GRANT SNAPSHOT

2005 Dr. Laurence A. Mack and Roselle Mack – Pancreatic Cancer Action Network – AACR Career Development Award

Grantee:	Sunil R. Hingorani, MD, PhD
Institution:	Fred Hutchinson Cancer Research Center, Seattle WA
Project Title:	*The Cell-of-Origin in Pancreatic Cancer*
Award Period:	July 1, 2005 – June 30, 2007 (No-Cost Extension: June 30, 2008)
Amount:	$100,000

Biographical Highlights

After receiving his MD and PhD in cellular and molecular physiology from Yale University, Dr. Hingorani completed his residency at Brigham and Women's Hospital in Boston and a clinical fellowship in hematology and oncology at Dana-Farber Cancer Institute/Brigham and Women's Hospital/Massachusetts General Hospital Cancer Care Program. Subsequently, he held a postdoctoral fellowship at the Massachusetts Institute of Technology, taught at the University of Pennsylvania, Abramson Cancer Center and Abramson Family Cancer Research Institute, and was an attending physician at Philadelphia Veterans' Administration Medical Center. He joined the Hutchinson Center in 2005, where his laboratory focuses on the use of genetically engineered mouse models to learn about the biology of pancreas cancer and how these findings can be used to advance the detection and treatment of the disease in humans.

Project Description

Dr. Hingorani and colleagues developed a genetically engineered mouse model that develops pancreatic cancer that faithfully mimics human pancreatic cancer. These mice first develop preinvasive lesions called pancreatic intraepithelial neoplasias (PanINs). Preinvasive cancer is defined as a cluster of malignant cells that has not yet invaded the deeper epithelial tissue or spread to other parts of the body. PanINs are thought to be the precursors to human pancreatic adenocarcinoma. As part of the funded project, Dr. Hingorani analyzed different strains of these mutant mice for the development of PanINs, and specific pancreatic cells from the different strains with the goal of identifying the specific cell that gives rise to preinvasive and invasive adenocarcinoma. The ability to define the cell-of-origin of pancreatic cancer and recognize the cancer when the cells are abnormal but not yet fully cancerous is a crucial step in developing early detection methods and possibly a cure for this disease.

Results/Outcomes

The project identified compartments that were able to support the formation of precursor lesions that had the capability to progress to invasive disease. It appears that there may be more plasticity in this capability than previously realized, particularly in the setting of different associated influences, such as inflammatory injury. Collectively, the studies conducted by Dr. Hingorani and his colleagues still seem to implicate the centroacinar cell as the most likely and frequent origin of the highly aggressive and invasive form of this disease. In complementary studies, significant

progress has been made in identifying a subpopulation of cells with so-called "cancer stem cell" (CSC) properties from their various mouse models. The CSC likely represent the cells-of-origin identified in the studies described above, the cells in which the relevant mutations initiate disease (and potentially, therefore, the cells that sustain the tumor and confer its inherent resistance to chemotherapy and radiation). Further studies are underway to more fully characterize these cells.

Lessons Learned

The research identifies a potential limit of this genetic approach to identifying the cell-of-origin: the various so-called compartment-specific promoters (e.g. *Elastase, Pdx-1,* etc.) appear not to have strict enough temporal and spatial expression patterns to be definitive about the initiating cell. Thus, indirect inferences are sometimes required based on sampling of a large numbers of cells and assays.

Next Steps

Investigations are continuing on two primary fronts: (1) further characterization of the so-called "cancer stem cells" that maintain the tumor; and (2) discovery of how certain cell compartments in the pancreas are able to resist the effects of key genetic mutations that can otherwise cause cancer when they occur in the correct context. Both of these avenues of pursuit are motivated by trying to identify potential vulnerabilities in pancreas cancers that can be exploited therapeutically.

Follow-Up Funding

Two proposals for NIH grants are currently under review that benefit directly or indirectly from the studies performed under the current grant. In addition, applications have been submitted to private foundations.

Publications

Izeradjene K, Combs C, Best M, Gopinathan A, Wagner A, Grady WM, Deng C, Hruban RH, Adsay NV, Tuveson DA, Hingorani SR. Oncogenic *Kras*^{G12D} and *Smad4/Dpc4* haploinsufficiency cooperate to induce mucinous cystic neoplasms and invasive adenocarcinoma of the pancreas. *Cancer Cell*, 2007;11:229-243.

Hingorani SR. Location, location, location: precursors and prognoses for pancreatic cancer. *Gastroenterology*,2007;133:345-350.

Izeradjene K, Hingorani SR. Targets, trials and travails in pancreas cancer. *JNCCN*, 2007;5(10):1042-1053.