Research and Educational Interests

Briefly outlined below are my future research plans for the two programs I am pursuing and a brief summary of my educational interests. These programs are complementary to programs in the Department of Nutrition, Dietetics, and Hospitality Management.

I foresee collaboration with other investigators in the Department of Nutrition, Dietetics, and Hospitality Management and interdisciplinary collaboration with investigators in the Boshell Diabetes and Metabolic Disease Research Program and potentially in the Harrison School of Pharmacy as important elements for the success of these programs.

Research Interests

Protein Kinase C delta (PKCδ) and Metabolic Disease Program

My *long term goal* is to identify and delineate the mechanism(s) by which signaling molecules and pathways activated by nutritional factors regulate insulin resistance and obesity-related liver disease. The *objective of this Program* is to determine the role of PKCδ in diet-induced nonalcoholic steatohepatitis and hepatic insulin resistance. **I will test the central hypothesis that PKCδ mediates the development of nonalcoholic steatohepatitis and hepatic insulin resistance.** This hypothesis is based on my initial observations and those of others. *First*, hepatic PKCδ activation occurs in lipid-induced and diet-induced animal models of insulin resistance. *Second*, PKCδ activation is associated with cellular events commonly observed in nonalcoholic steatohepatitis, namely high fat diet induced oxidative stress, endoplasmic reticulum stress, and lipotoxicity related apoptosis. The *rationale* for the research proposed here is that, once the *in vivo* role of PKCδ in nonalcoholic steatohepatitis and hepatic insulin resistance is known, novel therapeutics can be designed to inhibit PKCδ, thus preventing or treating nonalcoholic steatohepatitis. Importantly, my research team has obtained preliminary data on: 1) the activation of PKCδ in diet-induced nonalcoholic steatohepatitis; 2) the use of cellular models to investigate nonalcoholic steatohepatitis and insulin signaling; and 3) preliminary mechanistic and *in vivo* data linking PKCδ to nonalcoholic fatty liver disease and nonalcoholic steatohepatitis.

I will pursue the following three specific aims for an R01 grant application:

1. Determine the expression and activation of PKCδ in the progression of non-alcoholic fatty liver disease.
The working hypothesis is that liver and fat PKCδ activation and expression are upregulated in animal models of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis and in the liver of humans with obesity-linked nonalcoholic steatohepatitis.

2. Determine the role of PKCδ in a genetic model of obesity-linked insulin resistance and diabetes.
The working hypothesis is that PKCδ regulates lipid metabolism and, when chronically activated, cell death. PKCδ null mice bred into a db/db background will be used for these studies.

3. Determine the *in vivo* role of PKCδ in diet-induced steatohepatitis and hepatic insulin resistance.
The working hypothesis is that PKCδ null mice are protected from diet-induced nonalcoholic steatohepatitis and hepatic insulin resistance in relevant models of human nonalcoholic steatohepatitis. We also hypothesize that mice with elevated or reduced expression of PKCδ in the liver are more or less, respectively, susceptible to nonalcoholic steatohepatitis and hepatic insulin resistance.

I will pursue the following specific aims for a small grant or post-doctoral fellowship equivalent grant application:

1. Determine the sites of PKCδ catalyzed serine or threonine phosphorylation in Foxo1.
The working hypothesis is that PKCδ phosphorylates Foxo1, a key transcription factor that regulates the expression of genes involved in glucose and lipid metabolism, stress resistance, and apoptosis. Our preliminary data shows that Foxo1 is a substrate of PKCδ.

2. Determine the role of PKCδ in the expression of Foxo1 regulated genes in animal models of obesity-linked insulin resistance and diabetes as well as in cellular models of insulin resistance.
The working hypothesis is that PKCδ regulates the expression of hepatic genes involved in glucose and lipid metabolism, stress resistance, and apoptosis. Our preliminary data shows that Foxo1-regulated gene expression in primary hepatocytes treated with fatty acids is significantly reduced in cells isolated from PKCδ null mice compared to PKCδ wildtype mice.

3. Determine whether PKCδ catalyzed phosphorylation of Foxo1 affects the subcellular localization and/or acetylation of Foxo1.
The working hypothesis is that PKCδ catalyzed phosphorylation of Foxo1 modulates Foxo1 acetylation, which affects the localization of Foxo1 in the cell.

Obesity and Cancer Program

My *long term goal* is to identify and delineate the mechanism(s) by which obesity regulates cancer. To achieve this goal I have developed a novel animal model in which human cancer can be studied in genetically obese animals. To complement this approach, I seek to develop a diet-induced model of obesity-linked insulin resistance in which human cancer can be studied.

I will pursue the following directions for this Program (each with the potential for funding):

1. Investigate the mechanism(s) by which obesity is linked to cancer.
The working hypothesis is that hyperinsulinemia and elevated serum IGF-1 stimulate human cancer growth. Our published and unpublished data in human breast cancer supports this hypothesis. We are currently conducting experiments in obese nude rats using human colon cancer to determine whether obesity regulates colon cancer tumor growth.

2. Determine the efficacy of cancer therapeutics towards human cancer in animals that are obese, insulin resistant, and with or without diabetes.
The working hypothesis is that obesity, insulin resistance, and diabetes modulate efficacy of cancer therapeutics.

3. Determine whether obesity and diabetes therapeutics inhibit or promote human cancer growth.
The working hypothesis is that certain classes of obesity and diabetes therapeutics inhibit human cancer growth while other classes promote human cancer growth.

Educational Interests

As a doctoral student, I was actively involved in teaching undergraduates. Teaching the laboratory sections of three different biology courses at two institutions was invaluable towards my growth as an educator. My more recent experience has centered on mentoring and teaching post-graduates. Of the six Internal Medicine Residents that have worked under my direction, two have been awarded the Best Poster Prizes at the Bassett Hospital E. Donnall Thomas Resident Research Day and a third was awarded a prestigious best poster prize in the National Abstract Competition at the American College of Physicians Annual Meeting in 2009. All six Internal Medicine Residents have been accepted to

highly competitive fellowships with research as a major component. I'm currently mentoring four Internal Medicine Residents and a Surgical Resident. Because of my commitment to education and training, I was appointed to the Mary Imogene Bassett Hospital Graduate Medical Education Committee and the E. Donnall Thomas Resident Research Committee, in which I now serve as Chair. Across all levels of academic education, my experience has provided me with an appreciation of the demands and commitment necessary to be an effective, caring, and respected educator.

My research in the disciplines of Nutrition, Biochemistry, and Animal Physiology has lead to my interest in the study of energy metabolism and integrative metabolism of macronutrients. Thus, a teaching responsibility in this area is of interest to me. I would eventually like to teach or contribute to the teaching of two classes that inspired me as a graduate student. The first is a graduate seminar in Cell Signaling which first inspired me to pursue research focused on insulin signaling. The second is a seminar class in the analysis of the scientific method. My interaction with graduate students and post-doctoral fellows at several institutions has led me to conclude that a great many of our graduates in scientific disciplines are lacking a thorough understanding of the scientific method. It would be personally satisfying to me to help students thoroughly understand the scientific method.

Summary

My experience and enthusiasm for teaching is well suited for the tenure track position open in the Department of Nutrition, Dietetics, and Hospitality Management. Further, the research programs I have outlined above represent a vigorous, innovative research agenda with the potential to flourish. I have already made considerable progress on the programs outlined above; however, for the programs to achieve their full potential my laboratory requires an environment dedicated to outstanding research.