CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP101073

Project Title:
Molecular mechanisms of novel inhibitors of the multidrug resistance P-glycoprotein

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Texas Tech University Health Sciences Center

Lay Summary:

One of the main problems in the treatment of cancer is that tumor cells are either resistant to chemotherapy or develop resistance during treatment. Frequently, tumors are not only resistant to an agent used for initial treatment, but to a variety of chemically unrelated anticancer drugs (multidrug resistance). P-glycoprotein, a protein in the membrane of some cancer cells, is a key mediator of multidrug resistance. It acts by “pumping out” the drugs intended to kill the tumor, preventing their intracellular accumulation and cytotoxic effect. Inhibition of P-glycoprotein reverses multidrug resistance in the laboratory, but the inhibitors used so far in clinical trials have unacceptable toxicity towards normal cells. Therefore, there is an urgent need to develop better inhibitors. We identified a series of small molecule compounds from the National Institutes of Health repository that are potent inhibitors of P-glycoprotein in laboratory studies. The goals of this grant are to define the molecular mechanism of P-glycoprotein, and to elucidate how the new inhibitors block its function. These studies will be invaluable for the development of effective P-glycoprotein inhibitors, and to optimize the use of the inhibitors to reverse multidrug resistance during chemotherapy.