Award ID:
RP130219

Project Title:
The cephalostatin/ritterazine antineoplastics; Synthesis, activity, and structural and mechanistic studies of novel cancer-selective chemotherapeutics

Award Mechanism:
Individual Investigator

Principal Investigator:
Lee, Seongmin

Entity:
The University of Texas at Austin

Lay Summary:
The cephalostatin/ritterazines (CSTAT) are amazing anticancer agents: First, they are extremely efficacious in killing most cancer cells and among the most potent anticancer agents ever tested by the National Cancer Institute; Second, they destroy cancer cells through a mechanism that is completely different from those of any known anticancer drugs; Third, they are 10-20 fold more toxic to cancer cells than normal cells, thereby being promising cancer-selective chemotherapeutics; Lastly, they inhibit novel anticancer targets called oxysterol-binding proteins. Despite their enormous potential for being cancer-selective anticancer drugs, the development of CSTAT-based drugs has been very greatly hampered by an availability problem. Although addressing this problem is crucially important for the CSTAT drug development, so far neither extraction (~100 mg from a half ton of a tube worm) nor synthesis (~70 steps) provided a solution to the problem. Our long-term goals of the proposed research are to develop structurally simple (thus readily accessible through synthesis) yet powerful CSTAT drugs, and to understand the mechanism of action of CSTAT. Our initial efforts have led to a 21-step synthesis of a novel potent CSTAT analog, which is 5 times more active than taxol against skin cancer cells. With these strong preliminary data in hand, we propose to prepare derivatives of our CSTAT analog and evaluate their bioactivity against cultured cancer cells and mouse tumor models. We also propose to determine the anti-tumor mechanism of CSTAT using tools of chemical and structural biology. The proposed study, if successful, will not only provide enough quantities of several potent CSTAT analogs worthy of preclinical evaluation, but also significantly advance our understanding of the mechanism of action of CSTAT drugs. Our proposed program will pave the way for the development of potent, cancer-selective CSTAT chemotherapeutics with minimal side effects.