CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP160462

Project Title:
Systematic identification of small molecule inhibitors that manipulate telomerase activities

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

The telomerase consists of the TERT enzyme and the TERC RNA template. Telomerase expression and activity are up-regulated in cancer cells, and telomerase dysregulation has been linked to poor prognosis and drug resistance. These studies indicate that the telomerase is an attractive target for anti-cancer therapies. Telomerase inhibition should specifically target tumor cells and work in a broad spectrum of cancers. Treating cancer cells with telomerase inhibitors, however, can provoke cells to adopt telomerase-independent mechanisms, leading to drug resistance. Here, we propose strategies that target regulatory pathways of the telomerase, not the telomerase itself. Specifically, we will target the interaction between TERT and the essential telomere regulator TPP1. Direct binding of TPP1 and TERT recruits TERT for telomere elongation and up-regulates TERT activity. We will systematically screen small compound libraries including those with known pharmacological profiles for inhibitors that directly block TERT-TPP1 interaction. These inhibitors should block telomerase access to telomeres, cause telomere shortening, and lead to cancer cell death. Our pilot screen identified several promising candidates, which also validates our screen design.The proposed study may identify novel cancer-fighting activities for existing drugs. Such drug repurposing is hugely cost-effective for translating bench science to clinical applications. Importantly, our target-driven design promises to identify new inhibitors with high specificity for sustained inhibition of cancer growth, and they may be effective either as stand-alone therapy or in combination with other drugs. The proposal builds on my years of experience in studying protein-protein interactions, telomere and telomerase regulation, and large-scale screens using genomic and proteomic platforms. We are confident that this study will yield novel anti-cancer drugs that can be moved into clinical investigations.