Drug Development
IN PANCREATIC CANCER

UC RIVERSIDE School of Medicine
CENTER FOR HEALTH DISPARITIES RESEARCH

City of Hope
UC RIVERSIDE
U54 CARE Partnership

UCR/City of Hope Comprehensive Cancer Center Partnership
(Full Project #2 Development of Inhibitors of the PIN1 Oncoprotein in Pancreatic Cancer)

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SUMMARY

Pancreatic cancer is particularly deadly, with one of the worst survival rates of all cancers. Hence, it is particularly urgent to identify key features of its behavior, so that medical treatments can target the unique features of the pancreatic cancer, while avoiding toxic side effects on normal tissues in the body. Cancer develops from tissue cells that not only lose normal regulation of cell growth but also acquire other changes that cause the tumors to survive through cancer treatment . The behavior of our tissue cells is complex and involves the interactions of several different types of proteins that can regulate multiple downstream processes and mechanisms. Thus, altering the action of a single gene or protein can result in a series of changes in a cancer cell, and this research project focuses on the action of the PIN1 gene and protein.

Illustration by UCR Grad Student, Isaac Rodriguez

The PIN1 protein is aberrantly expressed in several cancers including pancreatic, breast, ovary, and in other tumors, where it can alter the structure and expression of tumor suppressors and oncogenes in a complex fashion. Hence, it is considered a potential target or cancer therapy.

RESEARCH PROJECT

In these studies, a main goal is to identify ways to block the function of PIN1 with potential novel therapeutics. One way to do this that we discovered is to derive possible drugs that when attach to PIN1 cause it to become naturally degraded inside the cell. These studies require detailed structural information of the complex with our agents and PIN1 at the atomic level. We have developed two classes of agents: some drugs might act by binding and blocking PIN1 function, while others bind and cause the degradation of PIN1 molecules within cells. Hence, even if the downstream processes controlled by PIN1 are not fully known, studies on the drug's effects can help identify their usefulness against pancreatic cancer and further understand the mechanism by which PIN1 promote cancer progression. One such mechanism involves the crosstalk between pancreatic cancer and surrounding cells. In pancreatic cancer, stromal cells are a crucial part of the tumor microenvironment, including cancer-associated fibroblasts, and tumor-associated macrophages, which play a significant role in pancreatic cancer development, progression, and treatment resistance. Those cells too express high level of PIN1 and we believe play a role in cancer progress and resistance of pancreatic cancer to chemotherapy and immunotherapy.

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NEXT STEPS IN RESEARCH

Drug discovery is a lengthy, and iterative process: currently, our prototype drugs are tested for their ability to inhibit tumor growth in animal models of pancreatic cancer, and the results help us design further improvement of the chemical composition of our PIN1 targeting experimental therapeutics, their dose, regimen and route of administration, for maximal efficacy and minimal toxicity. Here, human pancreatic cancer cells are grown in mice, and the effects of drug treatment are studied, along with analysis of drug circulation in the body and ability to reach the tumors. These efforts are the first critical steps toward advancing the drugs in human clinical studies.

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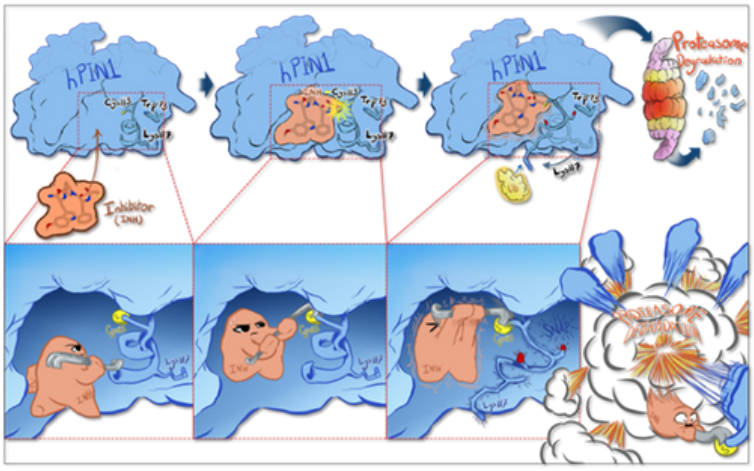

Schematic Illustration of how a molecular crowbar induces Pin1 Degradation. The inhibitor acts as a molecular crowbar that opens up and destabilizes Pin and subsequent cellular degradation.

RESEARCH TEAM

Lead PI: Maurizio Pellechia, PhD (UCR)
Co-Lead: Mustafa Raoof, MD, MS (CoH)
Co-Investigators: Gregor Blaha, PhD (UCR) and David Horne, PhD (CoH)

PUBLICATION

Targeted degradation of Pin1 by protein-destabilizing compounds

MORE INFORMATION

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