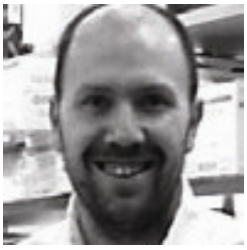
GRANT SNAPSHOT

2007 Carole and Bob Daly – Pancreatic Cancer Action Network – AACR Career Development Award

Grantee:	Martin E. Fernandez-Zapico, MD
Institution:	Mayo Clinic, Rochester, MN
Project Title:	*Characterization of the Hedgehog Interacting Pathway in Pancreatic Cancer*
Award Period:	July 1, 2007 – June 30, 2009
Amount:	$100,000



Biographical Highlights

After receiving his MD from the University of Cordoba in Argentina, Dr. Fernandez-Zapico completed postdoctoral studies in Biochemistry, Molecular and Cell Biology at the Mayo Clinic in Rochester. He is currently Assistant Professor in the Departments of Biochemistry and Molecular Biology, and Medicine at Mayo Clinic and is a faculty of the Schulze for Novel Therapeutics (Mayo Clinic Cancer Center Laboratories). Dr. Fernandez-Zapico serves on the editorial boards of *Pancreatology* and *Journal of Gastrointestinal Cancer*. In 2005, he was awarded a Mayo Clinic Pancreatic SPORE Career Development Award and currently serves as a principal investigator of one of the SPORE projects

Project Description

Pancreatic cancer has one of the poorest prognoses among human neoplasms. Besides surgical resection, which is only possible in less than 20% of pancreatic cancer patients and is rarely curative, current therapies for pancreatic cancer rely on traditional nonspecific cytotoxic agents (cell-killing agents as used in chemotherapy and radiotherapy) with limited effects. There is a strong need to develop effective therapies that target the signaling cascades involved in pancreatic cancer. Interactions between these signaling pathways are crucial to the initiation, progression and maintenance of the transformed cellular features. Thus, characterization of these signaling interactions is fundamental to understanding the complex and varied networks of events that lead to the development and spread of pancreatic tumors. The funded study will focus on (a) understanding the molecular interaction between Hedgehog, a new and important pancreatic carcinogenic cascade, and EGF, a well-characterized oncogenic (i.e., tumor-promoting) signaling pathway in pancreatic cancer, and (b) the role this signaling interaction has on the growth of pancreatic cancer cells. Study results are expected to have important implications for the development of new therapeutic strategies.

Results/Outcomes

A molecular interaction was identified between EGFR-AKT pathway, an established oncogenic cascade, and Hedgehog, a novel pro-carcinogenic pathway in pancreatic cancer. Specifically, the

study demonstrates the ability of EGFR-AKT to activate GLI1 transcription factors, essential effectors of the Hedgehog oncogenic role in pancreatic cancer cells. A combination of genetic and pharmacological manipulations of the EGFR-AKT pathway shows that this cascade is able to activate GLI transcription activity even in the absence of an active Hedgehog signaling. GLI sequence analysis identified candidate AKT phosphorylation sites within domains that are essential for its transcriptional activity, such as the coactivator binding domain, suggesting potential molecular mechanisms underlying the modulation of GLI function by this kinase in pancreatic cancer cells. Further analysis of this molecular interaction shows that GLI requires an intact EGFR-AKT activity to initiate a survival cascade in pancreatic cancer cells. Blockade of EGFR-AKT using RNA interference or dominant negative molecules impairs GLI-mediated activation of the anti-apoptotic molecules and its survival function in pancreatic cancer cells in vitro and in vivo. Conversely, constitutively active EGFR-AKT synergize with GLI1 in the activation of pro-survival molecules in pancreatic cancer cells. Taken together, these results provide novel insight into mechanisms underlying Hedgehog-mediated pancreatic carcinogenesis. Moreover, since pharmacological inhibitors of EGFR-AKT and Hedgehog pathways are currently being used in clinical trials, the knowledge from this study presents new avenues for the development of therapeutic regimens for this dismal disease.

Next Steps

The data collected from this project provided the preclinical data and rationale to develop a Phase I trial targeting the EGFT and Hedgehog cascades in pancreatic cancer. Plans are to start this trial in early 2009.

Follow-Up Funding

Mayo Clinic Pancreatic Cancer SPORE (9/1/08 – 8/31/13; Amount: $197,249/year).
NIH-NCI-Mayo Clinic Pancreatic SPORE
SPORE Project #3: Hedgehog and EGF Pathway Interaction – A Novel Approach for a Multi-Target Therapy in Pancreatic Cancer

Publications Related to Funded Project

Nolz JC, Fernandez-Zapico ME, Billadeau DD. TCR/CD28-stimulated actin dynamics are required for NFAT1-mediated transcription of c-rel leading to CD28 response element activation. *J Immunol*, 2007;179:1104-1112.

Fernandez-Zapico ME. GL1: more than Hedgehog? *Pancreatology*, 2008 (in press).

Fernandez-Zapico ME. P300-GLI, a novel mediator of Hedgehog survival function. *Biochemical J* (under review).