

## **Discovery of Novel Small-Molecule Reactive Oxygen Species (ROS) Inducers for Treating Pancreatic Cancer**

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Pancreatic cancer is the fourth deadliest cancer around the world. Despite recent advancement in understanding the molecular biology of pancreatic cancer, current treatments don't significantly increase survival of patients. Due to the late diagnosis for pancreatic cancer, treatment regimes are more dependent on chemotherapy. However, conventional chemotherapies have little impact on this disease because of drug resistance and rapid metastasis. ROS-inducing compounds, such as imexon and nimbolide, have shown efficacy in this disease. In this project, I aim to discover novel small-molecule ROS inducers that are potent and efficacious in pancreatic cancer, and to elucidate their mechanisms of action. Based on compounds previously discovered in our lab, we have developed two libraries of potential ROS inducers with different chemical scaffolds. Using cell-based assays, I have identified a top compound candidate QD394. To explore its mechanisms of action, we performed RNA sequencing using Bru-Seq technology and conducted combination studies with signaling inhibitors. The preliminary data show that this compound causes cell death via different mechanisms from gemcitabine, a standard-of-care drug for pancreatic cancer, and QD394 may have similar MOAs as napabucasin, which is an orally administered cancer stemness inhibitor that is currently under clinical trials in multiple cancers. I am now using western-blotting and different assays to explore its mechanisms and to identify affected pathways and genes. Our long-term goal is to develop novel ROS inducers that can be optimized for clinical trials in pancreatic cancer. Overall, this project will provide a new therapeutic option for pancreatic cancer and shed light on the biology of ROS inducers in cancer.