GRANT SNAPSHOT

2008 Michael C. Sandler – Pancreatic Cancer Action Network – AACR Pilot Grant

Grantee:	Matthias Hebrok, PhD
Institution:	University of California, San Francisco
Research Project:	*NF-kB Signaling in PanIN Formation*
Award Period:	July 1, 2008 – June 30, 2010
Amount:	$100,000

Biographical Highlights

Dr. Hebrok received a PhD in Developmental Biology from Max-Planck Institute for Immunobiology in Freiburg, Germany and completed his postdoctoral training at Harvard University and Howard Hughes Medical Institute. Currently, he is Associate Professor and Hurlbut-Johnson Endowed Chair in Diabetes Research at University of California, San Francisco. His research has focused on understanding how islets of Langerhans, the endocrine component of the pancreas, are formed during organogenesis, how their function is regulated in the mature organism, and how changes in gene expression might allow islet regeneration.

Project Overview

Pancreatic ductal adenocarcinoma (PDAC) develops through a sequence of precancerous lesions called “pancreatic intraepithelial neoplasias” or PanINs. Recently, mouse models of PDAC have been created that recapitulate (repeat in its development) human PanIN progression. However, because lesion formation in these mice occurs gradually and the onset of specific stages is variable, the molecular requirements for the different stages have been difficult to interpret. A rapid and synchronized mouse model of PDAC precancerous lesions has been developed using chemical induction of pancreatitis (inflammation of the pancreas), which is frequently correlated with PDAC in humans. The use of this model allows the role of specific pathways to be efficiently determined in the earliest disease stages. Preliminary data using this model show that NF-kB signaling, a pathway that is involved in inflammation and cell proliferation and is highly active in human pancreatitis and PDAC, plays a significant role in lesion formation.

The funded project involves genetic experiments that explore the role of NF-kB signaling in the progression of healthy pancreatic epithelium (the cellular covering of the pancreas) to pre-cancerous lesions. This study aims to better understand the mechanisms by which this pathway guides the progression from normal pancreatic cells to PanINs. Plans are to characterize the effects of disrupting NF-kB signaling in PanIN progression and to determine which cells, in the transition from normal to disease state, possess active NF-kB signaling. Results are expected to provide the field with important indications of the therapeutic and diagnostic possibilities involving the NF-kB pathway.