Novel Genotoxins That Target Breast Cancer Cells

The overall objective of this research is to design, in a rational manner, DNA damaging agents that selectively form un-repairable genetic damage in breast cancer cells, thereby being toxic to just that tissue type. Approximately 50% of breast tumors express the estrogen receptor (ER) in high levels compared to other non-cancer cells, providing a unique biochemical feature to exploit for selective toxicity. Bifunctional agents, which both damage DNA and interact with the estrogen receptor, can recruit this transcription factor to the damage site, and motivate death of that cell. Two models have been proposed to explain this toxicity. In one model, the damage site acts as a decoy binding site for the transcription factor and cellular growth is subsequently impaired. In another model, the ER shields repair of the DNA damage, resulting in persistence of the adduct, ultimately leading the cell to programmed death. By either model, tumorous cells expressing higher levels of the ER should be more sensitive to the proposed bifunctional toxins. Experimental studies support this prediction.