CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140271

Project Title:
Targeting p53 in Cancer Through Manipulation of p63 and p73

Award Mechanism:
Individual Investigator

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

Lay Summary:

The p53 tumor suppressor gene is widely mutated in over 50% of human cancers. Over a decade ago, p53 was found to be part of a family of genes known as the p53 family, which includes p63 and p73. Many current therapies for cancer patients and molecular studies on p53 as an effective therapeutic target, focus on p53 solely, ignoring the existence of the other p53 family members. Over the last decade, we have learned that this family of genes acts together to suppress tumorigenesis; therefore, a clear understanding of the cross-talk between the p53 family as a whole is needed to effectively treat cancers with alterations in the p53 family of genes. p53 has been classified as undruggable due to its complex biological functions. p53 reactivation suppresses tumors in mouse models, yet this strategy has proven difficult to implement therapeutically in human cancer. One alternative strategy to overcome p53 loss is to manipulate p63 and p73, which are not commonly mutated in cancer and have tumor suppressive functions. When p53 is deleted, p63 and p73 are still functional and we hypothesize can be used to compensate for p53 tumor suppression. Indeed, we found by manipulating p63 and p73 that genes involved in tumor metabolism are upregulated. In this proposal, we aim to further understand the molecular mechanisms of genes involved in tumor metabolism as tumor suppressing agents and to identify small molecule inhibitors that disrupt interactions of the p53 family to free them to perform their tumor suppressive functions. This proposal is innovative, because we have identified a novel way of potentially treating p53 deficient and mutant tumors, and we aim to identify additional compounds that can be used to treat these tumors. Additionally, this proposal is highly relevant to all tumor types with p53 loss or mutation because of the high frequency of p53 alterations in human cancer.