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Department of Anatomy and Cell Biology *2005 Program*
University of Florida *New Investigator (3-year project)*

Project Title: Tumor Suppression Function of Daxx in Tobacco Smoke Mediated c-met Dependent Breast Malignancy.

Project Summary: Breast cancer is the leading cause of death in women, affecting more than 10 million women worldwide. North American women have a one in eight lifetime risk of developing breast cancer, and approximately one in three women with breast cancer will die of metastases. It is estimated in the US alone, per year,
208,000 women will be diagnosed with breast cancer and 40,200 will die of this disease. With the introduction of more effective treatments, mortality rates from breast cancer are declining and it may be treated as a chronic disease, particularly for hormone-sensitive tumors, which may be managed with sequential endocrine therapy. The prognosis for breast cancer is highly dependent on the stage of disease at diagnosis. Five-year survival rates range from 84% for early disease to just 18% for advanced cancers; hence, the goal of treatment also depends on stage at diagnosis; therefore, an
active search is ongoing for new targets for breast cancer therapy and for new markers for early diagnosis.

Tyrosine kinase receptors (TKR) have been implicated in the development of multiple tumors, including breast malignancy. Therefore, these proteins may be important therapeutic targets. One of TKR group member, protein c-met, is a proto-oncogene with established functions in tumor invasiveness and metastasis. C-met is over expressed in many types of tumors, including breast cancer, and is associated with bad survival prognosis and increased metastasis rate. It was recently shown that high levels of expression of c-met is associated with invasive human breast cancer and is
linked to metastasis. This high level of c-met has been considered as a possible indicator of earlier recurrence and shortened survival in breast cancer patients. C-met pathway and c-met itself are therefore candidate targets for therapeutic intervention in the treatment of breast cancer. Although substantial effort has been committed toward understanding the c-met function in the process of carcinogenesis, the molecular mechanisms that control c-met gene expression are less clear. We have recently observed that accumulation of c-met is repressed by protein called Daxx.
Moreover, we found that Daxx is down regulated in several cancer cell lines, including breast carcinoma cell lines that overproduce c-met. We hypothesize that Daxx can inhibit activation of breast cancer proto-oncogene c-met recruiting negative regulators of gene expression. Hence, Daxx is a potential tumor suppressor and is an ideal target to study the physiological regulation of c-met in carcinogenesis, more specifically, in breast cancer progression.

Several studies have reported a link between tobacco smoke, including environmental tobacco smoke (ETS) and increased risk of breast cancer. Cigarette smoke condensate (CSC) contains free radicals and induces oxidative stress and DNA damage resulting in gene mutations. Down-regulation of Daxx or spontaneous mutation inactivating Daxx resulted from tobacco smoke exposure can release Daxx-mediated repression leading to elevation of c-met gene expression. This event, in turn, can result in carcinogenic transformation of cells and, finally, in breast tumor progression. The proposed project is to test for the tumor suppression function of Daxx and to study the mechanisms of this suppression including CSC-induced stress conditions. Understanding of these mechanisms will advance our knowledge of etiology of tobacco smoke induced breast cancer. Eventually, we hope to find a way to regulate c-met protein production in order to block breast malignancy.