Award ID:
RP140648

Project Title:
New Therapeutic Strategies for Metastatic Melanoma

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas at Austin

Lay Summary:

Melanoma is a deadly form of skin cancer killing approximately ten thousand Americans per year, with a disproportionate number residing in Texas. Patients with melanoma have a poor prognosis, because while current targeted therapies are initially effective against the most common forms of melanoma containing a specific type of mutant BRAF kinase, their efficacy is limited by the near universal acquisition of resistance and resulting progressive disease. Furthermore, no effective targeted therapy exists for patients with melanomas driven by mutations in other genes, such as NRAS, which also have a substantially worse prognosis. Our multi-disciplinary team at UT Austin, and MD Anderson performed a screen in a mouse model for protein kinases capable of complementing the most common mutation associated with melanoma to impart cancerous properties onto non-cancerous melanocytes. This helped us identify and confirm the c-jun N-terminal kinase 2 (JNK2) as a potential Achilles' heel for metastatic melanomas, including currently untreatable forms of melanomas driven by mutant NRAS. Our long-term goal is to target pathways complementary to the BRAF and NRAS driven pathways of melanoma, as a strategy for treating melanoma and for overcoming intrinsic and acquired resistance to current targeted therapies. In this proposal our central hypothesis is that "Inhibitors of JNK2, will block the proliferation and survival of a subset of BRAF- and NRAS-driven melanoma, both in vitro and in vivo." We have already identified several unique molecules that selectively and potently inhibit JNK2; in this project, we will optimize these to enable the greatest antitumor potency against melanoma. We expect this study to lead to development of an effective new JNK2-targeted therapy for melanoma that will improve the survival of patients with this disease.