BIOGRAPHICAL SKETCH

NAME: **W. Sean Davidson** (ORCID = https://orcid.org/0000-0003-2756-2989)

eRA COMMONS USER NAME: DAVIDSWM

POSITION TITLE: Professor, Vice Chair of Research

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Indiana University, Bloomington, IN	B.S.	05/1990	Biochemistry
Medical College of Pennsylvania, Philadelphia, PA	Ph.D.	05/1995	Biochemistry
University of Illinois, Urbana, IL	Postdoctoral	03/1998	Lipoprotein Metabolism

A. Personal Statement

I am a lipid biochemist and structural biologist who tends to take a reductionist and mechanistic approach to complex problems in human physiology related to chronic diseases. The laboratory's mission is to determine the molecular basis underlying the roles played by lipoproteins in metabolic diseases such as diabetes and cardiovascular disease. We use a wide range of techniques spanning biophysical chemistry, molecular biology, and cell biology to understand: 1) the structural organization of the major proteins, called apolipoproteins, on lipoproteins and their transitions in response to lipid, 2) the molecular details of apolipoprotein interactions with cell surface receptors and transporters, 3) the protein and lipid compositions of lipoprotein subspecies and their plasma distribution in the settings of cardiovascular disease, obesity and diabetes, and 4) the specific functions/mechanisms of apolipoproteins and how they interact on the particles. Since its establishment in 1998 at the University of Cincinnati, my laboratory has gained international recognition in these areas.

- RO1 HL157260 (MPI: Shah/Davidson), 04/01/21-03/31/26, *"Lipoprotein interactions in the vessel wall"*
- RO1 HL155601 (PI: Davidson), 09/01/20-08/31/25, *"The molecular basis for the role of apolipoprotein A-II in cholesterol and triglyceride metabolism"*.
- RO1 HL153118 (PI: Davidson), 09/01/20-07/31/24, "*The structural basis for cholesterol esterification in human plasma*"

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022	Member (ad hoc), Advisory Council of the NIH Center for Scientific Review
2019-now	Associate Editor, Journal of Lipid Research
2019	Program Organizing Committee, International Atherosclerosis Society – HDL Workshop, Valencia Spain
2018-now	Chair, NIH Specialized Centers of Research Excellence (SCORE) on Sex Differences Study Section (usually 1 per year)
2015-now	Vice Chair of Research/Division Chief, Department of Pathology and Laboratory Medicine, Division of Experimental Pathology, University of Cincinnati, Cincinnati OH, USA
2014-2016	Chair, NIH, Integrated Nutrition and Metabolic Processes (INMP) Study Section
2012-2016	Member, NIH, Integrated Nutrition and Metabolic Processes (INMP) Study Section
2010-2012	Council on Atherosclerosis Thrombosis and Vascular Biology, Leadership Committee.
2006-now	Professor, Department of Pathology and Laboratory Medicine, University of Cincinnati, Cincinnati OH, USA

2003-2006	Associate Professor (tenured), Department of Pathology and Laboratory Medicine, University of Cincinnati, Cincinnati OH, USA
2005-2020	Journal of Lipid Research, Editorial Board (five 3-year terms).
2005-2016	Journal of Biological Chemistry, Editorial Board (two 5-year terms).
2005	Member, Protein Society
2000	Member, American Society for Biochemistry and Molecular Biology
1998-2003	Assistant Professor, Department of Pathology and Laboratory Medicine, University of Cincinnati, Cincinnati OH, USA, (tenure track in 2001).
1998	Fellow, American Heart Association Council on Arteriosclerosis, Thrombosis, and Vascular Biology.
1995-1998	Postdoctoral Fellow, Department of Biochemistry, University of Illinois Urbana IL, USA. Advisor: Ana Jonas, Ph.D.
1990-1994	Graduate Student, Department of Biochemistry, The Medical College of Pennsylvania (now Drexel University) Philadelphia PA, USA. Advisor: Michael C. Phillips, Ph.D., DSc.
1989-1990	Undergraduate Student, Department of Chemistry, Indiana University, Bloomington IN, USA. Advisor: Dr. Alexandra C. Newton, Ph.D.

Honors

2022	Special Recognition Award in Arteriosclerosis, American Heart Association, Council on Arteriosclerosis, Thrombosis, and Vascular Biology
2015-now	President, HDL Spring Workshop LLC
2004	Peter Dolphin Award for outstanding HDL research. International HDL Awards Program
2003	Richard Akeson Award for Excellence in Teaching. University of Cincinnati Medical Center
2000,01,03,04	"Teacher of the Year", Pathobiology Graduate Program, University of Cincinnati.
1999	"Established Investigator" National American Heart Association

C. Contributions to Science

1. Apolipoprotein A-I structural biology: A focus of my laboratory has been the structure of apolipoprotein A-I (APOA1), an important and dynamic protein that is not amenable to traditional high-resolution structural techniques such as NMR or X-ray crystallography. My laboratory has pioneered the use of cross-linking chemistry combined with high resolution mass spectrometry to derive distance constraints defining the structure of HDL apolipoproteins as they truly exist in solution. Since our initial publications, many other laboratories in the HDL field have followed suit. Along this journey, we *i*) developed the first full-length all-atom model for the structure of monomeric APOA1, *ii*) provided some of the first experimental evidence for the now widely accepted double belt model of APOA1 in discoidal HDL particles, and *iii*) were the first to extend cross-linking to spherical HDL, both in the test tube and, importantly, in "real" HDL particles in human plasma. These are the first molecular visualizations of holo-HDL particles. Although there are pockets of controversy in this field, I feel that my laboratory's work has contributed significantly to the current view of HDL structure. This is exemplified by invitations to write many reviews on this subject.

a. Melchior, J.T., Walker, R.G., Cooke, A.L., Morris, J., Castleberry, M., Thompson, T.B., Jones, M.K., Song, H.D., Rye, K., Oda, M.N., Sorci-Thomas M.G., Thomas, M., Heinecke J.W., Mei, X, Atkinson, D., Segrest, J.P., Lund-Katz, S., Phillips, M.C., and **Davidson, W.S**. A Consensus Model of Human Apolipoprotein A-I in its Monomeric and Lipid-free State. (2017) *Nature Structure and Molecular Biology* 2(1):1093-1099. PMID: 29131142

b. Lima, D.B., Melchior, J.T., Morris, J., Barbosa, V.C., Chamot-Rooke, J., Gozzo, F.C., Souza, T.A.C.B., Fischer, J.S.G., Carvalho, P.C. and **Davidson, W.S.** Characterizing Homodimer Interfaces with Cross-linking Mass Spectrometry and Isotopically-labelled Proteins. (2018) *Nature Protocols* 13(3):431-458. PMID: 29388937

c. Melchior, J.T., Street, S.E., Vaisar, T., Hart, R., Jerome, J., Kuklenyik, Z., Clouet-Foraison, N., Thornock, C., Bedi, S., Shah, A.S., Segrest, J.P., Heinecke, J.W., and **Davidson, W.S**. Apolipoprotein A-I modulates HDL particle size in the absence of apolipoprotein A-II. (2021) *Journal of Lipid Research.* 62:100099. PMID: 34324889

d. Bedi S., Morris J., Shah A., Hart R.C., Jerome W.G., Aller S.G., Tang C., Vaisar T., Bornfeldt K.E., Segrest J.P., Heinecke J.W., **Davidson W.S**. Conformational Flexibility of Apolipoprotein A-I amino- and carboxy-Termini is necessary for Lipid Binding but not Cholesterol Efflux. (2022) *Journal of Lipid Research*. Mar; 63(3):100168 PMID: 35051413.

2. Apolipoprotein A-IV and A-V structural biology: With colleague Patrick Tso, we became interested in APOA4, a related HDL apolipoprotein that plays diverse roles in food intake, lipid absorption and glucose control. While much was known about APOA4's physical properties, there was almost no knowledge of its 3-D structure. With our recombinant expression system, we *i*) used cross-linking to derive the first all atom model of APOA4, *ii*) identified operational sequences that mediate various functions, *iii*) derived the first X-ray crystal structure of APOA4, and *iv*) confirmed that structure in solution using small angle X-ray scattering. It is not an exaggeration to suggest that our lab has been the major driving force for understanding the structure and function of APOA4. Recently, we have focused on triglyceride lipolysis and have begun studying the structure and function of the related protein APOA5, which has profound effects on circulating triglyceride levels in humans.

a. Deng X, Morris J, Dressmen J, Tubb MR, Tso P, Jerome WG, **Davidson WS***, Thompson TB*. The structure of dimeric apolipoprotein A-IV and its mechanism of self-association. Structure. 2012 May 9;20(5):767-79. PubMed PMID: 22579246.

b. Walker RG, Deng X, Melchior JT, Morris J, Tso P, Jones MK, Segrest JP, Thompson TB, **Davidson WS**. The structure of human apolipoprotein A-IV as revealed by stable isotope-assisted cross-linking, molecular dynamics, and small angle x-ray scattering. *J. Biol. Chem.* 2014 Feb 28;289(9):5596-608. PubMed PMID: 24425874.

c. Xu, X.R., Wang, Y., Adili, R., Ju, L., Spring, C.M, Jin, J.W., Yang, H., Neves, M.A., Chen, P., Yang, Y., Lie, X., Chen, Y., Gallant, R.C., Xu, M., Zhang, H., Song, J. Ke, P., Zhang, D., Carrim, N., Zhu, G., She, Y., Cyr, T., Fu, W., Liu, G., Connelly, P.W., Rand, M.L., Adeli, K., Freedman, J., Lee, J.E., Tso, P., Marchese, P., **Davidson, W.S.**, Jackson, S.P., Zhu, C., Ruggeri, Z.M., and Ni, H. Apolipoprotien A-IV is a Novel Ligand of Platelet αIIbβ3 Integrin and Inhibits Thrombosis. (2018) *Nature Communications* Sept. 6:9(1):3608. PMID: 31090457

d. Castleberry M., Davis X., Liu M., Thompson T.B., Tso P., **Davidson W.S.** Functional Recombinant Apolipoprotein A5 that is Stable at High Concentrations at Physiological pH (2019) *J. Lipid Res.* 61(2):244-251. PMID: 31831525

3. HDL proteomics and subspecies relationships in metabolic disease: Recent advances in mass spectrometry (MS) technology have opened our eyes to the variety of functional proteins in HDL. We have been a leader in characterizing the protein content of lipoproteins (aka the lipoproteome) and are major proponents of the hypothesis that HDL is not just one entity, but in fact is a whole family of phospholipid-rich particles that mediate a diverse array of functions that go well beyond cardiovascular disease. Our proudest accomplishments here have been *i*) the introduction of phospholipid affinity resins allowing the analysis of lipoproteins without the need to isolate them with disruptive centrifugation techniques, *ii*) showing that HDL apolipoproteins cluster together in distinct patterns across particle density, size, and charge character, *iii*) showing that specific pairs of proteins migrate together across orthogonal separation techniques, and *iv*) that the mouse lipoproteome is as diverse as the human. We have written numerous reviews on the subject and, as a service to the field, we maintain The HDL Proteome Watch website (http://homepages.uc.edu/~davidswm/HDLproteome.html) which tracks published data from proteomics studies across the world. We are beginning to make clear connections between certain HDL subspecies and disease states in humans. Working with my clinical colleague Amy Shah, we have identified and characterized a large subspecies of HDL that contains APOA1 (but not APOA2) that is highly inversely correlated with vascular stiffness and early atherosclerosis in human adolescents.

a. Furtado, J.D., Yamamato, R., Melchior, J.T., Andraski, A.B., Gamez-Guerrero, M., Mulcahy, P., He, Z. Cai, T., **Davidson, W.S.,** and Sacks, F.M. Distinct Proteomic Signatures in 16 HDL Subspecies. (2018) *Atherosclerosis, Thrombosis and Vascular Biology* 38(12): 2827-2842. PMID: 30571168

b. **Davidson, W.S**., Cooke, A.L., Swertfeger, D.K., and Shah, A.S. The Difference Between High Density Lipoprotein Subfractions and Subspecies: An Evolving Model in Cardiovascular Disease and Diabetes (2021) *Current Atherosclerosis Reports.* 2021 Mar 27;23(6):23

c. Melchior, J.T., Street, S.E., Vaisar, T., Hart, R., Jerome, J., Kuklenyik, Z., Clouet-Foraison, N., Thornock, C., Bedi, S., Shah, A.S., Segrest, J.P., Heinecke, J.W., and **Davidson, W.S**. Apolipoprotein A-I

Modulates HDL Particle Size in the Absence of Apolipoprotein A-II. (2021) *Journal of Lipid Research*. Jul 26:100099. Epub ahead of print. PMID: 34324889.

d. Melchior J.T., Swertfeger D.K., Morris J., Street S.E., Warshak C.R., Welge J.A., Remaley A.T., Catov J.M., **Davidson W.S.**, Woollett L.A. Pregnancy is accompanied by larger high-density lipoprotein particles and compositionally distinct subspecies. (2021) *Journal of Lipid Research*. 62:100107. PMID: 34416270

4. Mechanisms of HDL function: Our laboratory has also made important contributions toward understanding how HDL promotes cholesterol efflux from peripheral cells. Using cultured cell assays we have *i*) identified key sequences in APOA1, APOA2, APOA4 and APOC1 that are required for promoting cholesterol efflux through the ABCA1 transporter, *ii*) elucidated the intracellular itinerary of apolipoproteins that interact with ABCA1 suggesting that a retroendocytosis pathway is not required in macrophages, *iii*) identified the role of key charged sequences in APOA1 in mediating ABCA1-mediated cholesterol efflux and *iv*) worked out the role of ceramide in the control of ABCA1 cell surface expression. We have also recently explored the role of HDL in contributing to the antioxidation activity of human plasma and in maintaining cells of the immune system.

a. Swertfeger, D.K., Rebholz, S., Li, H., Shah, A.S., **Davidson, W.S.**, and Lu, L.J. Feasibility of a Plasma Bioassay to Assess Oxidative Protection of Low Density Lipoproteins by High Density Lipoproteins. (2018) *Journal of Clinical Lipidology* 12(6): 1539-1548. PMID: 30244943

b. He, Y., Ronsein, G.E., Jarvik, G.P., **Davidson, W.S**., Kothari, V., Song, H.D., Segrest, J. Bornfeldt, K.E., and Heinecke, J.W. Diabetes Impairs Cellular Cholesterol Efflux from ABCA1 to Small HDL Particles (2020) *Circulation Research Online*, Oct 9;127(9):1198-1210.

c. Han, Y.H., Onufer, E.J., Huang, L.H., Sprung, R.W., **Davidson, W.S**., Czepielewski, R.S., Wohltmann, M., Sorci-Thomas, M.G., Warner, B.W., and Randolph, G.J. Enterically Derived High-density Lipoprotein Restrains Liver Injury Through the Portal Vein. *Science*. 2021 Jul 23;373(6553) PMID: 34437091.

d. Bedi S., Morris J., Shah A., Hart R.C., Jerome W.G., Aller S.G., Tang C., Vaisar T., Bornfeldt K.E., Segrest J.P., Heinecke J.W., **Davidson W.S**. Conformational Flexibility of Apolipoprotein A-I Amino- and Carboxy-Termini is Necessary for Lipid Binding but not Cholesterol Efflux. (2022) *Journal of Lipid Research*. Mar; 63(3):100168 PMID: 35051413.

4. Apolipoprotein function and particle composition in control of triglyceride hydrolysis: Although not as well known in this area, our lab has recently focused on how exchangeable apolipoproteins affect triglyceride-rich lipoprotein metabolism. Our initial studies point to important roles for APOE and APOA2 and form the basis for our general directions for the next several years.

a. Bedi, S., Garcia, E., Jeyarajah, E.J., Shalaurova, I., Perez-Matos, M.C., Jiang, Z.G., Dullaart, R.P.F., Matyus, S.P., Kirk, W.J., Otvos, J.D., **Davidson, W.S.**, Connelly, M.A. Characterization of LP-Z Lipoprotein Particles and Quantification in Subjects with Liver Disease Using a Newly Developed NMR-Based Assay. (2020) *Journal of Clinical Medicine* 9(9):2915 PMID: 32927635

b. Whitacre B.E., Howles P., Street S., Morris J., Swertfeger D., **Davidson W.S.** Apolipoprotein E Content of VLDL Limits LPL-mediated Triglyceride Hydrolysis. (2021) *Journal of Lipid Research*. Jan; 63(1):100157. PMID: 34863862

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http://www.ncbi.nlm.nih.gov/sites/myncbi/w.davidson.1/bibliography/40799356/public/?sort=date&direction=descending