Evaluation of Non-Nuclear Estrogen Receptor Signaling In Vivo Through the Use of an Estrogen Dendrimer Conjugate

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Estrogen receptors have long been considered to function classically in the nucleus as ligand-activated transcription factors. However, recent studies have indicated that estrogens can also initiate nongenomic responses via activation of a subpopulation of these receptors that are non-nuclear. Although the nongenomic pathway of estrogen signaling has been less thoroughly studied than their genomic counterparts, there is an increasing appreciation of the important biological effects in the activation of this pathway and thus has been the focus of intense investigation.

Herein, we report the development of a novel selective estrogen receptor modulator (SERM), termed the estrogen dendrimer conjugate, or EDC, that has been shown to be effective at stimulating the nongenomic pathway and because of its size and charge, which excludes it from the nucleus, possesses minimal capacity for stimulating genomic activities. Moreover, we have also demonstrated that the non-nuclear ER pathway is operative *in vivo*, and its selective activation provides remarkably selective cardiovascular protection with minimal impact on estrogen sensitive tissues. Further investigations of EDC's *in vivo* properties, through the use of radioactive fluorine-18 and versatile Si-^{18}F acceptors recently developed in our laboratory, revealed biodistribution data that is consistent with that of a small particle, but also shows intriguing uptake in the heart and aorta, and low uptake in the uterus. Thus, targeting the non-nuclear ER signaling pathway, as exemplified through the use of EDC, provides a novel avenue for cardiovascular benefit without increasing the risk of uterine or breast cancer.