CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140612

Project Title:
Collateral Genomic Deletions as Targetable Vulnerabilities in Cancer

Award Mechanism:
Individual Investigator

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

Lay Summary:

One way a normal cell becomes a cancer cell is by deletion of genes that normally prevent uncontrolled cell proliferation, termed tumor suppressor genes (“drivers”, as in drivers of cancer formation). Because the deletion of such tumor suppressor genes occurs stochastically, these deletions often include additional neighboring genes, that do not directly play a role in regulating cell growth, and in many instances, play important roles in cell metabolism (deletion of genes which does not directly contribute to cancer progression are termed “passenger”). Because most critical metabolic processes are carried out by multiple related genes, loss of single one can be readily tolerated by in-built redundancy. Think of a chair with four legs: it can still stand after losing one leg. But this creates a vulnerability in the cancer cell, as removing another leg from the three-legged chair will cause it to fall. Imagine a drug that attacks one leg: a normal cell/chai would still stand, but the cancer cell/chair having lost one leg would collapse. In our previous work, we have presented proof of principal data in cell culture that a deleted passenger gene could be used as a target for personalized molecular therapy. In this proposal, we will continue this line of research by demonstrating that the concept of collateral lethality can be applied in animal models of cancer (one key step closer to the clinic) and we also plan to identify small molecule compounds that selectively kill cancer cells with specific passenger deletions, which may eventually lead to a drug. Our novel approach has yielded many potential therapeutic targets hitherto not thought of in brain cancer. We, therefore, will set up experimental systems to study and validate many of these potential drug targets employing our proven strategy. It is important to note that while immediate work will specifically make an impact in brain cancer therapeutic development, our strategy is generally applicable in all cancers.