

Project Update

Development of nuclear receptors as target for prevention

- **Introduction:** The goal of project 6 is to assess whether PPAR α can represent a suitable target for the treatment of ER- breast cancer. Furthermore, we would like to assess whether other nuclear receptors are expressed in ER- tumors and could represent new potential useful targets in the treatment of this disease.
- During the first year of this project we have performed experiments aimed to address the statements of work 1 and 2.
SOW 1) In order to determine PPAR α ligands can be used as chemotherapeutic agents we have proposed to identify genes that could be markers of PPAR α biological function in normal and breast cancer cells. We have began our analysis by performing a transcriptional analysis of the ER+breast cancer cell line MCF7, treated with the ligand rosiglitazone, for 3, 6 12 hours and 5 days. We are currently in the process of analyzing the effects of PPAR α activation also in the ER- cell line MDA-MB-231 and in normal mammary epithelial cells, using a cell line recently developed in Dr. Brown's laboratory. We are using the human chip HU95 in order to identify the specific genes induced by PPAR α in mammary cells and we will compare the data obtained in the MCF7, MDA and primary cells with the results of the gene expression profiling obtained in the same cell lines in which PPAR α has been knocked down via siRNA. The results obtained from these experiments will allow to identify genes that appear to be specifically regulated by PPAR α in breast mammary cells.
SOW 2) In order to improve our understanding of the role of PPAR α in the development of the mammary gland and in breast tumorigenesis, we have analyzed the effects of PPAR α ablation on those processes. Hystological analysis of the virgin inguinal mammary gland of PPAR α in wild type and heterozygous animals at 4 months indicates that the development of this tissue occurs normally. To determine whether PPAR α plays a protective role in the development of breast cancer, we have performed a first set of experiments looking at the tumor burden in PPAR α heterozygous mice crossed with c-neu mice, between 18 to 26 weeks of age. C-neu transgenic mice develop mammary tumors around 5 months of age. Preliminary data show that c-neu-/PPAR α heterozygous mice develop tumors earlier than c-neu/ PPAR α wild type mice. We are currently evaluating tumor incidence in a larger number of mice.
- **Key Research Accomplishments:**
 - analysis of PPAR α targets in the ER+ breast cancer cell line MCF7;
 - analysis of normal mammary glands obtained from wild type and heterozygous PPAR α mice;

- analysis of tumor burden in PPAR α heterozygous mice crossed with a mouse model of breast cancer (c-neu transgenic mice).
- **Conclusions:** We have completed part of the research that we proposed aimed to identify PPAR α target genes in breast cancer cells and the analysis of PPAR α genetic requirements for mammary, normal and tumorigenic, development. We are in the process now of assessing tumor incidence in c-neu mice crossed with wildtype or heterozygous mice. We will also determine the effects of PPAR α ligands on tumor development in these animal models.