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Review

Introduction to the 2016 Keith L. Parker Memorial Lecturer: Douglas M. Stocco, Ph.D.

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ABSTRACT

Douglas M. (Doug) Stocco is Professor Emeritus at Texas Tech University Health Sciences Center in Lubbock, TX, and is internationally renowned for his work characterizing the steroidogenic acute regulatory protein, StAR. Stocco's laboratory isolated and cloned StAR from mouse Leydig MA-10 cells, collaborated on the demonstration that StAR mutations cause congenital lipoid adrenal hyperplasia, and delineated much of what is known about the intracellular pathways that regulate its production. This work resolved a decades-long quest to identify the mechanism underlying the acute regulation of steroidogenesis.

Beginning in 1984, housed in horribly uncomfortable undergraduate quarters at The University of Buffalo, an informal international amalgamation of investigators who share an interest in the mysteries of the adrenal cortex has gathered at venues prominent and obscure under the organizational leadership of Alistair Brownie and, later, Bernard Schimmer. Arguably the most brilliant adrenal investigator who regularly graced this biennial meeting was Keith L Parker, MD, PhD, whose studies of the transcriptional regulation of steroidogenic enzymes let to the discovery of SF1 (also known as Ad4BP or as NR5A1) and its characterization as the key factor in the embryonic determination of the adrenal. This work was done both by Keith (Rice et al., 1991; Lala et al., 1992; Luo et al., 1994), and by his friend and competitor, Ken Morohashi (Honda et al., 1993; Hatano et al., 1994). Keith died suddenly and tragically in 2008 while jogging; he was only 55. A brief biography of Keith was presented at this meeting previously (Auchus and Wilson, 2011). Beginning with the Adrenal Cortex meeting in 2010, the meeting organizers designated a biennial Keith L. Parker Memorial Lecturer, which has come to be one of the most honorific Lecture Awards in the fields of adrenal biology and steroidogenesis. The previous Parker Lecturers have been Ken-ichirou Morohashi (2010), Walter L. Miller (2012) and Bernard L. Schimmer (2014). After the 2014 meeting, the organization of this informal biennial meeting fell to the group at the University of Michigan, headed by Bill Rainey, Gary Hammer and Rich Auchus. For the 2016 meeting they asked me to institute a more formal process for choosing the Parker Lecturer, so I asked Wibke Arlt, Rich Auchus, Ken Morohashi and Amanda Swart to join me on a selection committee. Each committee member generated a ranked list of up to five nominees, and candidates were scored from 5 to 1. Only one name appeared on all five ballots, and had an aggregate score that doubled that of the next nominee. Thus we are proud to announce that the 2016 Keith L. Parker Lecturer is Professor Douglas M. Stocco.

Douglas M. (Doug) Stocco is Professor Emeritus at Texas Tech University Health Sciences Center (TTUHSC) in Lubbock, TX, and is internationally renowned for his work characterizing the steroidogenic acute regulatory protein, StAR. Doug was born in Windsor, Ontario (Canada) in June 1945, the second-youngest of six children in a non-academic family. Doug thrived academically and athletically in high school. He played lacrosse and hockey, was quarterback of the football team, and outstanding basketball player (Fig. 1). His all-star status in basketball clearly presaged his all-StAR status in adrenal research (Fig. 2). He attended his home-town school, the University of Windsor, receiving a B.Sc. in 1967 and a M.Sc. in 1969, then pursued advanced studies at the University of Toronto, where he received a Ph.D. in Biology in 1972 for work on nucleotide metabolism during reproduction in brine shrimp (really!) (Stocco et al., 1972). He then moved to California, for a two-year post-doctoral fellowship at UCLA, where he met the lovely

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Kathy Haren, who has remained by his side for over 40 years (Fig. 3). Doug left Los Angeles for Texas and was appointed Assistant Professor of Biochemistry at TTUHSC in 1974, and has remained at that institution for his entire career. Throughout the next 16 years, Doug was steadily productive studying testicular endocrinology, notably showing that peritubular cells secrete a substance that governs the production of androgen-binding protein by Sertoli cells (Hutson and Stocco, 1981). He was promoted to Associate Professor of Biochemistry in 1980 and to Professor of Biochemistry and Molecular Biology in 1990.

In the late 1980's Doug became intrigued by the regulation of cholesterol import into the mitochondria of steroidogenic mouse Leydig MA-10 cells (Stocco and Kilgore, 1988). By that time it was well known that the cleavage of the cholesterol side-chain to yield pregnenolone was the first and rate-limiting step in steroidogenesis, and that the responsible cholesterol side-chain cleavage enzyme system resides on the inner mitochondrial membrane. Kinetic studies of steroidogenesis using soluble analogues of cholesterol indicated that the rate-limiting event was not the enzymatic conversion of cholesterol to pregnenolone, but was instead the movement of insoluble cholesterol across the aqueous intramembranous space separating the inner and outer mitochondrial membranes. Work in the 1960s, mainly by Ferguson and by Garren, indicated that this process required the ongoing synthesis of new proteins, as it could be inhibited with puromycin or cycloheximide (Ferguson, 1963; Garren et al., 1965; Davis and Garren, 1968). Nanette Orme-Johnson provided the first evidence that the responsible protein(s) could be seen as rapidly-appearing

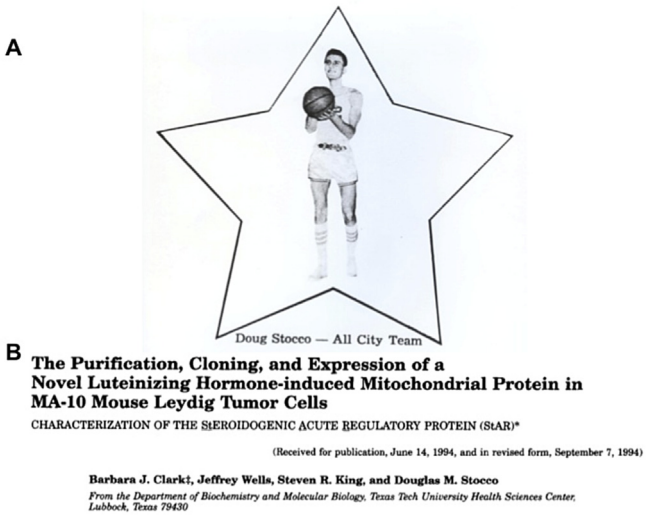

Fig. 2. A StAR is born. A. Doug as a high school all-star. B. The cloning of StAR: J. Biol. Chem. 269:28314, 1994.

(and disappearing) spots on two-dimensional gels (Pon et al., 1986; Pon and Orme-Johnson, 1988). In contemporaneous, independent publications, Orme-Johnson and Stocco showed that the responsible agent appeared to be a 30 kDa phosphoprotein that was derived from a 37 kDa precursor (Epstein and Orme-Johnson,

Fig. 1. Growing up in Windsor. Doug is circled.