CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP100516

Project Title:
An Improved Transgenesis Platform for Systematic Screening of Tumor Suppressor Activity in Complete Gene Families in Drosophila

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Many mutations causatively contribute to cancer development, yet obvious phenotypes of an unknown number of mutations in isolation are masked by redundant, compensatory functions of close homologs. Genes affected by such mutations are potentially excellent target genes for cancer therapy. However, without the knowledge about redundant and synergistic functions of closely related genes, mutant screens as well high-throughput drug profiling will miss these targets. Such knowledge is ideally obtained using model organisms, which provide rapid and decisive platforms for determining gene function. Here, we propose to utilize Drosophila as a model to systematically knock out all members of three complete gene families for which individual members have recently been shown to act as tumor suppressors. As a proof of principle, we will target 55 genes in all, including every rab GTPase, histone demethylase and histone deacetylase within the Drosophila genome. We will then test how individual and double mutants of close homologs affect cell growth and proliferation using a robust and quantitative clonal assay that has already been proven successful in the identification of novel cancer genes. Our work will extend the utility of the Drosophila model system by establishing a straight-forward new technology to systematically knock out all the members of entire gene families implicated in cancer. This analysis will yield comprehensive information about redundancies and the relative contribution of individual genes to tumor suppression. Currently, targeted gene knock-out in Drosophila is labor-intensive and needs to be carefully designed for individual genes. The approach presented in this proposal makes full use of the key strengths of the model organism to yield a comprehensive in vivo comparison of the functions and pathologies of dozens of genes within whole gene families. Importantly, the technology developed in our laboratories may be of commercial interest if validated on a larger scale.