GRANT SNAPSHOT

2007 Pancreatic Cancer Action Network Pilot Grant

Grantee:	Douglas Hanahan, PhD
Institution:	University of California, San Francisco
Project Title:	*Assessing Mechanisms and Therapeutic Potential of an Aspartyle Protease in Pancreatic Cancer*
Award Period:	July 1, 2007 – June 30, 2008
Amount:	$60,000

Biographical Highlights

Dr. Hanahan is an American Cancer Society Research Professor in the Department of Biochemistry and Biophysics at the University of California, San Francisco, where he is leader of the Mouse Models of Cancer Program in the Comprehensive Cancer Center, and a member of the Diabetes Center. He received a PhD in Biophysics from Harvard, where he was a Harvard Junior Fellow. He worked at Cold Spring Harbor Laboratory, first as a graduate student and then as a faculty member before moving to University of California, San Francisco. In the mid-1980's, Dr. Hanahan produced some of the first transgenic "oncomice", genetically engineered to develop organ-specific cancers. He has used mouse models of cancer both to investigate the multistage pathways that govern tumor formation and progression, and to explore the benefits of targeted therapies (in particular angiogenesis inhibitors) aimed at different stages of disease progression; He co-discovered the "angiogenic switch", which is activated to produce new blood vessels in early stage neoplastic lesions preceding overt tumors. Dr. Hanahan has authored approximately150 publications, including a number of influential perspectives.

Project Description

The funded project uses tumor-bearing mice to test the hypothesis that Cathepsin E expression in neoplastic ductal epithelial cells of the pancreas promotes carcinogenesis and is therefore an attractive therapeutic agent for pancreatic cancer. It also examines the role of ritonavir, an FDA-approved drug which inhibits Cathepsin E, in improving disease prognosis. Cathespsin E is an aspartyl protease which is expressed at very low level in normal pancreas. Dr. Hanahan's research has shown that the expression of this protease is increased by 400 fold in pancreatic tumors. In addition, published clinical studies show that cathespin E expression in pancreatic tumors correlates with poor prognosis. Based on these findings, the role of Cathepsin E in pancreatic cancer is evaluated using a pharmacological inhibitor (ritonavir) and a genetic knockout of Cathepsin E in a mouse model of pancreatic cancer. Bearing in mind this high expression of Cathepsin E in these tumors, the project also focuses on generating monoclonal antibodies against Cathespin E to serve as targeting agents for imaging pancreatic cancer potentially for early detection.

Results/Outcomes

The biochemical analysis of the protease Cathepsin E in the pancreatic tumor microenvironment revealed that the majority of the Cathepsin E in these tumors exists as an inactive zymogen ,which

can auto-activate itself when subjected to acidic pH *in vitro;* surprisingly, however, it is not catalytically active in the pancreatic tumor microenvironment. This finding suggests that the aspartyl protease activity of Cathepsin E may not play an integral role in tumor progression. The possibility remains that Cathepsin E protein may perform a non-protease role, similar to what has been reported for its close homologue Cathepsin D in breast tumors. This latter possibility is currently being evaluated by crossing a gene knockout of Cathepsin E into a mouse model of pancreatic cancer, and assessing the effect of Cathepsin E loss on tumor volume, lifespan and other parameters of the desmoplastic microenvironment of pancreatic cancer.

Lessons Learned

The observation that Cathepsin E is expressed in very high amounts both at mRNA and protein level, coupled with the finding that the enzyme can be catalytically active under appropriate conditions but is still functionally inactive in the PDAC microenvironment, suggests a novel functional contribution of the protein, distinct from its protease activity. Alternatively, Cathepsin E may be exemplary of a class of candidate biomarkers that are revealed by expression profiling but lack functional significance and thus may not constitute therapeutic targets.

Next Steps

Efforts are underway to (1) determine whether Cathepsin E plays a noncatalytic role in the tumor microenvironment using the Cathepsin E knock out mice in the mouse PDAC model;
(2) delineate the cause of elevated expression of Cathepsin E in the tumor microenvironment, in particular the possibility that it is up-regulated by the actions of the mutant K-Ras oncogene; and
(3) use monoclonal antibodies that have been generated which recognize the inactive form of Cathepsin E as the targeting component of a molecular imaging probe that could be used for early detection of PDAC and/or for monitoring disease progression.

Follow-Up Funding

The results from this pilot project have been leveraged into a partnership with a NCI PO1 Grant focused on pancreatic cancer, based in Boston and headed by Prof Ron DePinho of the Dana Farber Cancer Center at the Harvard Medical School. This program project has an antibody core (headed by Prof James DeCaprio of the Dana Farber Cancer Center), which has been generating the monoclonal antibodies. Another core, with world class expertise in noninvasive imaging, led by Ralph Weissleder of Massachusetts General Hospital, will collaborate in assessing the utility of these antibodies when linked to imaging agents for detection of pancreas cancer, initially in the genetically engineered mouse models of the human disease.