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Tissue-Specific Estrogen Action
Novel Mechanisms, Novel Ligands, Novel Therapies

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Editors

With 42 Figures

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Preface

Nuclear hormone receptors are not only important drug targets, but have also been the focus of decades of active and highly insightful research. Ten years ago, a review on nuclear receptors was entitled “The Second Decade” and a special issue of Molecular Endocrinology in 2005 dealt with the results of these research efforts. The consensus from nuclear receptor research was of course that the signaling pathways mediated by these receptors warrant further research, even though in principle they appeared to represent the most immediate, seemingly simple signaling pathway from hormone (ligand) binding to gene expression changes.

In nuclear receptor molecular biology, estrogen receptor research has additional unique facets: since the discovery of ethinyl estradiol by Inhoffen and Hohlweg in the laboratories of Schering AG in the 1930s—and therefore several decades longer than nuclear receptor research itself—estrogen receptors have been targets of widely used, orally administered drugs. Thus, accumulating clinical experience on estrogen action in vivo helps to support the progress in molecular biological research.

Strikingly, research challenges were faced then and again when clinical observations suggested more complex effects and actions than were evident in cell culture and animal studies. On the other hand, the apparent conflicts of clinical data with well-established paradigms in preclinical models of estrogen action, e.g., in the cardiovascular system, hold both
inspiration and demand for estrogen receptor research to develop better models and provide more detailed explanations of estrogen action in vivo. Newer models and explanations should not only accommodate current clinical experience, but should also open up the opportunity to develop novel treatment paradigms and better estrogen-receptor-based therapies to meet medical needs in oncology, hormone therapy, fertility control, and gynecological diseases.

In order to discuss the latest research development in this field and to foster the interaction between basic researchers and drug developers, the Ernst Schering Research Foundation held a symposium entitled “Tissue-Specific Estrogen Action: Novel Mechanisms, Novel Ligands, Novel Therapies?” The present volume of the *Ernst Schering Research Foundation Symposium Proceedings* series covers the different areas of estrogen receptor research that were the focus of the symposium: the basic molecular biology of transcriptional regulation by estrogen receptors has become dynamic thanks to the work of Frank Gannon and co-workers, who established in a series of time-resolved promoter studies that ER works in a cyclical manner on target gene promoters. The molecular biology of estrogen receptor action in vivo in both classical (reproductive) and nonclassical (e.g., blood vessels, heart, brain) target organs has been studied thoroughly using the estrogen receptor knock-out (ERKO) mouse models, as well as tissue-specific mutants (Kenneth S. Korach, Tim M. Wintermantel, and Günther Schütz). Evan Simpson elucidated estrogen actions in nonclassical target organs using both genetic models and clinical examples of estrogen deficiency. Using in vivo models for complex disease processes in the cardiovascular system, Jean-François Arnal studied ERKO models and carried the understanding of estrogen—and selective ER action—in atherosclerosis and vascular disease to unforeseen detail. In addition to receptor isoform-specific knockouts, receptor isoform-specific ligands gain tremendous impact on research: Theo Pelzer, Richard Williams, and Gail Risbridger used isoform-selective ligands to unravel estrogen receptor function in in vivo models of blood pressure regulation, rheumatoid arthritis, and benign prostate hyperplasia, respectively. Receptor subtype-specific ligands also hold promise in clinical development, as illustrated by Heather Harris’s work on Wyeth’s ERB-041 compound. Novel signaling mechanisms of estrogens such as rapid, membrane-initiated signaling are
a starting point to identify mechanism-specific (as opposed to isoform-specific) ligands: Christiane Otto (Bayer Schering Pharma AG) presented ‘status reports’ on this new quest for ligands. Those ligands that trigger selective ER pathways might also one day provide novel treatment options, but they will without doubt generate more data to discuss in future symposia.

K.S. Korach
T.M. Wintermantel
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