CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170633

Project Title:
The Role of the CACNA1D Calcium Channel in Melanoma

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Morrison, Sean

Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Melanoma is responsible for over 80% of deaths from skin cancer. Certain genes are frequently mutated in melanoma cells and cause the cells to proliferate and to metastasize. Drugs that inhibit the functions of these mutant gene products are used to treat patients. These drugs commonly shrink melanoma tumors in patients but within months the melanoma cells develop therapy resistance and disease progression resumes. New therapies are required.

We recently discovered that melanoma cells are particularly sensitive to changes in ion gradients. All cells need sodium, potassium, and calcium ion gradients across their membranes to regulate the movement of biologically important molecules throughout the cell. We discovered that inhibitors of a transporter that creates the sodium/potassium gradient are particularly toxic to melanoma cells and that they synergize with other anti-melanoma drugs to promote tumor regression. Based on these data we performed a clinical trial that showed significant tumor shrinkage in 20% of late stage melanoma patients and stopped melanoma growth in another 45% of patients. Nonetheless, none of the patients were cured. We are thus trying to identify additional ion transporters that have even stronger effects on melanoma cell survival.

We discovered that a calcium transporter, CACNA1D, is produced at unusually high levels and is frequently mutated in melanoma cells. Moreover, we found that CACNA1D inhibitors are more toxic to human melanoma cells than to normal human melanocytes. We therefore propose to test whether CACNA1D promotes the proliferation or survival of human melanoma cells and whether it is necessary for these cells to form tumors or to metastasize. If so, CACNA1D would represent a new therapeutic target. Positive results in these preclinical studies could lead to clinical trials in patients who have run out of options with existing therapies.