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# Development of drug resistance and clonal selection of *ESR1* mutants in a breast cancer model

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Estrogen receptor-α (ER, encoded by *ESR1*) is expressed in two-thirds of the breast cancer patients. Ligand-binding domain mutations in *ESR1* have emerged as a clinically significant mechanism of endocrine therapy resistance in ER+ MBC. Over one-third of the identified *ESR1* mutations cluster as "hotspot" missense mutations at the 537 and 538 amino acid residues. We have generated variants of T47D and MCF7 cell-lines by introducing the mutation at 537 or 538 amino acid positions using CRISPR-Cas9 targeting. We monitored the growth advantage of *ESR1* mutant versus wild-type clones using digital droplet PCR in a competition assay. D538G and Y537S mutants were selected when the cell population was treated with the estrogen receptor degrader, Fulvestrant. These mutants were also enriched during growth in estrogen-depleted media, which mimics aromatase inhibitor treatment. Combination drug treatment with fulvestrant and inhibitors of cdk4/6 (palbociclib), mTOR (everolimus) and PI3K (alpelisib) reduced the selective advantage of the *ESR1* mutant clones. The use of palbociclib with fulvestrant worked best to control the clonal expansion of T47D-D538G mutants, while fulvestrant with either palbociclib, everolimus or alpelisib was effective in controlling the growth of T47D-Y537S mutants. Our results are consistent with clinical findings that combination drug therapy is more effective than endocrine therapy alone in patients with *ESR1* mutations. The cellular competition-based assay described here may also be applicable to the study of how mutations in other cancer genes impact drug sensitivity in a preclinical model system.

## Biography

Sunil Kumar has expertise in biomarker discovery with the particular focus on Translational Research and Targeted Therapy. His research is focused on finding novel biomarkers for breast cancer and head and neck cancer. His breast cancer research aims to find biomarkers and early drivers of metastatic breast cancer. He has used CRISPR targeting to study drug sensitivity. He has been serving as an editorial board member for three journals and reviewed more than 50 manuscripts.

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