CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP110330

Project Title:
Bacterial Antitermination Elements as Synthetic Tools that Improve Production of Anticancer Compounds

Award Mechanism:
High Impact/High Risk

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

Lay Summary:

Most anti-cancer drugs were originally discovered as natural products, usually produced by microbes. Unfortunately, researchers have only gained experimental access to a small subset of the natural products that can be produced in theory by microbes, even for organisms that have been scrutinized for decades. Further complicating matters, even when a microbe is found to produce a novel anti-cancer agent the overall production yields of these chemicals are typically well below what is needed for commercial production, or for detailed experimental study. A seemingly simple solution is to excise the genomic region that encodes for the anti-cancer compound and place it in a more amenable host microbe. Unfortunately, for reasons that are currently unclear, this strategy has generally proved to be unsuccessful. Therefore, if genetic tools could be discovered that even modestly improved the success of these experiments they would have a dramatic impact on the discovery and characterization of new natural products, such as those that exhibit anti-cancer activity. Our lab normally researches the mechanisms that harness control over RNA polymerase, the molecular machine that synthesizes messenger RNAs (mRNAs) for their use as templates during protein production. Recently, we discovered a unique mechanism, involving a process called processive antitermination, which triggers an exceptionally stable conformation of RNA polymerase, such that it produces mRNAs with improved efficiency. We theorize that this unique mechanism will particularly enhance the synthesis of unusually long mRNAs, which typically encode for complex metabolites like natural products. Therefore, we propose to investigate whether addition of processive antitermination mechanisms will significantly improve synthesis of mRNAs encoding for anti-cancer compounds. If so, these simple synthetic gene reagents would have a profound and immediate impact on the discovery and production of anti-cancer therapeutics.