Bryan Spring, Ph.D. received a **NIH Ruth L. Kirschstein NRSA Postdoctoral Fellowship (F32).**

Award Period: October 1, 2010 - September 30, 2013

Project Title: "Hyperspectral Microendoscopy to Monitor VEGF During Pancreatic Cancer Therapy"

Project Overview:

Pancreatic cancer (PanCa) is a devastating disease with the lowest 5-year survival rate of all malignancies (<5%); therefore, there is a desperate need for improved treatment regimens. Pancreatic cancer cells and other cancer cell types up-regulate their expression of specific genes during therapy to promote tumor cell proliferation and survival. For example, cancer cells can increase production of cellular signaling factors, such as cytokine growth factors and their receptors. Vascular endothelial growth factor (VEGF) exemplifies the multitude of cytokines that play a role in tumor survival and metastasis. The Hasan group and others have shown that VEGF expression is up-regulated by cancer cells in response to subcurative cytotoxic therapies, such as chemotherapy, radiotherapy and photodynamic therapy (PDT). This tumor response often leads to disease recurrence and increased metastasis, paradoxical to the goals of therapy. During investigation for strategies to mitigate this effect, the Hasan group has found that secreted VEGF levels are elevated during a short time window following PDT. This result underscores the importance for developing tools to monitor cytokines online during cancer therapy.

The overall goal of the proposed research is to capture the spatiotemporal dynamics of tumoral VEGF expression in an orthotopic, murine PanCa tumor model during combined PDT and anti-VEGF therapy. This study will also investigate the enhanced treatment outocome found using a newly developed nanoparticle to target the intracellular pool of VEGF. Our first aim is to construct a minimally invasive, quantitative molecular imaging system. A flexible, submillimeter-diameter fiber-optic imaging bundle will be used to access and image pancreatic tumors in situ. This probe will be coupled to a hyperspectral fluorescence detection system to facilitate rigorous quantification of relative changes in secreted VEGF levels. That is, each pixel of the image will contain a fluorescence emission spectrum and each pixel will be analyzed to isolate the anti-VEGF monoclonal antibody-fluorophore conjugate fluorescence (the imaging agent we will employ to visualize VEGF) from the tissue autofluorescence. The proposed design will enable frequent imaging during longitudinal studies. Based on the recorded VEGF expression and secretion dynamics, we will implement timed delivery and optimal dosing of an anti-VEGF therapeutic agent targeted to the appropriate tissue compartments (using the nanoconstruct to target intracellular VEGF and free Avastin to target extracellular VEGF) to optimally block VEGF activity. This work will assess the potential for image-guided PanCa therapy to improve treatment outcomes, and will investigate the mechanism of impoved therapeutic outcome using nanotechnology to target and neutralize intracellular pools of cytokine growth factors.