

Bankhead-Coley Cancer Research Program

Brown, Kevin

*Department of Biochemistry and Molecular Biology
University of Florida*

*2006 Program
Bridge (1-year project)*

Project Title: ATM in Breast Cancer Suppression

Project Summary: Cancer arises when changes occur with a cell's DNA that allow a normal cell to become a cancerous cell. The ATM protein is a critical molecule in maintaining normal, healthy DNA by activating a series of appropriate cellular responses following DNA damage. The importance of the ATM protein is underscored by the fact that children born without functional ATM develop a cancer-prone disorder termed Ataxia-Telangiectasia (A-T). For this and other reasons, ATM is widely viewed as a critical member of a class of anti-cancer genes termed tumor suppressors. Studies of A-T families indicate that reduced ATM function leads to heightened rates of breast cancer occurrence. Others have observed that in sporadic breast cancer that ATM expression is markedly reduced. The reason for this defect was unknown until our group found that the ATM gene is efficiently turned off in invasive breast cancer and other tumor types by a process termed epigenetic silencing. Based on this finding and the important role ATM plays in tumor suppression, the research team hypothesizes that silencing of ATM is a key event in the development or progression of breast cancer. The team submitted an NIH R03 proposal in March, 2006, to fund development of critical tools and techniques necessary to test the role of ATM in limiting breast cancer development. This grant received a priority score of 212 and was thus unfunded since the funding cut-off is a score of 212. This Bankhead Coley Bridge Grant will be used to develop key tools/techniques applicable to this R03 proposal with the firm expectation that these advances will make the federal proposal stronger.

This Bankhead Coley Bridge Grant has two Specific Aims:

1. To develop a mouse line with conditional deletion of the ATM gene in mammary epithelium. Several groups have developed mice that do not express ATM, and these mice have proven a powerful model to study the A-T disorder. However, these mice, much like humans with the A-T disorder, exhibit very high rates of lymphoma and die early in life. This fact makes the study of other tumor types using these mice impracticable. We propose to develop a mouse strain with mammary epithelial cells (the cell type that gives rise to mammary tumors) that do not express the ATM protein. To do this we will use conventional genetic engineering technology and carefully document loss of ATM expression in the mammary epithelium of these mice using a number of approaches.
2. To determine when during breast cancer progression in humans ATM is targeted for epigenetic silencing. The team plans to dissect cancer cells at various stages of breast cancer progression from tumor samples taken from breast cancer patients. After this, DNA will be extracted and analyzed for epigenetic silencing of the ATM gene. In addition, this experiment will provide information as to when during breast cancer development the ATM gene is silenced.