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May 28, 2009

Dear SSAT Board of Trustees:

I was honored to be the recipient of a Career Development Award from the Society for Surgery of the Alimentary Tract in 2006 and would like to express my appreciation for this grant. As a result of this grant, we have learned a great deal regarding the importance of the tumor-associated stroma to the progression of pancreatic cancer. A no-cost extension of the award was granted and I am pleased to submit my final progress report on our work.

Pancreatic cancer remains a very challenging disease with a dismal prognosis and currently has no currently effective therapy. It is notoriously associated with a dense desmoplastic stroma, which in other cancers, has been shown to be associated with tumor progression. However, relatively little is known about the contribution of the stroma to pancreatic cancer.

As a result of support from the SSAT Career Development Award, we established a novel carcinoma-associated fibroblast cell line (human pancreatic stellate cell, HPSC) derived from human pancreatic adenocarcinoma. We demonstrated that conditioned media from HPSCs (HPSC-CM) increased pancreatic cancer cell proliferation, migration, invasion and soft agar colony formation in a dose-dependent fashion. Moreover, cancer cells exposed to HPSC-CM were also more resistant to chemotherapy and radiation. In an orthotopic nude mouse model of pancreatic cancer, the HPSCs significantly increased growth of the primary pancreatic tumor and metastases. The HPSCs also appeared to influence tumor initiation since a lower number of cancer cells was required to form tumors when HPSCs were present.

We have presented the results above at several major national meetings (American Association for Cancer Research, Society of Surgical Oncology, Pancreas Club, SSAT, American Pancreatic Association). In February 2008, our manuscript on the effects of cancer-associated fibroblasts, or human pancreatic stellate cells (HPSCs) on pancreatic tumor progression and metastasis was published in *Cancer Research* as a "highlighted article" and was included on the cover (Hwang R.F. *et al.*, *Cancer Res*, 2008, 68(3):918-926).

In order to identify specific factors produced by the HPSCs that may be responsible for its effects in pancreatic cancer, we performed expression profiling of the HPSCs with and without co-culture with cancer cells. These results provided a wealth of interesting molecules expressed by the HPSCs that may be rational therapeutic targets. To expand our own efforts to investigate

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these possible targets, we have shared the HPSC cell line with several collaborators to further characterize the role of these cells in pancreatic cancer. We have shown that HPSCs express the adrenomedullin receptor, CRLR, and CRLR-associated binding proteins (Ramachandran *et al.*, *Cancer Res* 2007; 67(6):2666-2675). Recently a follow-up manuscript was submitted that shows that HPSCs secrete adrenomedullin (AMA) and growth is inhibited by an antagonist to AMA. Furthermore, silencing adrenomedullin receptor in the stroma strongly reduced tumor development and metastasis (Ramachandran *et al.*, submitted to *PLOS Medicine*). In collaboration with Dr. Carol Otey at the Univ. of North Carolina-Chapel Hill, the HPSCs also appear to be play a role in upregulation of the expression of palladin, which was recently identified in a rare inherited form of pancreatic adenocarcinoma (Goicoechea *et al.*, submitted to *Cancer Research*). Two additional manuscripts are in preparation, describing our results on the effects of HPSCs on tumor angiogenesis and the distinctive expression profile of HPSCs compared to pancreatic cancer cells.

With the initial preliminary data generated by the SSAT Career Development Award, I was awarded a career development award in 2007 from the pancreatic cancer SPORE grant from the NIH/National Cancer Institute which focused on specific stromal factors (e.g.-stromelysin-3, periostin) that influence pancreatic cancer. I have submitted a K08 Mentored Clinician-Scientist Award application focused on the role of stromal-derived periostin on pancreatic fibrosis, the progression of chronic pancreatitis to pancreatic cancer and tumor progression. In this proposal, we plan to cross a novel periostin-knockout transgenic mouse with a new high Kras-expressing mouse model of pancreatic fibrosis and cancer developed by my lab mentor, Dr. Craig Logsdon. Although the grant was not funded on the first submission, it did receive a favorable score and was re-submitted in March 2009. Finally, I am preparing for submission of an NIH R21 grant for June 2009 on the role of the putative Wnt inhibitor, Dickkopf-3 (DKK3) in tumor-stromal interactions in pancreatic cancer. In this project, we will examine the effects of HPSC-derived DKK3 on tumor-stromal crosstalk to determine whether DKK3 actually has a tumor-suppressive or -promoting effect.

The mentor for my SSAT Career Development Award, Dr. Craig D. Logsdon, Ph.D., Professor in the Department of Cancer Biology continues to be an enthusiastic supporter of my efforts and a tremendous resource for his expertise. In addition, I am fortunate to have very supportive clinical mentors in the Departments of Surgical Oncology and GI Medical Oncology in Douglas Evans, M.D. (recently moved to the Medical College of Wisconsin), Jason Fleming, M.D. and James L. Abbruzzese, M.D.

The SSAT Career Development Award was the first significant achievement in my early research career. The data generated with the support of this award has opened up an entire career's worth of interesting studies to pursue to better understand the role of the stroma in pancreatic cancer. Again I would like to thank the SSAT for this tremendous opportunity.

Warmest regards,



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