



**Pancreatic Cancer Collective Research Team:
“Exploiting DNA-Repair Gene Mutations in Pancreatic Cancer New Therapies Challenge”**



[This abstract was provided by the scientists when their application was accepted.]

Up to 20% of pancreatic ductal adenocarcinoma (PDAC) patients harbor germline or somatic mutations in genes involved in double-strand DNA damage repair (DDR), including BRCA1, BRCA2, PALB2, ATM and CHEK2, suggesting the potential for therapeutic use of poly(ADP-ribose) polymerase (PARP) inhibitors in this population. Two completed trials testing PARP monotherapy have raised optimism about the potential of PARP inhibitors in PDAC and several PARP inhibitor trials are ongoing. However, clinical trial data thus far indicate that many PDAC patients (including those with and without DDR alterations) have de novo resistance to PARP inhibitor monotherapy and that PDAC patients who are initially sensitive to PARP inhibitor monotherapy inevitably develop acquired resistance. Therefore, it is imperative to define strategies capable of reversing both de novo and acquired resistance.

Studies on the molecular mechanism of PARP resistance have revealed that virtually all PARP inhibitor-resistant tumors hyperactivate the ATR/CHK1 pathway. The Team hypothesizes that therapeutic targeting of the ATR/CHK1 pathway will overcome PARP inhibitor resistance in PDAC.

An easily manipulatable and inexpensive preclinical model system is required for functional assays to test this hypothesis. Organoid cultures of patient-derived PDAC tumors offer such an opportunity. Organoids are three-dimensional structures of human primary tumor cells embedded in a gel matrix that have organized into structures that anatomically and functionally mimic the human organ or tumor. While organoid cultures allow inexpensive, large-scale preclinical testing, PDAC patient-derived xenograft (PDX) models are an ideal system for rigorous in vivo preclinical drug testing.

Accordingly, in this project, the Team will comprehensively study PARP, CHK1, ATR inhibitors both as monotherapy and combination therapy in both PDAC organoid and PDX models. During these studies, they will evaluate functional assays dissecting the specific DNA damage repair defects to help molecularly delineate populations responsive to inhibitors of DNA damage repair. Their goal is to utilize these studies to identify the most potent combinatorial strategy, along with predictive biomarkers, that will inform the design of a clinical trial for PDAC patients.

