

Background

A major limitation to the efficacy of hormonal therapies in the management of advanced breast cancers is the frequent development of acquired resistance. The mechanisms under-lying such resistance are complex, but likely involve alterations in Estrogen Receptor (ER)-cofactor associations at Estrogen Responsive Elements (EREs) on the DNA and/or enhanced ER phosphorylation through growth factor signaling.

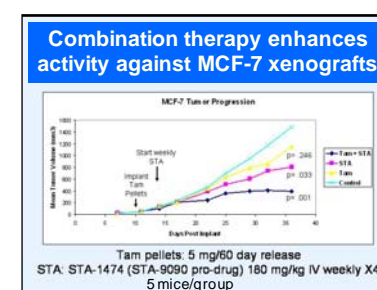
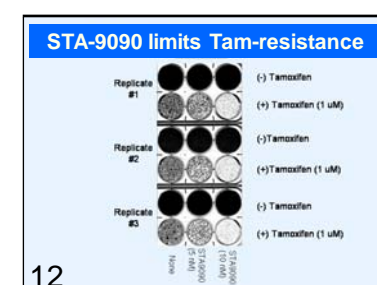
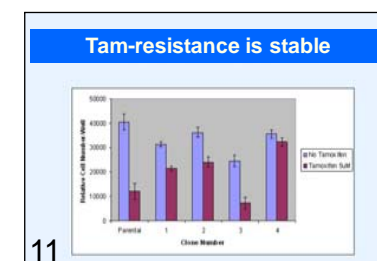
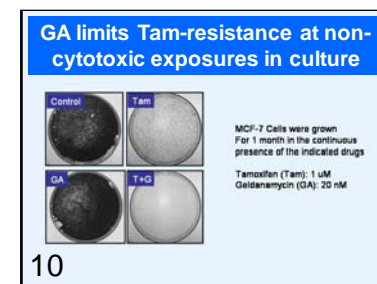
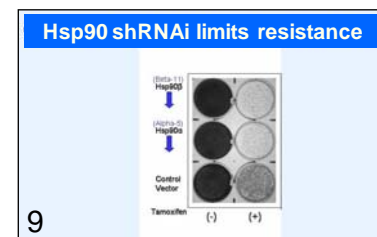
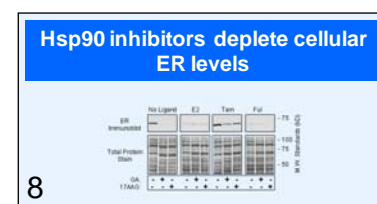
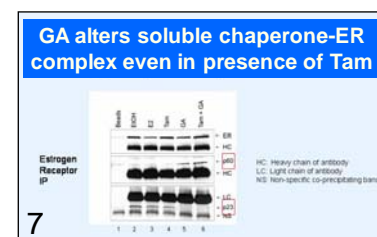
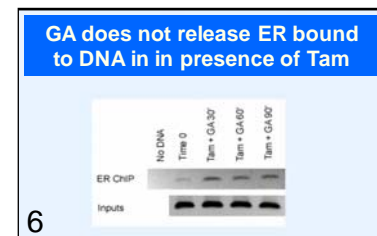
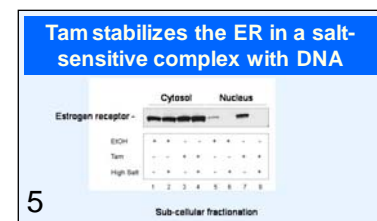
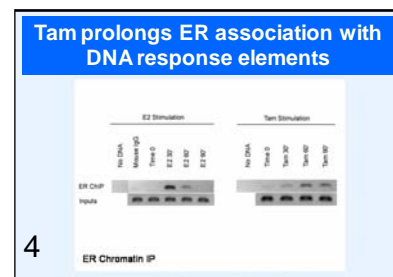
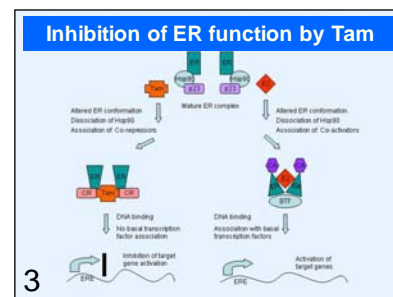
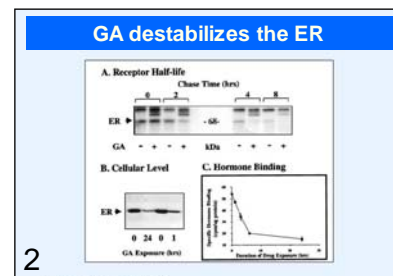
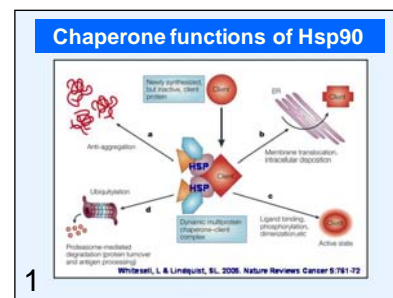
Objective

Because resistance poses such a prominent problem in the use of SERMs, we have examined inhibition of the molecular chaperone Heat shock protein 90 (Hsp90) as an alternative approach to targeting ER function, one that could be used in combination with Tamoxifen (Tam) to enhance activity, limit resistance and provide more durable disease control.

Materials & Methods

The effects of ansamycin-based Hsp90 inhibitors [geldanamycin (GA) & 17AAG] and a newer, totally synthetic compound (STA-9090) on ER protein levels, localization, and DNA binding were measured in the presence and absence of Tam. Lentiviral-mediated RNAi knockdown of Hsp90 and small molecule inhibitors were used to determine the impact of Hsp90 compromise on the emergence of Tam-resistant clones in colony-forming assays. Anti-tumor activity of combination Tam+Hsp90 inhibitor therapy against MCF-7 xenografts was measured in estrogen-supplemented mice.

Results



Summary

Hsp90 inhibitors markedly deplete cellular ER levels by stimulating its proteolytic degradation. Depletion is inhibited in cells exposed to Tam and the related antagonist, raloxifene, but not the pure antiestrogen fulvestrant. Mechanistic studies indicate that Tam induces prolonged association of ER with the DNA in stalled transcriptional complexes, thereby retaining the protein in the nucleus and diminishing its apparent destabilization by Hsp90 inhibitors. Nevertheless, Hsp90 inhibition enhances the activity of Tam in cell culture by depleting a pool of residual ER that is not tightly associated with promoter elements in the presence of Tam. The net effect of combining Tam with very modest levels of Hsp90 inhibition is to dramatically limit the emergence of Tam resistance in culture. Initial experiments in mice bearing MCF-7 xenografts demonstrate that combination therapy with Tam and the Hsp90 inhibitor STA-1474 limits tumor progression more effectively than either agent alone without increasing systemic toxicity.

Discussion

Hsp90 inhibition limits the survival of ER+ breast cancer cells in the face of Tam exposure, thus increasing its efficacy in culture and in mice. These results provide a strong rationale for evaluating combined Tam-Hsp90 inhibitor treatment in patients with metastatic breast cancer who have progressed on prior hormonal therapy.