Eradication of Estrogen Receptor Alpha Positive Breast Tumors

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Treatment of advanced ERα-positive breast cancer remains a major clinical challenge, as the standard therapeutics are mostly cytostatic agents, ultimately leading to drug resistance. Resistant ERα-positive tumors typically retain ERα expression, suggesting an opportunity to develop new therapeutics that move beyond inhibition of this nuclear receptor. Through a medicinal chemistry campaign, we have discovered an estrogen receptor selective activator, the compound **ErSO**, that – in stark contrast to current ERα modulators – potently kills ERα-positive breast cancer cells. **ErSO** is effective even against breast cancer cell lines with known mutations in ERα that confer drug resistance. **ErSO** hyperactivates the anticipatory unfolded protein response, leading to quantitative cell death. **ErSO** is well-tolerated in mice, orally bioavailable, and blood-brain-barrier penetrant. **ErSO** treatment often leads to quantitative tumor eradication (without recurrence) in multiple mouse models of ERα-positive breast cancer, including those utilizing breast cancer cell lines harboring mutant ERα. **ErSO** and related derivatives exhibit exciting potential for the treatment of advanced ERα-positive cancer.