



Research

PANCREATIC CANCER ACTION NETWORK

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GRANT SNAPSHOT

2007 Ralph H. Hruban, MD – Pancreatic Cancer Action Network – AACR Career Development Award

Grantee:	Ben Stanger, MD, PhD
Institution:	University of Pennsylvania, Philadelphia
Project Title:	<i>Investigation of the Pancreatic ‘Ductome’</i>
Award Period:	July 1, 2007 - June 30, 2009
Amount:	\$100,000



Biographical Highlights

After receiving his MD and PhD from Harvard Medical School, Dr. Stanger completed a residency program in Internal Medicine at the University of California, San Francisco, a research and clinical fellowship in Gastroenterology at Massachusetts General Hospital, and a research fellowship in Molecular Biology at Harvard University. Currently, Dr. Stanger is Assistant Professor of Medicine in the Gastroenterology Division of the University of Pennsylvania and Assistant Investigator in the Abramson Family Cancer Research Institute. Awareness of the devastating impact of pancreatic cancer came to Dr. Stanger as a medical student, when he was caring for a patient diagnosed with the disease. Concerned about the lack of therapeutic options that were available, he resolved to become personally involved in discovering improved detection methods and treatment strategies.

Project Description

The funded project focuses on the cellular basis of pancreatic cancer, and specifically examines cells in the normal pancreas that give rise to pancreatic cancer and how cellular features (referred to as a cell’s “phenotype”) change as the cancer becomes more advanced. In previous research, Dr. Stanger and his colleagues found that a specialized cell type in the normal pancreas – the centroacinar cell – may be particularly susceptible to cancer-causing mutations and may be the basis for cancer formation. The funded study more closely expands upon earlier studies to improve general understanding of how pancreatic cancer progresses.

Dr. Stanger’s research relies on the use of a mouse model of pancreatic cancer in which the animals predictably develop tumors that closely resemble human pancreatic tumors. Through genetic engineering, he is able to make the tumor cells manufacture a protein that makes them turn green as the tumor is developing. Microscopes and other instruments that are capable of detecting these fluorescent cells permits them to be tracked as they acquire more malignant features and spread to distant organs (“metastasis”). Through the ability to isolate cancer cells at each step during the process of malignant progression, Dr. Stanger’s laboratory is able to study the mechanism of progression. The goal is to understand each step of malignant progression in detail, which hopefully will provide clues on how to prevent metastasis in pancreatic cancer and to improve detection and treatment.



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Some key questions that are being addressed include:

- What makes a cancer cell that has invaded its normal tissue boundary (the “basement membrane”) different from a premalignant cell that respects this boundary?
- What makes a cancer cell that has escaped into the bloodstream different from one that remains in the primary tumor?
- What makes a cancer cell that establishes a metastasis in the liver different from one that is trapped in the bloodstream or is able to metastasize to a different tissue?

Results/Outcomes

To date, normal pancreatic cells have been genetically marked and a large cohort of genetically altered animals have been generated that are destined to develop pancreatic cancers. By virtue of the cell labeling techniques described above (making cancer cells green), the changes that cells adopt early in the metastatic process have begun to be characterized.

Dr. Stanger’s laboratory has initially focused on a specific change known as “epithelial-mesenchymal transition” (EMT), which is thought to be an important feature of cells as they invade and spread. (Epithelial are cells that relate to the epithelium, which covers the internal and external surfaces of the body and provides protection; mesenchymal are cells that originate from the mesoderm and comprise the connective tissues of the body.) The process of EMT is characterized by the loss of cell adhesion and increased cell mobility, and consequently it is widely believed to augment cancer spread. But the process has been difficult to study in the past because of the challenge of directly observing the process during cancer progression, as a tumor develops within an animal. The cell labeling techniques employed in this study allow direct observation of the cells that have undergone EMT within the mouse tumor model.

Next Steps

Dr. Stanger is in the process of isolating these cells to better understand the mechanism of this cellular transformation and is developing techniques to test the importance of the changes that are identified, to determine whether any of the genes that cells use to undergo EMT represent an “Achilles heel” for pancreatic cancer metastasis.

Follow-Up Funding

Dr. Stanger plans to apply for funding through the NIH/NCI once the funded project has reached a more advanced state. The grant from the Pancreatic Cancer Action Network has helped support the work of a clinical fellow in the laboratory, Dr. Andrew Rhim. Based on the research efforts described above, Dr. Rhim has successfully obtained NIH funding to repay a sizable portion of his outstanding medical school loans, funding that permits him to remain focused on pancreatic cancer research. Dr. Rhim is currently applying for additional funding to support his work.