

EXECUTIVE SUMMARY: (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 for California.)

The American Cancer Society estimates that 54,600 Californians died from cancer in 2009. At least 28,130 of these deaths were from cancers that are known to depend, at least in part, on Wnt signaling. Wnts are secreted proteins that instruct target cells to make important decisions about whether to 1) proliferate or differentiate and 2) survive or die. Dysregulation of these instructional cues can lead uncontrolled cell proliferation, thus resulting in cancerous growths. For over a decade, researchers have been trying to develop effective inhibitors of Wnt signaling. To date, these efforts, which have primarily focused on the inhibition of components downstream of Wnt ligands, have largely failed. The *long-term objective* of our lab is to utilize our expertise to develop Wnt pathway specific tools for the diagnosis and treatment of cancer. Recently, we and others have identified a protein called Porcn that regulates the activity and distribution of Wnt proteins. Porcn is found in all cells and plays important roles in normal and abnormal cells. Thus, one approach to harnessing this protein for therapeutic uses would be to specifically inhibit the function of Porcn in cancerous cells while preserving its function in normal cells. We have preliminary data suggesting the possibility that the Porcn protein is folded into a different three-dimensional conformation in normal cells than it is in cancerous cells. Thus, we *hypothesize* that distinct Porcn conformers are present in normal and cancerous tissues. The *aims* of this proposal are to determine the three dimensional conformation of Porcn and to compare the conformation of Porcn in normal cells to that in cancerous cells. If our hypothesis is validated, the experiments in this proposal will provide the basis for the development of diagnostic and therapeutic tools to prolong the lives of Californians.