

**MOLECULAR
ENDOCRINOLOGY
AND STEROID
HORMONE ACTION**

MOLECULAR ENDOCRINOLOGY AND STEROID HORMONE ACTION

Proceedings of the Fourth International Symposium on
Cellular Endocrinology held in Lake Placid,
New York, August 24-27, 1988

Editors

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Preface

Molecular Endocrinology and Steroid Hormone Action is the fourth in the International Cellular Endocrinology Symposium series held at the W. Alton Jones Cell Science Center in Lake Placid, New York. It is fitting that the meeting honors the contributions that Drs. Elwood Jensen and Jack Gorski have made to our knowledge of steroid hormone action. These two scientists have been at the forefront of research on steroid hormone action for more than 20 years. Indeed, the work of Drs. Jensen and Gorski has changed the way in which we think about steroid hormones. Through their research, and that of others, it has become apparent that steroid hormones act via specific receptors which translocate from the cytosol to the nucleus to change gene expression. This concept has become the central dogma of steroid hormone research.

The goal of the symposium was to highlight several areas of importance for steroid hormone action: steroid hormone receptor structure and function, steroid hormone receptors and their role as transacting factors, the posttranslational modification of receptors, the relationship between receptor activation and biological activity, and the use of steroid hormones in cancer. In achieving this goal, a diverse group of biologists, biochemists, molecular biologists, and clinicians was assembled. The diversity of the group served to underscore the extent to which the study of steroid hormone action has permeated many areas of biology and medicine. Perhaps more importantly, major unanswered questions were framed and refined.

It is our hope that this book reflects the level of scientific enthusiasm and discussion that was apparent during the meeting. A quick glance at the table of contents summarizes the organization of the text and will direct the reader to specific areas of interest. The section on structure and function provides an up-to-date comparison of estrogen, progesterone, glucocorticoid, and androgen receptors. In the following section, the role of steroid hormone receptors as transacting factors is compared to the current knowledge on transacting factors in the *Xenopus laevis* oocyte model to provide an overview of

the current state of knowledge and directions for the future. The chapter on steroid hormone modification summarizes the current knowledge on an important and intriguing area of steroid hormone action, the role of receptor phosphorylation in hormonal regulation. The final two sections bring together knowledge on the role of steroid hormones in biology and pathobiology. The interplay of steroid hormones with growth factors is covered in several of the papers in these sections.

We hope that the reader will not only acquire a current knowledge of this exciting area of research, but will also gain a further appreciation for the contributions of Elwood Jensen and Jack Gorski as scientists and educators.

Gordon H. Sato
James L. Stevens

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A TRIBUTE TO JACK GORSKI: ESTROGEN RECEPTOR MODEL BUILDER
AND SCIENTIFIC FRIEND TO MANY

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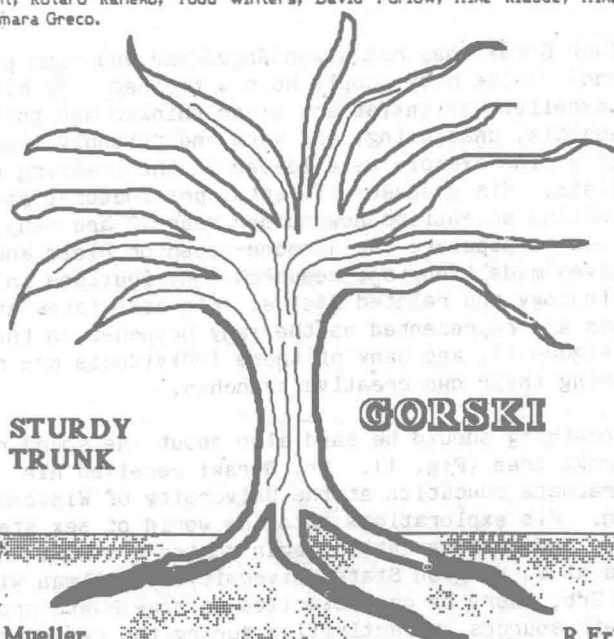
Jack Gorski has had a wonderful and enduring positive influence on the many people he has trained. By his example as an excellent scientist and clear thinker and through his approachable, unassuming, and warm and friendly manner he has set a fine example as a leader in the training of young scientists. His graduate students, postdoctoral associates and visiting scientists now number near 90 and many have continued to populate the hormone-receptor field and have themselves made important research contributions in endocrinology and related fields. His associates and students are represented as the many branches on the Gorski tree (Figure 1), and many of these individuals are now generating their own creative branches.

Something should be said also about the sound roots of the Gorski tree (Fig. 1). Dr. Gorski received his undergraduate education at the University of Wisconsin at Madison. His explorations into the world of sex steroid hormones and hormone action began during his M.S. and Ph.D. studies at Washington State University at Pullman with Dr. Robert Erb, where he characterized estrogens and progestins, and their sources and activities during the reproductive cycle and pregnancy in cattle. During this period, his studies were enriched by his association as an NIH Predoctoral Fellow with Dr. Leo Samuels and the Steroid Biochemistry Training Program at the University of Utah. His expanding interests in estrogen action were further pursued during his return to the University of Wisconsin as an NIH Postdoctoral Fellow with Dr. Gerald Mueller at the McArdle Laboratory for Cancer Research. Here, his studies with Dr. Mueller revealed the early effects of estrogens on RNA and protein synthesis in the rat uterus.

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**MANY
BRANCHES**



**STURDY
TRUNK**

GORSKI

G C Mueller

L T Samuels

R Erb

SOUND ROOTS

Figure 1. The Gorski tree, as of 1988.

In 1961, Jack Gorski assumed an Assistant Professorship position at the University of Illinois at Urbana-Champaign where he remained for 12 very productive years. During this period, Dr. Gorski attracted many excellent graduate students and postdoctoral fellows to his laboratory and made numerous observations of fundamental importance to our understanding of estrogen action (Figure 2). These include landmark studies on the identification of the receptor molecule for estrogen and the quantitative evaluation of its intracellular localization and interaction with nuclear binding sites; the characterization of the estrogen-induced synthesis of specific uterine proteins that documented, at an early time, the control of gene expression by estrogen; and, in an imaginative series of thoughtful studies, the analysis of the effects of estrogen on the synthesis of macromolecules in target cells. Dr. Gorski was recruited back to the University of Wisconsin-Madison in 1973 as a Professor in the Department of Biochemistry, Dairy Science and Meat and Animal Science, where he now holds a Paul H. Phillips Professorship and where his laboratory has continued to refine an evolving model of estrogen receptor action and to analyze growth regulation by estrogens and pituitary hormone syntheses and their modulation by estrogen.

Figure 3 presents a collage of just a sampling of some of these early, landmark papers on estrogen action. As shown in Figure 4, studies of Noteboom and Gorski in 1965 employing radiolabeled estradiol documented the nuclear localization of the hormone in the uterus after *in vivo* injection into rats, confirming the important independent observations of Elwood Jensen and Herbert Jacobson (1962). Studies by Toft and Gorski (1966) and Toft, Shyamala and Gorski (1967) (Figure 5) identified the hormone-binding receptor by sucrose gradient centrifugation techniques, and important studies by Williams and Gorski, Figure 6, presented an equilibrium model for hormone binding in the uterus documenting approximately 90% of the bound estradiol being firmly associated with the nucleus regardless of the degree of the fractional saturation of binding sites.

Concurrent studies in the early 1960s documented the stimulation of RNA polymerase activity (Figure 7) and a variety of early biosynthetic activities stimulated in the uterus by estradiol (Figure 8) and their dependence on protein synthesis. These findings implied that estrogens

TIME COURSE: GORSKI RESEARCH HIGHLIGHTS

TIME (Scientific career units $\times 10^{-3}$)	1984	present	Evolution of a Model of ER action
	1976	present	Growth regulation by estrogen
	1976	present	Molecular biology of estrogen regulation of pituitary hormone biosynthesis
	1976		Estrogen regulation of prolactin, TSH, FSH and other pituitary hormones in cell cultures
	1976		Stimulatory and inhibitory effects of estrogen on uterine DNA synthesis
	1973		Forms of ER in vivo and in vitro
	1972		Estrogen stimulation of specific RNA and protein synthesis (IP) in vitro
	1970	Clark & Gorski	- Ontogeny of ER during uterine development
	1967	1972	Estrogen receptors: Cytoplasmic-Nuclear interactions Subcellular distribution of bound estrogen in the uterus
	1966	Notides & Gorski	- Estrogen-induced synthesis of a specific uterine protein (IP)
	1966	Toft & Gorski	- Characterization of a receptor molecule for estrogen
	1965	Noteboom & Gorski	- Stereospecific binding of estrogens in the uterus
	1961	1965	Early effects estrogen on RNA, phospholipid, glucose metabolism, protein synthesis and uterine growth
	1957	1960	Characterization of Estrogens and Progestins and their metabolism in the bovine

Figure 2. Time course of Jack Gorski's research highlights.