



## CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:  
RP140661

Project Title:  
Analyses of the Regulatory Mechanisms of Tankyrase and Its Role in Tumorigenesis

Award Mechanism:  
Individual Investigator

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

### Lay Summary:

Tankyrases are members of a group of enzymes called PARPs, which modify their target proteins by adding one or a polymer chain of the ADP-ribose group. This modification regulates various aspects of many proteins, including their biological activity and destruction. Through this modification, tankyrase controls several important cellular processes such as cell proliferation and telomere homeostasis. Dysregulation of these processes is often associated with cancer. Therefore, inhibition of tankyrases by small molecule inhibitors is a promising strategy for targeted cancer therapy. However, side effects of current inhibitors of tankyrases, due mainly to off-target inhibition of other PARP family proteins, hinder their application in clinic. Besides the catalytic domain, tankyrases possess multiple additional domains that are functionally important. These additional domains endow unique regulatory mechanisms that distinguish tankyrases from other PARPs. These mechanisms are poorly understood at present. Through determining the crystal structure of tankyrase's catalytic domain bound to its inhibitor, we have uncovered a potentially novel regulatory mechanism controlling tankyrase activity through conformational changes in its catalytic domain. Furthermore, we have identified an endogenous inhibitor of tankyrases that is specifically expressed in cancer cells, suggesting that tankyrase activity is deregulated in cancer. This proposal will examine these hypotheses. This study will lead to a better understanding of the unique regulatory mechanisms of tankyrases and ultimately facilitate development of novel anti-cancer therapeutics.