

## **“Targeting Inhibitor of Apoptosis Proteins for Cancer Therapy”**

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**Abstract:** Inhibitor of Apoptosis Proteins (IAPs) are frequently over-expressed in human tumors and promote cancer cell survival, hence they have become major pharmacological targets for developing new anti-cancer drugs. The goal of this proposal is to generate a novel class of highly specific and potent cancer therapeutics based on the natural IAP-antagonist and tumor suppressor protein ARTS. We will also develop pre-clinical models to evaluate ARTS-agonists, identify human tumors that are candidates for ARTS-based therapy, conduct a high-throughput chemical library screen for small-molecule ARTS-agonists, and evaluate the properties of these compounds for IAP-inhibition and selective cancer cell killing. To achieve these goals, we plan to (1) define the role of ARTS in mouse models of hepatocellular carcinoma (HCC) and breast cancer, (2) perform a survey of human tumors for loss of ARTS expression, (3) use a high-throughput chemical library screen to develop ARTS-based IAP antagonists, and (4) assess the ability of ARTS-agonists to selectively kill cancer cells. These studies will provide proof-of-concept to initiate clinical trials in lymphoma, breast cancer, hepatocellular carcinoma, melanoma and possibly other forms of cancer.