CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP160183

Project Title:
Exploiting molecular and metabolic dependencies to optimize personalized therapeutic approaches for melanomas

Award Mechanism:
Individual Investigator

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

Lay Summary:

Melanoma is the most aggressive form of skin cancer. Almost 50% of melanomas have an activating mutation in the BRAF gene that activates the MAPK pathway and causes melanoma growth and metastasis. New targeted therapies that inhibit the mutated form of BRAF and/or the MAPK pathway achieve significant tumor shrinkage in over 50% of metastatic melanoma patients with a BRAF mutation, leading to the FDA approval of three such agents for these patients since 2011. While these treatments are beneficial, many patients fail to respond, and almost all responding patients develop resistance in a short period of time. To date no treatment has been effective at overcoming resistance in patients after it occurs. In addition, these agents are not effective in patients who do not have a BRAF mutation. Thus, there is a critical need to identify new treatments that can prevent or overcome resistance to targeted therapies in patients with BRAF mutations, and to identify effective strategies for patients with a normal BRAF gene. Our proposal tests a new treatment strategy that overcomes both of these challenges. We have found that 30-50% of melanomas that are resistant to targeted therapy have abnormal cellular metabolism, with high levels of energy production due to increased oxidative phosphorylation (OxPhos). We have identified two novel treatments that inhibit OxPhos in cancer cells, and our preliminary data shows that these treatments overcome MAPK inhibitor resistance specifically in melanomas with high OxPhos- regardless of their BRAF status. We will further investigate the molecular events that drive the OxPhos metabolic phenotype, and optimize the new treatment strategies to accelerate the development of personalized clinical trials for patients with advanced melanoma. Our studies have the potential to rapidly translate into new treatments for patients with melanoma, and to improve our understanding of the significance of metabolism in cancer.