GRANT SNAPSHOT

2007 Nancy Daly Riordan – Pancreatic Cancer Action Network – AACR Career Development Award

Grantee:	Paul J. Grippo, PhD
Institution:	Northwestern University, Chicago, IL
Project Title:	*Evaluating Kras Oncogene Addiction in Pancreatic Precancer and Cancer*
Award Period:	July 1, 2007 – June 30, 2009
Amount:	$100,000

Biographical Highlights

Dr. Grippo received his PhD in Animal Health and Biomedical Sciences from the University of Wisconsin in 2000. Currently, he is an Assistant Research Professor in the Department of Surgery at Northwestern University. Working with mouse models of pancreatic cancer for over ten years, Dr. Grippo continues to generate new models in an effort to further understanding of the disease progression. In addition to his contributions as a researcher, he has been a volunteer since 2002 with the TeamHope Affiliate in Northern Illinois, which has brought him face-to-face with pancreatic cancer patients and their families. Since receiving the Nancy Daly Riordan Career Development Award in 2007, Dr. Grippo has received numerous invitations to present at professional conferences and to participate in research collaborations. He credits the award with helping establish his career.

Project Description

The main objective of this research is to engineer and employ a modeling system of pancreatic cancer in mice that expands our understanding of pancreatic precancer and cancer. The center of this work revolves around a gene called Kras, which is mutated in nearly all pancreatic cancers. Kras has the ability to promote cell growth as well as alter other cellular functions. When persistently active, this protein appears to initiate the early stages of cancer (or precancer) as demonstrated in several mouse models of pancreatic cancer. In addition, it appears that multiple cell types can respond in a similar manner to generate precancer and cancer in the pancreas.

One significant limitation with current mouse models is that the mutation in Kras occurs prior to the birth of the animals. In the human, this event appears to be confined to adults. Based on these facts, this work addresses three issues: (1) the effects of mutant Kras expression in adult tissue; (2) the differences among three targeted pancreatic cell types as a means of disciphering which ones can derive pancreatic cancer; and (3) the dependence of developing precancer and cancer on the expression of mutant Kras. The cell types examined in #2 above include mature, enzyme-producing acinar cells (marked as EL) and two cell types (marked as Pdx and Nestin) that may be progenitor cells for several adult cell types. These two cell types may be exclusive of each other, overlap with each other, or have varying degrees of both. At the point mice develop precancerous lesions and/or pancreatic cancer, mutant Kras expression will be abrogated to determine if these cells are addictive to the effects of mutant Kras expression and if and when the cancer cells achieve a level of independence from mutant Kras. The results of this project are expected to have

significant practical impact by helping determine the value of targeting specific cell types with inhibitors that block persistently active Kras.

Results/Outcomes

Study results demonstrate that upon expression of mutant Kras, both of the potential progenitor cell types (Pdx and Nestin) can lead to the development of aberrant ductal lesions bordering a precancerous appearance. One of these adult cell types (Pdx) was capable of initiating the development of pancreatic precancer similar to its human counterpart. It was unclear if the other cell type (Nestin) could do the same in adult tissue. Targeting with adult enzyme-producing cells (EL) did generate several tissue abnormalities, though none of these appeared precancerous. Pancreatic cell type markers for mature acinar (amy), centroacinar (hes), ductal (CK19), and islet (insulin) cells as well as stem cell markers (Eppk1, Sox-9) are being employed in a staining regimen to determine which cell types are responsible for the development of precancer. Ultimately, the types of cells (for example, hes+/CK19+/Eppk1+/Sox-9+) that are being targeted for mutant Kras expression will be identified as the ones that generate pancreatic precancer (and ultimately cancer). This information will be valuable for identifying the cell type(s) responsible for human disease and aid in earlier detection and diagnostic efforts while determining if drug inhibition of mutant Kras is effective at either the preinvasive or invasive stages of pancreatic cancer.

Lessons Learned

The cell type targeted can make a profound difference, as Pdx-positive adult cell types are capable of generating precancer. However, these lesions require an extended period of time for their development (about 1 year), demonstrating that a single mutation may require a long incubation period as well as the need for an additional mutation for progression to cancer to occur. In addition, the background strain of the mice relative to the type of genetic mutation appears to be pivotal for the onset of pancreatic precancer and perhaps cancer.

Next Steps

Future work will focus on the dependence of mutant Kras-derived precancer by abrogating mutant Kras expression once the precancer has developed. To promote invasive disease from these precancerous lesions, the mice will be bred into background strains which are sensitive to the induction of pancreatic lesions and lack tumor suppressor genes (like p53 and p16). These mice will also be used to study the dependence of pancreatic cancer at various stages of expression of mutant Kras.