For the first time it is now possible to describe the molecular events whereby angular TPE estrogens initially bind to the receptor to block estrogen-induced apoptosis, but then the TPE:ER complexes trigger apoptosis. The fact that the precise molecular modulation of estrogen-induced apoptosis can be predicted under estrogen-deprived conditions in breast cancer, provides important insights into the clinical observation that conjugated equine estrogens alone used in women over the age of 60 (i.e.: estrogen-deprived menopause) can trigger estrogen-induced apoptosis to cause a prolonged decrease in breast cancer incidence. This new knowledge now allows for further investigations to develop safer hormone replacement therapies.

Breast cancer has the highest incidence of all cancers in women in the US with more than 200,000 new cases diagnosed each year and almost 40,000 deaths in 2015. High dose estrogen therapy was the standard therapy for advanced breast cancer for three decades until the discovery of tamoxifen. High dose estrogen was most effective in women at least five years past their menopause. Synthetic estrogens such as diethylstilbestrol (DES) and triphenylethylene (TPE) derivatives were tested, although only DES was used as the more effective agent, despite more systemic side effects than the TPE derivatives. Later these estrogens were classified into two different estrogen types: class I (planar compounds like 17β-estradiol (E2) and DES) and class II (angular) estrogens based on their interaction with the ER. Clinical data from the Women’s Health Initiative shows that low-dose estrogen was able to reduce the incidence of breast cancer in postmenopausal women. In the laboratory it was demonstrated that low doses of estrogens can cause apoptosis in antiestrogen resistant cells. Estrogen-induced apoptosis in long-term estrogen deprived breast cancer can explain the antitumor effect of high dose estrogens in advanced breast cancer patients in the 1940’s, the reduced breast cancer incidence in postmenopausal women over 60, taking conjugated equine estrogens (CEEs), and the effect of low dose estrogen treatment of patients with acquired aromatase inhibitor (AI) resistance. A cell line to model antiestrogen-resistance and estrogen-induced apoptosis was developed in our lab. Different classes of estrogens have different pro-apoptotic properties in these cells. In the first week of treatment with E2 and Z2OHTPE the cells undergo apoptosis completely; however, the BPTPE and 3OHTPE act as antiestrogens and inhibit E2-induced apoptosis. In the second week BPTPE and 3OHTPE induce apoptosis in these cells. We show that the TPE compounds induce novel conformations of the ligand-binding domain (LBD) of the ERα, leading to delayed apoptosis in these cells and stability of the ER protein. We demonstrate that the dynamics of the ER protein turnover, activation of the PERK-mediated apoptotic cascade and the coregulator recruitment are dependent of the conformation of the ER LBD. These results further advance our understanding of the structure-activity relationship of the ER and estrogen-induced apoptosis, which is a clinically relevant phenomenon.