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Aptamer-Mediated Sub-Molecular Modulation of Estrogen Receptor Activities

More than half of breast cancers are stimulated to grow by the female sex hormone estrogen. This activity of estrogen is mediated by the human estrogen receptors (ERs), and these breast cancers are treatable by ER antagonists. The biology and pharmacology of estrogen also rely on the protein cofactors or coregulators that associate with the ERs. A major challenge in the field is to understand the mechanistic details of this tripartite estrogen-ER-cofactor relationship, and to use the molecular data to expedite the development of new pharmaceutical leads. One effective strategy to study biological mechanisms is to alter specific genes or gene products and examine the consequences. In some cases this approach may provide a simulation of certain diseased states; in other cases, it may suggest effective means of intervention to correct the malfunction—both scenarios may be used to validate drug targets. However, the tools available for us to probe and perturb biological function have severe limitations. A long-term goal of our laboratory is to develop and apply a new strategy of mechanism-based drug target validation in living cells and organisms through intervening in molecular interactions that regulate biological processes. The objective of this project is to create novel reagents to modulate the human estrogen receptor alpha (hER alpha) and to search for drug target sites on this important protein. Here, RNA (ribonucleic acid) will be used as material to generate molecular partners for hER alpha. These novel molecular partners (termed aptamers) will bind to specific sites on ER and occlude certain areas on the molecular surface, thereby inhibiting ER activity. Currently, all ER antagonists in clinical use bind to one site on ER. This project will discover and validate non-traditional sites as drug targets. The aptamers identified in this project are valuable pharmaceutical leads, which can be used as templates for new drugs to treat breast cancer.