Targeting Endocrine Therapy Resistance in ER+ Breast Cancer Through a Combination of Tamoxifen and AhR Inhibition

Aboulsamh, Sarah (School: Dhahran Ahliyya Schools)

Endocrine therapy resistance affects ~40% of patients with estrogen receptor-positive (ER+) breast cancer, limiting treatment efficacy and contributing to relapse. The Aryl Hydrocarbon Receptor (AhR), a ligand-activated transcription factor, is a driver of therapy evasion. Despite prior efforts to target AhR, competitive antagonists have not been combined with endocrine therapy. This work investigated whether pharmacological AhR antagonism could act synergistically with tamoxifen to restore treatment sensitivity. T47D ER+ breast cancer cells were treated with tamoxifen alone and in combination with the AhR antagonist CH-223191. DNA cell-cycle progression and apoptosis were quantified using flow cytometry (n=3), and AhR activation was assessed via immunofluorescence (IF) imaging. To deepen mechanistic understanding and identify clinically relevant drug combinations, molecular docking and dynamics simulations were performed using Schrödinger software to evaluate ligand–receptor interactions of CH-223191 (validated experimentally) and the antagonist IK-175. In vitro, combination treatment with CH-223191 resulted in near-complete inhibition of DNA synthesis, and increased apoptosis compared to tamoxifen alone ($p<0.05$). IF confirmed suppression of AhR activation. In silico, both CH-223191 and IK-175 showed strong binding affinity; molecular dynamics simulations revealed stable ligand occupancy and persistent interactions within the PAS-B domain. These findings show a synergistic anti-tumor effect between tamoxifen and AhR antagonism. By enhancing the efficacy of an established therapy, this strategy provides a practical translational pathway to overcome therapy resistance and supports further investigation of clinically relevant antagonists such as IK-175.

Awards Won: