α-TEA induces apoptosis of human breast cancer cells via activation of TRAIL/DR5 death receptor pathway. W. Yu, R. Tiwary, J. Li, S.-K. Park, L. Jia, A. Xiong, M. Simmons-Menchaca, Bob G. Sanders,1 and K. Kline, *Mol. Carcinog.* **49**, 964-973 (2010).

Vitamin E derivative RRR-α-tocopherol ether-linked acetic acid analog (α-TEA) induces apoptosis in MCF-7 and HCC-1954 human breast cancer cells in a dose- and time-dependent manner. α-TEA induces increased levels of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and death receptor-5 (DR5) and decreased levels of antiapoptotic factor, cellular FLICE-like inhibitory protein (c-FLIP L). DR5/TRAIL induced apoptosis involves downregulation of c-FLIP (L), caspase-8 activation, activated proapoptotic mediators tBid and Bax, mitochondrial permeability transition, and activation of caspase-9. siRNA knockdown of either DR5 or TRAIL blocks the ability of α-TEA to enhance DR5 protein levels, downregulate c-FLIP(L) protein levels and induce apoptosis. Combination of α-TEA + TRAIL acts cooperatively to induce apoptosis, and increase DR5 and decrease c-FLIP (L) protein levels. siRNA knockdown of c-FLIP produces a low level of spontaneous apoptosis and enhances α-TEA- and TRAIL-induced apoptosis. Taken together, these studies show that α-TEA induces TRAIL/DR5 mitochondria-dependent apoptosis in human breast cancer cells, and that TRAIL/DR5-dependent increases in DR5 and decreases in c-FLIP expression are triggered by TRAIL or α-TEA treatments.