



Research

PANCREATIC CANCER ACTION NETWORK

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GRANT SNAPSHOT

2004 Pancreatic Cancer Action Network – AACR Career Development Award

Grantee:	Anirban Maitra, MD
Institution:	Johns Hopkins University School of Medicine, Baltimore, MD
Project Title:	<i>Notch Signaling in Pancreas Cancer</i>
Award Period:	July 1, 2004 – June 30, 2006
Amount:	\$100,000



Biographical Highlights

Dr. Anirban Maitra obtained his MD from the All India Institute of Medical Sciences at New Delhi, India in 1996. Subsequently, he completed a residency in anatomic pathology from the University of Texas Southwestern Medical Center, Dallas and a fellowship in pediatric pathology from Dallas Children's Medical Center. He arrived at Johns Hopkins in 2001 for a combined clinical-research fellowship in gastrointestinal/liver pathology, and joined the faculty in 2002. Dr. Maitra is currently an Associate Professor of Pathology and Oncology, and an affiliate faculty at the McKusick-Nathans Institute of Genetic Medicine. He is the Associate Editor of *Current Molecular Medicine*, and has received numerous awards for his research, including the Benjamin Castleman Award, the Warren R. Lang Award, the Gordon Vawter Award, the Harry Neustein Award, and the Lotte Strauss Award. Dr. Maitra's research goals focus on the identification and preclinical validation of rational, cancer-specific therapies for pancreatic cancer.

Project Description

The Notch signaling pathway is a series of cell receptors and ligands (molecules that bind to the receptors) that cause growth and changes in the cells. The Notch pathway is important in the development of cells in embryos. It is normally turned off or dormant in adult cells. However, active Notch signaling has been found in several human cancers. Dr. Maitra has demonstrated that Notch signaling plays a role in precancerous changes both in humans and mouse models of pancreatic cancer. The funded project tests the theory that the Notch signaling pathway plays a cancer promoting role in pancreatic cancer and attempts to determine if inhibiting Notch signaling has potential therapeutic value. Plans are to manipulate different components of the Notch pathway in pancreatic cancer cells and then grow them in the lab to determine if cell growth is affected. The Notch pathway will then be inhibited in pancreatic cancer mouse models to see if tumor growth is inhibited. The study will be the first functional characterization of Notch signaling in human pancreas cancer and will determine the basis for therapeutic targeting of the pathway in pancreatic cancer.

Results/Outcomes

The Notch signaling pathway is active in the vast majority of pancreatic cancers but this does not occur as a result of genetic alterations in DNA ("mutations"). More importantly, there are subsets of



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cells in pancreatic cancer with tumor initiating properties that are particularly susceptible to Notch inhibition (“cancer stem cells”). The application of pharmacological inhibitors of Notch signaling to pancreatic cancer selectively depletes them of these tumor initiating cells. This subset of cells is believed to be the basis for pancreatic cancer recurrence and for systemic metastases. Thus, Notch inhibitors provide a particularly compelling rationale to be evaluated in the clinic, in combination with more traditional chemotherapeutic strategies.

Lessons Learned

This project would not have been feasible without the collaborative efforts of colleagues and mentors. Science cannot be performed in isolation, and as a junior investigator, it is imperative that there is appropriate mentorship.

Next Steps

Targeting the Notch signaling pathway in pancreatic cancer has emerged as a major area of interest for many pharmaceutical companies. Dr. Maitra is currently testing some of these agents destined for the clinical track.

Follow-Up Funding

According to Dr. Maitra, the greatest asset of the Pancreatic Cancer Action Network - AACR Grant “...was to get my foot in the door for pancreatic cancer research. It gave me the opportunity to devote committed time to studying pancreatic cancer and to form fruitful collaborations with investigators who share this research interest.”

R01 CA113669-01 (04/01/05-03/31/10). NIH/NCI, Hedgehog Inhibitors in Pancreas Cancer.

1R21 DK072532-01 (08/01/05-07/31/08). NIH/NIDDK, Hedgehog Signaling in Pancreatic Neoplasia.

Publications Related to Funded Project

Mullendore ME, Koorstra J-B, Li Y, Offerhaus GJ, Fan X, Henderson CM, Matsui W, Eberhart CG, Maitra A, Feldmann G. Ligand-dependent notch signaling is involved in tumor initiation and tumor maintenance in pancreatic cancer. (under review).