Normally, these proteins are off until activated by G protein-coupled receptors. Drs. Brian Kobilka and Robert Lefkowitz shared the 2012 Nobel Prize in Chemistry for describing how G protein-coupled receptors activate G proteins in order to move information from the outside of cells to their interior. When G proteins are on, they directly bind and change other proteins inside of the cell. This leads to a wide range of cellular responses including cell growth, movement and division as well as communication between cells.
What happens if a G protein is always on? The outcome is often tragic. For example, in approximately 80% of
the cases of uveal melanoma, either of two closely related G proteins, G\(\alpha_q\) and G\(\alpha_{11}\) (gene names
GNAQ and GNA11) are mutated so that they cannot shut off. These mutations “drive” these melanomas and are
referred to as driver mutations since they promote these cancers. However, knowing that these mutated G
proteins often lead to uveal melanoma is only the first step toward a treatment. How can we use this
knowledge to help patients with uveal melanoma?

In the Sondek lab, we’ve focused on improving our understanding of how the movement of information
controlled by G proteins is regulated. In a 2010 paper published in the journal *Science*, we showed how an
activated G protein, G\(\alpha_q\) in the on state, interacts with one of its primary molecular targets within the cell by
determining the structure of the two molecules bound together at atomic resolution. This structure is a 3-D
roadmap for how to prevent the G proteins with driver mutations found in most cases of uveal melanoma from
communicating with their molecular targets.

We know that certain mutated G proteins found in the eye can result in uveal melanoma and we have a model
for how to prevent these mutated G proteins from communicating with their targets. And yet there’s still a long
way to go before this knowledge can help treat patients with uveal melanoma. Fortunately, a postdoctoral
fellow in the Sondek lab, Dr. Thomas Charpentier, was inspired by this work to develop that next step that will
help take us from the laboratory to clinical application. Dr. Charpentier devised a method to measure the
interaction of G\(\alpha_q\) in the on state with its molecular targets. He adapted this method so that it works with
exceptionally small amounts of protein and with hundreds of samples at a time. We are now collaborating with
Prof. Bill Janzen and the UNC Center for Integrative Chemical Biology and Drug Discovery to screen their
collection of 100,000 small molecules for ones that prevent the mutated G proteins from communicating with
their targets. We intend to turn the molecules we find into effective drugs for the treatment of uveal melanoma.

This exciting and potentially life-saving work was stalled due to a lack of funds. We are grateful to CURE OM
and the Melanoma Research Foundation for the opportunity to continue this work in the ongoing effort to
eliminate uveal melanoma and save lives.