Recent research has suggested that peroxisome proliferator activated receptors, which are present in high levels in breast cancer, may have opposing roles as compared to ER. PPAR has been shown to reduce malignancy by causing differentiation in breast cancer cells while PPAR gamma heterozygous (+/-) mice had increased susceptibility to DMBA-mediated carcinogenesis as compared to wildtype (+/+) mice. Furthermore, PPAR and ER have been repeatedly shown to interact with each other. Thus, the use of PPAR as a therapeutic target to inhibit the deleterious effects of ER in breast cancer is an attractive one. Regardless, elucidation of the interaction between ER and PPAR could be critical in the understanding of hormone receptor crosstalk in breast cancer and its application in improved treatment development.

Many nuclear hormone receptors heterodimerize with other receptors to enhance/repress their activation. For example, PPAR transactivation is enhanced by RXR heterodimerization, while ER heterodimerizes with a number of nuclear receptors including RAR, RXR, and TR, which differentially regulate ER transactivation. Direct interaction of PPAR and ER, however, has not been demonstrated.

The phosphorylation of nuclear hormone receptors is critical in regulation of their activity. Specifically, the phosphorylation of ER by Mitogen Activated Protein Kinase (MAPK) increases both the nuclear translocation and ligand independent activity of ER. Conversely, the phosphorylation of PPARγ by MAPK reduces PPARγ transcriptional activity. Despite these findings, it is still unclear how phosphorylation of ER/PPAR may affect their interactions in breast cancer cells.

ER/PPAR crosstalk may be dependent on the ability of ER and PPAR to selectively regulate the expression of individual target genes in breast cancer cells. These individual gene effects may additively contribute to the overall crosstalk seen between ER and PPAR in breast cancer cells. Once the exact genetic pattern that induces the resulting crosstalk between ER and PPAR is identified, it can be manipulated to produce a desirable effect in patients with hormone dependent breast cancer.

Thus my objective is to identify novel therapeutic targets for hormone dependent breast cancer by defining mechanisms involved in ER/PPAR crosstalk. The specific mechanisms of inhibition being examined are direct protein-protein interactions, regulation by MAPK phosphorylation, and the ability of PPAR/ER to regulate the expression of individual target genes in breast cancer cells. **Together, the proposed experiments should clarify the mechanisms of PPAR/ER crosstalk in breast cancer cells. Insight into this complex relationship is crucial in understanding more about the molecular mechanisms underlying breast cancer and the role that nuclear hormone receptors play in these cells.**