Recruiting Corepressors to Agonist-Activated Estrogen Receptors through Molecular Bypass

Estrogens play integral roles in the progression of many breast cancers, which are treatable by antagonists of estrogen receptors (ERs). All known ER antagonists in clinical use function by binding to the ligand-binding pocket to occlude agonist access, thereby passively prevent the assembly of ER-coactivator complexes. In contrast, this proposal explores a novel mechanism of active ER repression through the recruitment of corepressors even in the presence of an agonist such as the circulating estradiol (E2). This innovative concept of molecular bypass transcends the classical pharmacodynamics of antagonism.