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Probing Estrogen Receptor Structure and Function: Ligands, Fluorophores, and In Vivo Imaging.

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The transcriptional activity of nuclear hormone receptors is regulated by the binding of hormonal ligands, an interaction that stabilizes specific conformations reflecting the size and shape of the ligand. The rigidified external surface features of the ligand-receptor complex then serve as specific docking sites for coregulators, thereby altering the rate of target gene transcription. When agonists bind, the C-terminal helix-12 folds over the ligand to form a hydrophobic groove in which coactivators dock; by constrast, antagonist binding reorients helix-12 so that it interferes with coactivator binding. Our work has focused on the estrogen receptor (ER), a principal regulator of estrogen action in various target tissues.

We have developed a modular method for the synthesis of non-steroidal estrogens, adaptable to combinatorial approaches, through which we have prepared a number of ER ligands of novel structure that are highly selective for only one of the two ER subtypes, ER□ and ER□. Because these subtypes have different tissue distributions and different biological functions, these ligands are proving to be useful as pharmacological probes of the functions of the ER subtypes.

We developed fluorescence-based methods to monitor the conformation and dynamics in the ERs as regulated by their interaction with ligands and coregulators. ERs labeled site specifically with fluorophores are used in fluorescence resonance energy transfer, fluorescence polarization, and pyrene excimer studies to characterize how ligands function in a pharmacological class-specific manner to induce a stabilization of the receptor dimer interface and cause regional alterations in the conformational mobility of the helix11-helix 12 loop, and how coactivator binding causes further conformational stabilization of the receptor.

The elevated levels of steroid receptors are found in many tumors (ER and progesterone receptors (PR) in breast tumors and androgen receptors (AR) in prostate tumors). We have designed high affinity receptor ligands, labeled with the positron-emitting radionuclide fluorine-18, for positron emission tomographic (PET) imaging of these tumors. It is also possible to monitor by imaging certain hormone-induced changes in tumor metabolism as surrogate markers for the early assessment of tumor response to hormone therapy. [Supported by grants from the NIH and DOE.]

Profile: After receiving his Ph.D. degree in Chemistry from Harvard, Dr. Katzenellenbogen moved to the Department of Chemistry at the University of Illinois, where is he now the Swanlund Chair Professor of Chemistry, and holds appointments in the Department of Bioengineering and the Beckman Institute