

EXECUTIVE SUMMARY [NON-TECHNICAL ABSTRACT FOR PUBLIC INFORMATION OR PROGRAM PROMOTION]:

State **in layman's terms** the application's broad, long-term objectives and specific aims, making reference to the potential public benefits of the project relevant to California.

In 1962, a joint project between the U.S. Department of Agriculture and the National Cancer Institute aimed at the discovery of new anticancer agents isolated paclitaxel from the bark of the Pacific Yew tree.

Paclitaxel has been used effectively by doctors as a treatment for lung, ovarian, and breast cancer.

However, it is estimated that the sacrifice of one 100 year old, 40 foot tall yew tree would result in only 300 mg of paclitaxel, just about enough for one single dose for a cancer patient. This problem, when coupled with the environmental threat to the endangered spotted owl, has prompted great interest in the total synthesis of paclitaxel as a potential source of material for cancer treatment and research studies.

The paclitaxel molecule is distinguished by an eight-membered carbocyclic ring. The construction of an eight-membered ring in paclitaxel and other natural products has been the subject of intense effort by many research groups. It is usually the most difficult and interesting step in any such total synthesis. Our approach utilizes a novel intramolecular vinylcyclopropane cycloaddition-fragmentation. We will synthesize in the lab a variety of cyclization test substrates to validate our mechanistic hypothesis.

Another major goal of this project is to optimize any successful cyclizations to make the process amenable to large scale production. This project will provide an effective and economic route towards these complex anticancer agents and improve their availability to medium and lower class populations.