BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Kevin Jon Williams, M.D.	Professor of Medicine Chief, Section of Endocrinology, Diabetes, and Metabolism
eRA COMMONS USER NAME (credential, e.g., agency login) KJWILLIAMS	

EDUCATION/TRAINING *(Begin with initial professional education, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Johns Hopkins University, Baltimore, MD	M.D.	1980	Medicine
University of Chicago, Chicago, IL	Residency	1980-1983	Internal Medicine

A. Personal Statement

The research of the Williams laboratory encompasses three major areas focused on atherosclerosis and diabetes, two enormous, related health problems in the U.S. (literature citations come from Section C, the list of selected publications).

First is our work on the origins of atherosclerosis, which has received wide acceptance.[1-3] Atherosclerosis arises from the retention, or trapping, of LDL and other apoB-containing lipoproteins within the arterial wall. The body then mounts a series of strikingly maladaptive local responses to the retained and modified material, resulting in plaque development. The four key molecular mediators of apoB-lipoprotein retention that we identified in vitro (LDL, arterial matrix, lipoprotein lipase, and sphingomyelinase)[1, 4] have each been manipulated in vivo, with the predicted effects on arterial retention of apoB-lipoproteins and then plaque development.[5] This work provides a basis for the new unity among basic, epidemiologic, pharmacologic, and clinical approaches to this major killer. Importantly, these advances have allowed us and others to reclassify cardiovascular risk factors, which are epidemiologic concepts, into causative factors, exacerbators, and mere bystander phenomena.[2] Causative and exacerbating factors are targets for therapy; bystander phenomena are not.[2]

Second is our seminal work implicating unusual cell-surface molecules, called syndecan-1 heparan sulfate proteoglycans (HSPGs), as hepatic receptors for the rapid, healthy disposal of atherogenic apoB-containing lipoproteins.[6-9] This work explains LDL receptor-independent clearance of harmful apoB-lipoproteins, called 'remnants,' that originate from the intestine and liver and appear in plasma after each meal.[9, 10] Moreover, we discovered that the key molecular defect in T2DM liver is a vast overexpression of SULF2, which we showed to be an endogenous inhibitor of syndecan-1 (reference[11]). We recently reported that correction of this single defect in T2DM *db/db* mice flattens their postprandial plasma triglyceride excursion after a corn-oil gavage.[12] In humans, we found that a polymorphism of the *SULF2* gene strongly associates with fasting plasma triglyceride levels and especially postprandial lipid excursions.[13] These findings provide a key proof-of-concept in vivo to support *Sulf2* inhibition as an attractive strategy to improve metabolic dyslipidemia. The ultimate goal will be to avert the tremendous excess burden of cardiovascular disease in diabetes, to which postprandial dyslipoproteinemia makes a substantial – and potentially avoidable – contribution.[10]

Third is our work on insulin signaling. We discovered that functional disturbance of a single molecule, NOX4, is sufficient to induce the key harmful features of imbalanced insulin action in type 2 diabetes, obesity, and the atherometabolic syndrome.[14] Recently, we found that NOX4 is part of a novel multimolecular signaling complex, which we have called the 'NSAPP' oxide transport chain after its five major proteins.[15] Remarkably, our newly published findings on dysfunction of the NSAPP oxide transport chain indicate a unified molecular basis for fatty liver, atherogenic dyslipoproteinemia, hyperglycemia, and hence accelerated atherosclerosis and microvascular disease in type 2 diabetes (T2DM), obesity, and the atherometabolic syndrome.[14-16]

Overall, our research should continue to provide mechanistic insights into these important causes of morbidity and mortality in type 2 diabetes, possibly leading to new therapeutic approaches.

B. Positions and Honors

Positions

1984 - 1985 **Fellow in Metabolism**, Columbia University, New York, NY
1985 - 1987 **Instructor in Clinical Medicine**, Columbia University, New York, NY;
1987 - 1989 **Assistant Professor of Medicine**, Columbia University, New York, NY;
1989 - 1993 **Assistant Professor of Biochemistry**, Medical College of Pennsylvania, Philadelphia, PA
1989 - 1994 **Assistant Professor of Medicine**, Medical College of Pennsylvania, Philadelphia, PA
1993 - 1994 **Associate Professor of Biochemistry**, Medical College of Pennsylvania
1994 - 2000 **Associate Professor of Medicine**, Thomas Jefferson University, Philadelphia, PA
Associate Professor of Pharmacology, Thomas Jefferson University
2000 - 2009 **Professor of Medicine**, Thomas Jefferson University, Philadelphia, PA
Professor of Biochemistry and Molecular Pharmacology, Thomas Jefferson University
2003 - 2009 **Member**, Center for Human Virology and Biodefense, Thomas Jefferson University
2009 - present **Professor of Medicine**, Temple University School of Medicine, Philadelphia, PA
2009 - present **Chief, Division of Endocrinology, Diabetes and Metabolism**, Temple University
2010 - present **Professor**, Cardiovascular Research Center and Department of Physiology, Temple University
2013 - present **Visiting Professor (Gästprofessor)**, Department of Molecular and Clinical Medicine, Sahlgrenska Center for Cardiovascular and Metabolic Research, University of Gothenburg, SWEDEN

Honors

1985-1990 **Clinician-Scientist Award**, American Heart Association
June 1993 **Professeur Invité**, Faculté des Sciences Pharmaceutiques & Biologiques, Service de Biochimie, Université de Rennes I, Rennes, FRANCE
1993-1998 **Established Investigatorship**, American Heart Association
2003-2009 **Consulting Editor**, Journal of Clinical Investigation
2011-2013 **Elected member-at-large**, American Heart Association ATVB Leadership Committee
2012-present **Fellow of the American College of Physicians** (FACP)

C. Selected Peer-reviewed Publications (16 from over 60 published)

1. **Williams KJ** and Tabas I. The response-to-retention hypothesis of early atherogenesis. *Arterioscler Thromb Vasc Biol*. 1995;15:551-561. doi: 10.1161/01.ATV.15.5.551.
2. **Williams KJ** and Fisher EA. Apolipoprotein-B: the crucial protein of atherogenic lipoproteins. Chapter 24 in: *Atherosclerosis: Risks, Mechanisms, & Therapies* (Wang H & Patterson C, eds.), John Wiley & Sons, Inc.: Hoboken, NJ, USA; 2015, pp. 291-312. doi: 10.1002/9781118828533.ch24.
3. **Williams KJ**, Tabas I and Fisher EA. How an artery heals. *Circ Res*. 2015;117:909-913. doi: 10.1161/CIRCRESAHA.115.307609.
4. Tabas I, Li Y, Brocia RW, Xu SW, Swenson TL and **Williams KJ**. Lipoprotein lipase and sphingomyelinase synergistically enhance the association of atherogenic lipoproteins with smooth muscle cells and extracellular matrix. A possible mechanism for low density lipoprotein and lipoprotein(a) retention and macrophage foam cell formation. *J Biol Chem*. 1993;268:20419-20432.
5. Devlin CM, Leventhal AR, Kuriakose G, Schuchman EH, **Williams KJ** and Tabas I. Acid sphingomyelinase promotes lipoprotein retention within early atheromata and accelerates lesion progression. *Arterioscler Thromb Vasc Biol*. 2008;28:1723-30.
6. **Williams KJ**, Fless GM, Petrie KA, Snyder ML, Brocia RW and Swenson TL. Mechanisms by which lipoprotein lipase alters cellular metabolism of lipoprotein(a), low density lipoprotein, and nascent lipoproteins. Roles for low density lipoprotein receptors and heparan sulfate proteoglycans. *J Biol Chem*. 1992;267:13284-13292.
7. Fuki IV, Kuhn KM, Lomazov IR, Rothman VL, Tuszynski GP, Iozzo RV, Swenson TL, Fisher EA and **Williams KJ**. The syndecan family of proteoglycans: novel receptors mediating internalization of atherogenic lipoproteins *in vitro*. *J Clin Invest*. 1997;100:1611-1622.
8. Fuki IV, Meyer ME and **Williams KJ**. Transmembrane and cytoplasmic domains of syndecan mediate a multi-step endocytic pathway involving detergent-insoluble membrane rafts. *Biochem J*. 2000;351:607-612.

9. Chen K and **Williams KJ**. Molecular mediators for raft-dependent endocytosis of syndecan-1, a highly conserved, multifunctional receptor. *J Biol Chem*. 2013;288:13988-13999. doi: 10.1074/jbc.M112.444737.
10. **Williams KJ**. Molecular processes that handle – and mishandle – dietary lipids. *J Clin Invest*. 2008;118:3247-3259. doi: 10.1172/JCI35206.
11. Chen K, Liu M-L, Schaffer L, Li M, Boden G, Wu X and **Williams KJ**. Type 2 diabetes in mice induces hepatic overexpression of sulfatase 2, a novel factor that suppresses uptake of remnant lipoproteins. *Hepatology*. 2010;52:1957-1967. doi: 10.1002/hep.23916.
12. Hassing HC, Mooij H, Guo S, Monia BP, Chen K, Kulik W, Dallinga-Thie GM, Nieuwdorp M, Stroes ESG and **Williams KJ**. Inhibition of hepatic sulfatase-2 *in vivo*: A novel strategy to correct diabetic dyslipidemia. *Hepatology*. 2012;55:1746-1753. doi: 10.1002/hep.25580.
13. Hassing HC, Surendran RP, Derudas B, Verrijken A, Francque SM, Mooij HL, Bernelot Moens SJ, 't Hart LM, Nijpels G, Dekker JM, **Williams KJ**, Stroes ES, Van Gaal LF, Staels B, Nieuwdorp M and Dallinga-Thie GM. *SULF2* strongly predisposes to fasting and postprandial triglycerides in patients with obesity and type 2 diabetes mellitus. *Obesity (Silver Spring)*. 2014;22:1309-1316. doi: 10.1002/oby.20682.
14. Wu X and **Williams KJ**. NOX4 pathway as a source of selective insulin resistance and responsiveness. *Arterioscler Thromb Vasc Biol*. 2012;32:1236-1245. doi: 10.1161/ATVBAHA.111.244525.
15. **Williams KJ** and Wu X. Imbalanced insulin action in chronic over nutrition: clinical harm, molecular mechanisms, and a way forward. Atherosclerosis. 2016;247:225-282. doi: 10.1016/j.atherosclerosis.2016.02.004. Open-access hypertext and PDF available at http://www.atherosclerosis-journal.com/article/S0021-9150(16)30048-X/fulltext .
16. Wu X, Chen K and **Williams KJ**. The role of pathway-selective insulin resistance and responsiveness in diabetic dyslipoproteinemia. *Curr Opin Lipidol*. 2012;23:334-344. doi: 10.1097/MOL.0b013e3283544424.

Dr. Williams is also the sole or co-inventor of 11 issued U.S. patents to date, mostly on reverse lipid transport.

D. Research Support

Ongoing Research Support

Name of Project:
"Sulfatase-2: Key mediator of atherogenic postprandial dyslipoproteinemia"
Principal Investigator: Kevin Jon Williams
Agency: NIDDK; Type: R01 (DK100851), Period: 09/20/2013-06/30/2018
The major goals of this proposal are 1) to elucidate molecular mechanisms for the normal suppression of sulfatase-2 protein by insulin in cultured liver cells, focusing on AKT-dependent pathways that become resistant in T2DM; and 2) to use novel strategies to correct hepatic SULF2 overexpression in T2DM *db/db* liver, and hence attenuate postprandial dyslipoproteinemia in vivo, focusing on the novel AKT-dependent participants in SULF2 regulation that we identify in Aim 1.
Role: Principal investigator

Name of Project:
"Sulfatase-2: key mediator of residual atherosclerotic cardiovascular risk"
Principal Investigator: Kevin Jon Williams
Agency: Swedish Heart-Lung Foundation (Hjärt-Lungfonden); Unnumbered grant.
Period: 1/1/2016 - 12/31/2016
Aim 1 will examine atherosclerotic lesion development in SULF2-deficient mice. Aim 2 will be high-throughput screening of compound libraries for inhibitors and suppressors of SULF2.
Role: Principal investigator

Name of Project:
"Molecular resistance to appetite-suppressing effects of insulin and leptin in obesity"
Principal Investigator: Kevin Jon Williams
Agency: ALF-medel Västra Götalandsregionen; Reference number ALFGBG-542631.
Period: 1/1/2016 - 12/31/2016
Aim #1: To examine the role of the hypothalamic NSAPP pathway in acute satiety in lean vs obese rats. Aim #2: To examine the role of the hypothalamic NSAPP signaling pathway in chronic control of weight. Aim #3: To examine the NSAPP pathway in hypothalamic samples from lean vs obese human cadavers.

Role: Principal investigator

Completed Research Support (past three years)

Name of Project:
"NOX4 dysfunction as the basis for both fatty liver and poor glucose handling in type 2 diabetes"
Principal Investigator: Kevin Jon Williams
Agency: American Diabetes Association; Type: Basic Science Award (#1-13-BS-209),
Period: 01/01/13-12/31/15
The major questions this project addresses are 1) What is the basis for hepatic NOX4 dysfunction in simple chronic hyperphagia, leading to fatty liver and poor glucose handling?; and 2) Humans and animals with pathway-selective insulin resistance/responsiveness exhibit a marked impairment in overall insulin-stimulated tyrosine phosphorylation of the insulin receptor; so how does the insulin receptor still trigger vigorous phosphorylation of AKT at Thr308? We will study livers of hyperphagic, obese, T2DM *db/db* mice in vivo and cultured hepatocytes.
Role: Principal investigator

Name of Project:
"Residual cardiovascular risk: novel pathways and potential target discovery"
Principal Investigator: Kevin Jon Williams
Agency: Swedish Heart-Lung Foundation (Hjärt-Lungfonden); Unnumbered grant,
Period: 1/1/2014 - 12/31/2015
The major goals of this proposal are 1) to characterize defects in insulin action in obese KKA^y mice that drive hepatic oversecretion of triglyceride-rich VLDL1, and 2) to examine HDL-mediated removal of a specific set of pro-atherogenic lipids and peptides out of atherosclerotic plaques in vivo, to promote lesion stabilization and shrinkage.
Role: Principal investigator

Name of Project:
"HSPGs as remnant receptors: critical role in diabetic postprandial dyslipidemia"
Principal Investigator: Kevin Jon Williams
Agency: NHLBI; Type: R01 (HL094277), Period: 08/01/2009-07/31/2013
The major goals of this proposal are 1) to use specific gene transfer in vivo to test the hypothesis that Ndst1 suppression is responsible for impaired remnant clearance in type 1 diabetes mellitus; and 2) to use a specific knock-down in vivo to test the hypothesis that an overexpressed degradative enzyme impairs remnant clearance in type 2 diabetes mellitus.
Role: Principal investigator