SSR Research Award *(sponsored by Organon, NV).* Dr. Keith L. Parker is the recipient of the 2004 Research Award.

Dr. Parker received his undergraduate education at Williams College in Williamstown, Massachusetts, and then an MD/PhD from Washington University in St. Louis in 1981. Dr. Parker pursued his interests in research as a Fellow in the Department of Genetics at Harvard Medical School. He currently serves as the Wilson Distinguished Professor of Biomedical Research in the Department of Pharmacology at the University of Texas Southwestern Medical Center in Dallas.

Dr. Parker and his group have made key contributions to our understanding of multiple aspects of reproduction. His foremost contribution to reproductive biology has been the identification and cloning of the orphan nuclear receptor steroidogenic factor 1 (SF-1) and the elucidation of its roles in endocrine development. The Parker laboratory first identified conserved promoter elements that regulated the expression of several mouse steroid hydroxylase genes. They found that several of these elements interacted with the same cell- selective DNA-binding protein, which they designated steroidogenic factor 1 (SF-1). Following their successful cloning and characterization of cDNA and genomic clones encoding SF-1, Dr. Parker and his group demonstrated that SF-1 is an orphan member of the nuclear hormone receptor family that acts as a key determinant of cell-selective expression of essentially all the cytochrome P450 steroid hydroxylases in gonadal and adrenocortical cells.

Because developmental expression studies suggested an integral role for SF-1 in adrenal and gonadal development and function, the Parker laboratory used targeted disruption of the gene encoding SF-1 to examine its role in vivo. These gene knockout studies revealed that the absence of SF-1 was associated with a dramatic phenotype—adrenal and gonadal agenesis and male-to-female sex reversal—establishing essential roles for SF-1 in the development of the primary steroidogenic tissues. These studies further showed that SF-1 is essential for the expression of multiple gonadotrope-specific genes, linking SF-1 to a second level of the reproductive axis. Finally, they showed that SF-1 was also essential for the structural integrity of the ventromedial hypothalamic nucleus, a discrete hypothalamic region implicated in reproductive behavior and appetite control. SF-1 thus acts as a global regulator of reproduction, directing the expression of multiple genes required for reproduction at all three levels of the hypothalamic-pituitary-gonadal axis. In addition to their intrinsic relevance to reproduction, these studies provided a paradigm for potential key roles of other orphan nuclear receptors in mammalian development.

More recently, the Parker laboratory has developed novel approaches to explore detailed mechanisms by which SF-1 exerts its key influence in reproduction. In one line of studies, they have used the Cre-loxP technology to make tissue- specific knockouts of SF-1. In collaboration with Dr. Sally Camper, they showed that mice with selective SF-1 ablation in gonadotropes were sterile secondary to hypogonadotropic hypogonadism, proving that SF-1 is essential for normal pituitary gonadotrope function in vivo. In collaboration with Dr. Richard Behringer, they recently have shown that inactivation of SF-1 in Leydig cells causes impaired testes descent, feminization of the external genitalia, and sterility, associated with impaired expression of the steroidogenic enzymes. In females, SF-1 was inactivated selectively in the granulosa cells, and the mice were sterile, failed to ovulate, and developed hemorrhagic cysts in the follicles. These studies define essential in vivo roles of SF-1 in Leydig cells in processes of male sex differentiation and reproduction, and in granulosa cells in ovarian function. The Parker laboratory also recently used bacterial artificial chromosome transgenesis to develop a green fluorescent protein (GFP) marker for gonadal and adrenocortical cells that express SF-1. Using this marker to selectively purify eGFP-positive cells by fluorescence-activated cell sorting, they are starting to define additional target genes of SF-1 in the embryonic testis and ovary.

The second major focus of the Parker laboratory has been the steroidogenic acute regulatory protein (StAR), an essential component of regulated steroidogenesis in the adrenal cortex and gonads. In collaboration with Dr. Doug Stocco, Dr. Parker and his group isolated the mouse StAR gene and characterized its pattern of expression. These studies showed a tight link between the onset of StAR expression and the acquisition of the capacity to make steroid hormones, supporting an important role for StAR in steroidogenesis. The paper describing these studies, along with four others by the Parker laboratory, ranks among the 50 most frequently cited papers published in *Molecular Endocrinology.* The Parker laboratory was among the first to study the promoter of *Star,* showing that *Star* was also a target gene for SF-1. To provide a system to study its functions in vivo, the Parker laboratory developed knockout mice deficient in StAR. These mice exhibited male-to-female sex reversal and died shortly after birth, closely mimicking human subjects with congenital lipoid adrenal hyperplasia. In more recent studies, they showed that the characteristic lipid deposits in the gonads are driven by gonadotropin stimulation and derive predominantly from cholesterol taken up from HDL by the scavenger receptor B1. They have also collaborated with Drs. King and Lamb to show that StAR is expressed in the mouse brain, raising the possibility that

its expression may contribute to the generation of de novo production of ‘‘neurosteroids’’ in the central nervous system.

In addition to these accomplishments in his own laboratory, Dr. Parker and his group have collaborated with others to make important contributions in reproduction. These studies include: the demonstration with Birk, Westphal and colleagues that the homeobox gene *Lhx9* is essential for gonadal development, the finding with Mendonca and colleagues that a mutation in *SF-1* is associated with the syndrome of embryonic testes regression, and the demonstration with the Quaggins group that the bHLH transcription factor Pod1 represses *SF-1* expression to specify normal gonadal development and sexual differentiation.

Dr. Parker has become an internationally acknowledged leader in the area of gene regulation of the steroidogenic enzymes and in endocrine development. In recognition of his accomplishments, he has received a number of honors and awards that document the international recognition that his work has received. In 1990, he was elected to the American Society of Clinical Investigation and, in 1997, he was elected to the Association of American Physicians. In 1996, Dr. Parker received the Ernst Oppenheimer Award from the Endocrine Society (‘‘the premier award to a young investigator in recognition of basic or clinical endocrinology’’), and he was the Transatlantic Medalist of the British Endocrine Societies in 2003.

In support of SSR functions, Dr. Parker has been an invited speaker at three of our national meetings (in Davis, Ottawa, and Baltimore), certainly recognition of the caliber of science he is performing. In addition, he has served as chairperson for minisymposia in Ottawa, Baltimore, and Cincinnati. Lastly, he has proven to be a valuable member of the SSR in that he served very diligently on the Program Committee for the Cincinnati Meeting, putting together an excellent minisymposium as well as a platform session for that venue. He continues to serve on the Program Committee and provides very meaningful input regarding topics and potential speakers for plenary talks, minisymposia, and platform sessions. Indeed, he has been a highly functional and contributing member of our Society.