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## **II. LAY ABSTRACT**

Pancreatic cancer remains an extremely lethal cancer with the highest mortality rate of all major cancers. It is the tenth most commonly diagnosed cancer but the fourth leading cause of cancer death in the United States. Alarming, the number of patients diagnosed with pancreatic cancer and the numbers of deaths due to pancreatic cancer are on a constant rise. While we have recently made many advances to diagnose pancreatic cancer and improved our care for patient suffering from this disease the survival rate has not improved substantially over the forty years. Consequently, novel approaches to understand this disease are desperately needed.

Basic cancer research has made substantial progress within the last ten years teaching us valuable lessons about the biology of pancreatic cancer. This advancement was supported by the introduction of mouse models recapitulating the disease. The same animal models also help investigators to test new drugs for pancreatic cancer treatment before they enter the clinic. Accordingly, suitable animal models are of great value in the difficult fight against pancreatic cancer.

Surprisingly, we do not know which specific cell within the pancreas gives rise to pancreatic cancer, clearly an important step in stopping the development of this disease. One potential source of pancreatic cancer could be adult pancreatic stem cells. Stem cells are long-lived and have the ability to self-renew. While stem cells are crucial for living organisms, their special character makes them susceptible to malignant transformation. These so called “cancer stem cells” are thought to be responsible for uncontrolled tumor growth and relapse after treatment.

Recently, we have discovered a rare cell type in the pancreas that can be identified by a gene called *Dclk1*. We have generated mice that give us the opportunity to visualize and follow these cells and their progeny over time. Surprisingly, *Dclk1* cells appear to be pancreatic stem cells and regenerate the organ after injury. Furthermore, introduction of the most common mutation seen in human pancreatic cancer into *Dclk1* cells leads to pancreatic cancer with all features of the human disease. Therefore, we believe that we have identified a novel pancreatic (cancer) stem cell.

In this proposal we would like to investigate two specific aims. First we want to use our new mouse model in order to characterize the role of *Dclk1* in pancreatic cancer in mice and humans. Furthermore, it is known that *Dclk1* has a function in other stem cells and plays a role in various cancers. Consequently, we would like to target the function of *Dclk1* in order to specifically attack pancreatic cancer stem cells as our second specific aim. We will use available drugs as well as experimental approaches to directly target cells expressing *Dclk1*.

We have designed our project in order to help to answer fundamental questions about the initiation and the progression of pancreatic cancer. Targeting putative pancreatic cancer stem cells might offer a great opportunity to treat and prevent pancreatic cancer in the future.