CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170714

Project Title:
Optimization of a Novel Class of Microtubule Stabilizers That Circumvent Multiple Drug Resistance Mechanisms Through Crystal-Structure Guided Total Synthesis

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Frantz, Douglas

Entity:
The University of Texas at San Antonio

Lay Summary:

For more than 70 years, Nature has provided some of the most important medicines to combat cancer. A recent study in 2016 showed that of the 175 drugs approved to treat cancer since the 1940's, 85, or 49%, were actually natural products or direct derivatives. Natural products are chemical compounds produced by organisms as part of their normal daily fight for survival. With respect to cancer, most of these life-saving medicines including paclitaxel, vinblastine, etoposide, camptothecin and topotecan have been derived from various plant sources. Thus, the discovery and development of plant-derived natural products to identify new cancer treatments remains an important avenue of basic research.

The taccalonolides are a novel class of plant-derived natural products that bind to microtubules in a unique manner that circumvent multiple mechanisms of drug resistance currently observed with existing chemotherapies in this drug class. In spite of their efficacy against drug resistant tumors, limitations to the clinical development of the taccalonolides remain. This includes their limited supply based on the fact that they that are present in the plant in low quantities and are complex natural products not amenable to chemical synthesis. In response to this, we have evaluated the biological activity of over 50 naturally occurring and semi-synthetically derived taccalonolides to elucidate which parts of the molecule are important for their cytotoxic activities against cancer cells. With this and other information in hand, we are now in a position to rationally design new simplified derivatives of the taccalonolides amendable to chemical synthesis and clinical evaluation. This project proposes the synergistic collaboration between chemists at UTSA and biologists at UTHSCSA to design, discover and evaluate synthetically tractable analogs of the taccalonolides with translational potential as novel microtubule stabilizers for the treatment of drug resistant cancers.