Award ID:
RP170317

Project Title:
Developing Effective Immunotherapeutic Strategies for Advanced Uveal
Melanoma

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Uveal melanoma (UM) is the most common eye tumor in adults. Although the tumor in
the eye can be effectively treated, in half of cases, UM cells will have already traveled to
other organs well before the initial diagnosis and later develop into lethal metastases.
Metastatic UM patients have only a 10% one-year survival. No effective therapy exists.
We aim to develop rational, more effective therapies for metastatic UM. Immune
checkpoint blockade therapy (e.g., anti-CTLA-4, anti-PD-1) is revolutionizing cancer
treatment. By taking off the "brakes" that immune cells naturally apply when confronting
cancer cells, checkpoint blockade drugs enable the immune system to fight cancer cells.
These agents can provide long-term clinical benefit rarely achieved previously. Rapid
clinical advances have been observed in cutaneous melanoma (CM) using anti-PD-1
(nivolumab "Nivo") and anti-CTLA-4 (ipilimumab "Ipi"). These drugs gained FDA-approval
in CM, but UM patients were excluded from these studies. We, and others, have shown
that therapeutic benefit in CM from single-agent therapy correlates with the presence of
inflammation in the tumor. A striking observation, however, is that combination Nivo +
Ipi treatment shows efficacy even in "less inflamed" CM tumors, and we have observed
efficacy in UM tumors (which are "less inflamed") using combination Nivo + Ipi. We have
also shown in CM that the genetic alterations within cancer cells can promote an
environment that suppresses the function of cancer killing immune cells. Our early data
indicates that genetic alterations within UM, which are distinct from CM, may also
suppress immune function. Thus, in this proposal we aim to 1) determine the relationship
between the hallmark genetic and immune features in UM metastases to identify
mechanisms by which UM cells promote a "pro-tumor" microenvironment and evade
immune cell killing, 2)determine the unique molecular/immunological changes induced by
combination therapy in metastatic UM