

Classics

A PAPER IN A SERIES REPRINTED TO CELEBRATE THE CENTENARY OF THE JBC IN 2005

JBC Centennial 1905–2005 100 Years of Biochemistry and Molecular Biology

The Role of the Acyl Carrier Protein in Fatty Acid Synthesis: the Work of P. Roy Vagelos

Acyl Carrier Protein. III. An Enoyl Hydrase Specific for Acyl Carrier Protein Thioesters

(Majerus, P. W., Alberts, A. W., and Vagelos, P. R. (1965) *J. Biol. Chem.* 240, 618–621)

Acyl Carrier Protein. VII. The Primary Structure of the Substrate-binding Site

(Majerus, P. W., Alberts, A. W., and Vagelos, P. R. (1965) *J. Biol. Chem.* 240, 4723–4726)

P. Roy Vagelos was born in Westfield, NJ in 1929. He received an A.B. degree from the University of Pennsylvania in 1950 and an M.D. from Columbia University's College of Physicians and Surgeons in 1954. Following an internship and residency at the Massachusetts General Hospital in Boston, he joined the National Institutes of Health. There he launched a career as a research scientist under the guidance of Earl Stadtman, who authored a previous *Journal of Biological Chemistry* (JBC) Classic (1). With Stadtman, Vagelos demonstrated that long-chain fatty acid synthesis is catalyzed by an enzyme complex in which methylmalonyl-CoA is the source of active acetate.

From 1956 to 1966, Vagelos served as Senior Surgeon and then Section Head of Comparative Biochemistry in the National Heart Institute's Laboratory of Biochemistry. During this time, he continued to study fatty acid synthesis, focusing on the role of acyl carrier protein (ACP). He discovered that the intermediates in fatty acid synthesis in *Escherichia coli* are linked to an acyl carrier protein via a thioester linkage. Vagelos published a series of papers on acyl carrier protein in the JBC, two of which are reprinted here as Classics.

During fatty acid synthesis, the acyl groups of acetyl-CoA and malonyl-CoA are initially transferred by acetyl and malonyl transacylases to the sulfhydryl group of ACP. Acetyl-ACP and malonyl-ACP are then condensed to form acetoacetyl-ACP, which is reduced to D(-)- β -hydroxybutyryl-ACP. The transacylases, condensing enzyme (acyl-malonyl-ACP condensing enzyme), and reductase (β -ketoacyl-ACP reductase) were characterized by Vagelos. This first Classic focuses on the purification and properties of the enol hydrase (3-hydroxyacyl-ACP dehydratase) that catalyzes the dehydration of D(-)- β -hydroxybutyryl-ACP to crotonyl-S-ACP.

The second Classic deals with how substrates are linked to ACP. Vagelos had previously reported that, similar to CoA, substrates are bound to ACP via the sulfhydryl group of 4'-phosphopantetheine. However, he noticed that despite this similarity between the two carriers, thioesters of CoA could not substitute effectively for ACP in fatty acid synthesis. Upon further study of the structure of ACP, as reported in the second Classic, Vagelos discovered that 4'-phosphopantetheine is bound to ACP through a phosphodiester linkage to the hydroxyl group of a serine residue.

In 1966, Vagelos assumed the chairmanship of the Department of Biological Chemistry at Washington University's School of Medicine in St Louis, MO. He continued to work on fatty acid biosynthesis and metabolism and expanded his research to the synthesis of complex lipids and the role of cholesterol in the biochemistry of the cell. In 1973 he became Director of the University's Division of Biology and Biomedical Sciences, which he founded. This Division eventually became a model for other universities. It included both the undergraduate Department of Biology and the Medical School in one umbrella unit, which was unheard of at the time.



Photo courtesy of the Office of NIH History, National Institutes of Health.

Vagelos left academia in 1975 to join Merck Sharp & Dohme Research Laboratories as Senior Vice President for Research. In 1984 he was named an Executive Vice President of Merck and was elected to its Board of Directors, and in 1984 he became Merck's Chief Executive Officer. He served as CEO and Chairman of the Board until 1994. Under his direction, the company expanded its philanthropic efforts as well as its pharmaceutical research. He is perhaps best known for his decision to make Merck's Ivermectin (Mectizan) available free to millions of people in Africa and Central America for the treatment of river blindness, a disease spread by black flies that causes chronic rashes, itching, weight loss, and blindness.

In recognition of his contributions to science, Vagelos received the American Chemical Society's Enzyme Chemistry Award in 1967. He was elected to both the National Academy of Sciences and the American Academy of Arts and Sciences in 1972 and to the American Philosophical Society in 1993. In 1989 he received the Thomas Alva Edison Award from then New Jersey Governor Thomas Kean. He is currently Chairman of the Board of Regeneron Pharmaceuticals, Inc. as well as a member of the Board of Directors of the Prudential Insurance Company.¹

Vagelos' coauthors on several of the JBC acyl carrier protein papers, including the two reprinted here, are Philip W. Majerus and Alfred W. Alberts. Majerus went on to become a Professor at Washington University School of Medicine and has been a leader in phosphoinositide metabolism and signaling, platelet physiology, and blood coagulation. He is a member of the National Academy of Sciences and has won numerous awards for his research, including the 1998 Bristol-Myers Squibb Award for Distinguished Achievement in Cardiovascular/Metabolic Research. Alberts moved from Washington University to Merck with Vagelos and was the lead scientist in Merck's development of the statin drugs Lovastatin and Zocor.

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¹ All biographical information on P. Roy Vagelos was taken from Refs. 2 and 3.