tribute

In Memoriam: Roger A. Davis (1945–2008)

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On June 17, 2008, the lipid-research community lost a beloved friend and scholar, Roger A. Davis. Roger was a major contributor to our understanding of the regulation of lipoprotein production, bile acid metabolism, and atherosclerosis.

Roger gravitated to science at an early age; he loved to tinker and he felt that the truthfulness of science provided a refuge from the conflicting religious orthodoxies between the two sides of his family. During his senior year in high school in Wilmington, Delaware, he befriended Howard Simmons, a prominent chemist at DuPont. Simmons taught Roger how to smoke cigars, drink scotch, and love organic chemistry. Simmons' spell determined the trajectory of Roger's education; his undergraduate and graduate degrees were in chemistry. After earning his doctorate in organic chemistry at Washington State University in Pullman, he studied the biophysical aspects of bile acids in Fred Kern's laboratory at the University of Colorado. But, it was in Dan Steinberg's laboratory at University of California-San Diego where he first fell in love with biology and began what would become a lifelong involvement in the assembly and secretion of apoB-containing lipoproteins. After leaving University of California-San Diego, Roger served on the faculties of Louisiana State University, University of Colorado, and San Diego State University.

One of Roger's most influential discoveries occurred in 1987 when he discovered that although apoB is constitutively synthesized, a substantial fraction of what is synthesized is degraded somewhere in the secretory pathway; in fact, the amount of apoB that is secreted is determined by the amount rescued from degradation (1). These findings preceded the appreciation of proteasomal degradation and the endoplasmic reticulum-associated degradation pathway, now very active research fields in their own right. In elegant and technically challenging experiments, Roger went on to show that critical segments of the apoB molecule require an interaction with microsomal triglyceride transfer protein to be translocated across the endoplasmic reticulum membrane (2). His work in primary rodent hepatocytes emphasized that apoB secretion is sensitive

to microsomal triglyceride transfer protein but not to free fatty acids or triglycerides (3).

As early as 1983, Roger showed that, contrary to widespread belief, bile acids do not exert a direct feedback inhibitory effect on bile acid synthesis (4, 5). He also showed, predating the discovery of LXR, that cholesterol is "a positive effector of bile acid synthesis" (5). The work also predated the discovery of FGF-15 and FXR. Recent discoveries clearly establish that bile acids, through FXR, induce the expression of FGF-15 in the intestine and that the feedback effect on hepatic bile acid production is mediated by a signaling pathway involving the interaction of FGF-15 with its receptor and suppression of Cyp7A in the liver, rather than a direct effect of bile acids (6–8). Roger recently wrote commentaries about these findings (9, 10).

One of Roger's interests was to develop new therapeutic approaches. He reasoned that resident macrophages (Kupffer cells) could provide a useful vehicle for delivery

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of protective genes in the liver, a large organ with unrestricted contact with the blood. In a proof-of-principle study, he created transgenic mice expressing the atherosclerosis-protective enzyme paraoxonase-1 and transplanted their marrow into hyperlipidemic recipient mice. To achieve efficient transplantation, he treated the recipient mice with gadolinium chloride, an agent that destroys endogenous Kupffer cells. This clever strategy resulted in a dramatic reduction of atherosclerotic lesions (11). Roger pursued several ideas that led to inventions.

Roger had an unusually broad view of the important biologic problems. This undoubtedly derived from his insatiable curiosity. Although he liked to refer to himself as a chemist working in biology, his interests encompassed diverse areas of biology, including gene regulation, nutrition, metabolism, immunology, and genetics. He was not afraid to employ techniques from each of these areas. For example, he made use of natural variation among inbred strains of mice to help dissect regulatory pathways involving bile acids (12).

In recent years, Roger focused his attention on the role of thioredoxin interacting protein (*txnip*) in metabolism. His studies with *txnip* knockout mice led to the discovery that this gene plays a key role in mitochondrial function and insulin sensitivity in muscle. In a landmark study, which was his last research publication, Roger's research team showed that mice deficient in muscle *txnip* have a profound defect in fatty acid and ketone body oxidation and a dramatic increase in insulin sensitivity. He showed that the latter phenotype was associated with a suppression of PTEN and argued that this was a consequence of an altered NAD^+/NADH ratio (13). Roger was passionately excited about this new direction and, shortly before his death, obtained a new NIH grant to support this project.

Roger brought his passion for science to his battle with prostate cancer. He was simultaneously fascinated and frightened by his illness. He studied it and devised several novel therapies, all of which were attempted. He lived far longer than his doctors predicted, perhaps because of his own therapeutic interventions.

Roger was deeply devoted to his wife of 36 years, Kathy; his daughter, Kimmie; and his son, Harley. He enjoyed having family gatherings with friends and was especially proud of his Louisiana gumbo and jambalaya. He enjoyed sailing, golf, and was a lifelong avid motorcycle rider, with a special fondness for Harley-Davidson bikes.

Roger had an extraordinary capacity for friendship. He developed a wide network of lifelong friends from all walks of life and continually nurtured those friendships with his warmth, wit, companionship, and joie de vivre. He enjoyed traveling with friends and was a wonderful travel companion. Within his scientific milieu, he was deeply appreciated for his razor-sharp judgment, his inclination to stimulate critical discussions, and his ability to speak with scientific authority without being pretentious or pedantic. His love of science emanated from his belief in its integrity and authenticity. He had low tolerance for scientists who exaggerated or oversold their data. His sardonic, sometimes corny, wit; his hilarious puns; and his ability to make all of us take ourselves less seriously added much-needed levity to scientific conferences, committee meetings, and the *JLR* Editorial Board meetings. We all miss him terribly.

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