

The ACC would like to thank Dr. Linda Shapiro for allowing us to use an excerpt from one of her protocols as an example for the project overview section of the animal care and use form.

Section 4: Project Overview

Using layperson terms, describe the purpose of the study and its potential value to human or animal health, the advancement of knowledge, or the good of society.

Prostate cancer is the second leading cancer-related cause of death in men and the second most frequently diagnosed cancer behind skin cancer. Current therapies are insufficient to treat advanced, metastatic prostate cancer, and it is therefore imperative that we gain further insight into the molecular processes leading to prostate cancer initiation, progression, and metastasis to develop new, more effective treatments. In particular, fully understanding the processes leading to prostate tumor metastasis (cancer spread to distant sites), such as invasion and angiogenesis (new blood vessel formation), is critical to the success of improving prostate cancer treatment. Solid tumors, including prostate cancers, must build new blood vessels in order to invade, grow, and metastasize. Important to prevention strategies, these new blood vessels form very early in tumor development and can control the rate of disease progression. Since new blood vessel growth into prostate tumors increases tumor growth and metastases, identifying new regulators of angiogenesis will significantly contribute to the development of novel therapeutic modalities. Pertinent to this project, identifying novel molecular mechanisms that regulate both angiogenesis and prostate tumor cell invasiveness may result in improved prostate cancer therapies.

The cell surface peptidase Prostate Specific Membrane Antigen (PSMA) has been shown to be expressed at much higher levels in prostate tumors than in the normal prostate. It has also been shown to be expressed in the new blood vessels of solid tumors, whereas it is not expressed in normal blood vessels; however, the functional role of PSMA in prostate cancer progression and angiogenesis is unknown. Studies in our lab have shown that PSMA regulates signaling through beta-1 integrin, a molecule involved in cell adhesion, invasion, and motility, which are necessary for cancer cell angiogenesis and metastasis. We have shown that adhesion and invasion of both prostate cancer cells and blood vessel cells are exquisitely PSMA dependent. Therefore, we propose that PSMA regulates both angiogenesis and prostate tumor invasion. Our work has suggested that PSMA modifies the tumor environment by degrading the protein matrix surrounding cells. In addition to allowing tumor and blood vessel cells to invade surrounding areas once these protein barriers are removed, the small protein fragments (peptides) can act as attractants, through beta-1 integrin signaling, to induce the formation of new blood vessels. We propose that PSMA works with other enzymes to degrade these extracellular proteins and form small peptides which induce the formation of new blood vessels.

This research aims to understand mechanisms of prostate cancer progression through PSMA. To more effectively combat prostate cancer and other angiogenesis-dependent malignancies, it is essential that we identify new molecular targets for prevention and treatment. Although PSMA has attracted much attention as a marker of prostate cancer and angiogenesis, very little is known about its molecular function in these processes. Understanding the functional contribution of PSMA to prostate cancer progression and angiogenesis, and further investigation of the mechanisms of PSMA regulation of these pathologies may lead to future novel, more effective and specifically targeted anti-cancer therapies. Ultimately, if PSMA inhibition leads to

decreased invasion, metastasis, and angiogenesis, then therapies specifically targeting this molecule could be effective in cases where current treatment is not, and possibly would have fewer side-effects than traditional prostate cancer therapy.