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.	1990	Biochemistry
Medical College of Pennsylvania, Philadelphia, PA	Ph.D.	1995	Biochemistry

A. Personal Statement

The mission of my laboratory is to determine the molecular basis underlying the protective effect of high density lipoproteins (HDL) against inflammation and atherosclerosis. We use a wide range of techniques spanning biophysical chemistry, molecular biology, and cell biology to understand: *1)* the structural organization of the major HDL apolipoproteins and their transitions in response to lipid, *2)* the molecular details of HDL interactions with cell surface receptors and transporters, *3)* the protein and lipid compositions of HDL subspecies and their plasma distribution in the settings of cardiovascular disease, obesity and diabetes, and *4)* the specific functions of the many HDL proteins and how they interact on the particle.

B. Positions and Honors

Positions and Employment

1989-90	Undergraduate Research	Department of Chemistry, Indiana University Bloomington, IN 47405. Advisor: Dr. Alexandra C. Newton
1990-94	Graduate Research	Department of Biochemistry, The Medical College of Pennsylvania (now Drexel University) Philadelphia, PA 19129. Advisor: Dr. Michael C. Phillips
1995-1998	Postdoctoral Fellowship	Department of Biochemistry, University of Illinois Urbana, IL 61801. Advisor: Dr. Ana Jonas
1998-2003	Assistant Professor	Department of Pathology and Laboratory Medicine, University of Cincinnati, Cincinnati, OH 45267, (tenure track in 2001).
2003-2006	Associate Prof. (w/ tenure)	Department of Pathology and Laboratory Medicine, University of Cincinnati, Cincinnati OH, 45267
2006-now	Professor	Department of Pathology and Laboratory Medicine, University of Cincinnati, Cincinnati OH, 45267
2008-now	Director	Center for Lipid and Arteriosclerosis Science, University of Cincinnati, Cincinnati OH, 45267
2014-now	Vice Chair of Research	Department of Pathology and Laboratory Medicine, University of Cincinnati, Cincinnati OH, 45267
2016-now	Division Chief	Division of Experimental Pathology, Dept.of Pathology and Laboratory Medicine, University of Cincinnati, Cincinnati, OH 45267

Other Experience and Professional Memberships

1998	Fellow American Heart Association Council on Arteriosclerosis, Thrombosis, and Vascular Biology.
2000	American Society for Biochemistry and Molecular Biology.
2005	Protein Society

2010 Council on Atherosclerosis Thrombosis and Vascular Biology, Leadership Committee.
2010 Journal of Lipid Research, editorial board (third term).
2012 - 16 Study Section member, NIH, Integrated Nutrition and Metabolic Processes (INMP)
2014 - 16 Study Section chair, NIH, Integrated Nutrition and Metabolic Processes (INMP)
2019 Associate Editor, Journal of Lipid Research

Honors

2018 - 19 Study Section Chair, NIH Special Emphasis Panel (ZRG1 EMNR-A 70 R) Specialized Centers of Research Excellence (SCORE) on Sex Differences
2014 - 16 Chair of the Integrated Nutrition and Metabolic Processes Study Section (NIH)
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. Contribution to Science

1. Apolipoprotein A-I Structural Biology: A main focus of my laboratory has been the structure of apolipoprotein (apo)A-I, a dynamic and important 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 that define 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 apoA-I, *ii*) provided some of the first experimental evidence for the widely accepted double belt model of apoA-I in reconstituted 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 studies have resulted in 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., Morris, J., Jones, M. K., Segrest, J. P., Lima, D. B., Carvalho, P. C., Gozzo, F. C., Castleberry, M., Thompson, T. B. and **Davidson, W. S.** An Evaluation of the Crystal Structure of C-terminal Truncated Apolipoprotein A-I in Solution Reveals Structural Dynamics Related to Lipid Binding (2016) *J. Biol. Chem.* 291(10):5439-51. PMID: 26755744

b. 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

c. 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

d. Cooke, A.L., Morris, J., Melchior, J.T., Street, S.E., Jerome, W.G., Huang, R., Herr, A.B., Smith, L.E., Segrest, J.P., Remaley, A.T., Shah, A.S., Thompson, T.B., and **Davidson, W.S.**, A Thumbwheel Mechanism for APOA1 Activation of LCAT Activity in HDL (2018) *Journal of Lipid Research* 59(7): 1244-1255. PMID: 29773713

2. Apolipoprotein A-IV Structural Biology: Working with my long-time colleague Patrick Tso, we also became interested in apoA-IV, a related HDL apolipoprotein that plays diverse roles in food intake, lipid absorption and even glucose control. While much was known about the physical properties of this protein, there was almost no knowledge of its 3-D structure. With our recombinant expression system, we *i*) used the cross-linking technique to derive the first all atom model of apoA-IV, *ii*) identified operational sequences that mediate various functions, *iii*) identified a stable core domain that allowed us to derive the first X-ray crystal structure of apoA-IV in its dimeric form, and *iv*) first used small angle X-ray scattering to derive a full-length structure of monomeric and dimeric apoA-IV. I do not believe it is an exaggeration to suggest that our lab has been the major driving force for understanding the 3-D structure and function of this protein.

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. Deng X, Walker RG, Morris J, **Davidson WS***, Thompson TB*. Role of Conserved Proline Residues in Human Apolipoprotein A-IV Structure and Function. J Biol Chem. 2015 Apr 24;290(17):10689-702. PubMed PMID: 25733664.

d. 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

3. HDL Proteomics and Subspecies Identification: Recent advances in mass spectrometry technology have opened our eyes to the wide variety of functional proteins in HDL. Utilizing our mass spectrometry expertise, we have been a leader in characterizing the protein content of lipoproteins (aka the lipoproteome). We have been 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 may or may not be related to cardiovascular disease. One of our proudest accomplishments in this area has *i*) been the introduction of phospholipid affinity resins that allow the analysis of lipoproteins without the need to separate them from plasma via disruptive centrifugation techniques. We have also contributed evidence that shows *ii*) HDL apolipoproteins cluster together in distinct patterns across particle density, size, and charge character, *iii*) that specific pairs of proteins migrate together across orthogonal separation techniques, and *iv*) that the mouse lipoproteome is just 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 tabulates all of the published data from shotgun proteomics studies from labs across the world.

a. Shah AS, Tan L, Long JL, **Davidson WS**. Proteomic diversity of high density lipoproteins: our emerging understanding of its importance in lipid transport and beyond. J Lipid Res. 2013 Oct;54(10):2575-85 PubMed PMID: 23434634.

b. **Davidson, W.S.**, Heink, A., Sexmith, H., Dolan, L.M., Gordon, S.M., Otvos, J.D., Melchior, J.T., Elder, D.A., Khoury, J., Geh, E., and Shah, A.S. Obesity is Associated with an Altered HDL Subspecies Profile Among Adolescents with Metabolic Disease. (2017) *J. Lipid Research* 58(9): 1916-1923. PMID: 28743729

c. Melchior, J.T., Street, S.E., Andraski, A.B., Furtado, J.D., Sacks, F.M., Shute, R.L., Greve, E.I., Swertfeger, D.K., Li, H., Shah, A.S., Lu, L.J., and **Davidson, W.S.** Apolipoprotein A-II Alters the Proteome of Human Apolipoproteins and Enhances Cholesterol Efflux from ABCA1 (2017) *J. Lipid Research* 58(17): 1374-1385. PMID: 28476857

d. 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

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 apoA-I, apoA-II, apoA-IV and apoC-I 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 apoA-I 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. Smith LE, **Davidson WS**. The role of hydrophobic and negatively charged surface patches of lipid-free apolipoprotein A-I in lipid binding and ABCA1-mediated cholesterol efflux. Biochim Biophys Acta. 2010 Jan;1801(1):64-9. PubMed PMID: 19782154.

b. **Davidson, W. S.**, Heink, A., Sexmith H., Melchior, J.T., Gordon, S.M., Kuklenyik, Z., Woolett, L.A., Barr, J.R., Jones, J.I., Toth, C.A., and Shah, A.S. The Effects of Apolipoprotein B Depletion on HDL Subspecies Composition and Function (2016) *J. Lipid Res.* 57(4):674-86. PMID: 26908829

c. Rueda, C.M., Rodriguez-Perea, A.L., Moreno-Fernandez, M., Jackson, C.M., Melchior, J.T., **Davidson, W.S.**, and Chougnet, C.A. High Density Lipoproteins Selectively Promote the Survival of Human Regulatory T-cells. (2017) *Journal of Lipid Research* 58(8): 1514-1523. PMID: 28377425

d. 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

Complete List of Published Work in MyBibliography (123 published papers):
http://www.ncbi.nlm.nih.gov/sites/myncbi/w.davidson.1/bibliography/40799356/public/?sort=date&direction=descending

D. Research Support

ACTIVE

1R01HL136025-01A1(PI: Wang & Davidson - MPI)

"Autologous Cardiomyocytes from Masseter Muscles to Repair Myocardial Infarction (MI)"

This grant tests the hypothesis that masseter muscle derived progenitor cells can undergo cardiogenic commitment and provide a source of functional cardiomyocytes for repair of damaged tissue after MI. My role is to assist in determining changes in the global landscape of chromatin and proteomic signatures during cellular transdifferentiation into cardiomyocytes.

1R21AI128218-01 (PI: Chougnet)

"Direct Interactions with HDL Promote Regulatory T Cells Survival"

This grant examines the role of HDL in the promoting the survival of regulatory T cells (Treg), which are essential to curb exacerbated inflammatory processes. We hypothesize that HDL directly interact with Treg to increase their survival. The aims are to 1) Identify the pathways involved in HDL-mediated survival of Treg, 2) Identify the HDL components that are required for Treg survival.

Role: Co-Investigator

P01 HL128203-01A1 (PPG-PI: Segrest, Project Leader: Davidson)

"Multidisciplinary Approaches to HDL Structure, Assembly, and Functional Heterogeneity - Project 2"

This grant is to study the structural aspects of HDL maturation in humans. The specific aims are: 1) To test the Trefoil and other models of apoA-I in spherical reconstituted and native or "real" plasma HDL using new dual isotope cross-linking techniques and state-of-the-art all-atom and course grained molecular dynamics (MD) techniques. 2) To determine the molecular interactions between apoA-I and apoA-II using cross-linking and a new human apoA-II bacterial expression system to derive the first models of native HDL particles containing both proteins. 3) To determine the molecular interactions between apoA-I and two important HDL docking proteins, PON1 and CETP, using chemical cross-linking and site-directed mutagenesis.

P01 HL128203-01A1 (PPG-PI: Segrest: Project Leader: Davidson)

"Multidisciplinary Approaches to HDL Structure, Assembly, and Functional Heterogeneity – Core D"

The goals of Core D are: 1) To express, purify and distribute recombinant apolipoproteins and their mutants produced in bacteria. 2) To express and distribute PON1, CETP, apoA-II and ABCA1 and their mutants produced in eukaryotic cells. 3) To isolate, characterize and distribute lipoproteins and apolipoproteins isolated from human plasma. 4) To generate, characterize and distribute reconstituted HDL lipoproteins. 5) To perform chemical cross-linking analyses on individual proteins, enzymes, transfer proteins and lipoprotein complexes in synergy with the HDL Quantitation Core (Core C). 6) To develop innovative new cross-linking approaches aimed at increasing protein structure resolution.

1 R01 HL111829-01 (PI: Lu)

"A Network-Based Approach to Associate HDL Subspeciation with Function"

The objective of this study is separate human plasma by three orthogonal biochemical approaches and then track the HDL proteome across each. Using an advanced network-based computational framework, we will track comigrating proteins that may define HDL subspecies.
Role: Co-Investigator

Gates OPP1110668 (PI: Woollett)
"Improving Fetal Growth Rates in Developing Countries"
The goal of this research is to define targets for intervention or markers in pregnant women of resource-poor countries that are at risk to have small or preterm infants, focusing on maternal HDL and systemic inflammation.
Role: Co-Investigator

5 R01 HL123917-02 (PI: Sacks)
"HDL and Coronary Heart Disease."
Dr. Sacks is using immunoaffinity columns to isolate HDL particles in large patient cohorts. Our job is to use mass spectrometry to identify other proteins that are associated with these particles.
Role: Co-Investigator

2U2CDK059630-16 (PI: Tso)
NIH/NIDDK
"Cincinnati Mouse Metabolic Phenotyping Center"
Goals: This consortium is designed to provide a comprehensive array of mouse metabolic phenotyping services for investigators across the world.
Role: Co-Investigator