Kevin Jon Williams, M.D.

Dr. Williams has made several contributions to our understanding of common deadly maladies, particularly atherosclerotic cardiovascular disease (ASCVD) and the atherometabolic syndrome.

First is the 'response-to-retention' hypothesis, which is now the dominant model to explain how a normal artery becomes atherosclerotic. 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. This work provides a basis for the new unity amongst basic, epidemiologic, pharmacologic, and clinical approaches to this major killer. Importantly, advances in this area have allowed us and others to reclassify ASCVD risk factors, which are epidemiologic concepts, into causative factors, exacerbators, and mere bystander phenomena. Causative and exacerbating factors are targets for therapy; bystander phenomena are not.

Second is our seminal work implicating unusual cell-surface molecules, called syndecan-1 heparan sulfate proteoglycans (HSPGs), as hepatic receptors for the disposal of harmful cholesterol- and triglyceride-rich apoB-containing remnant lipoproteins (C-TRLs). This work resolved a quarter-century dispute over the nature of LDL receptor-independent clearance of C-TRL remnants, which originate from the intestine and liver and appear in plasma after each meal. Moreover, we discovered that a key molecular defect in T2DM liver is vast overexpression of SULF2, which we showed to be an endogenous inhibitor of syndecan-1. In T2DM patients, we identified a polymorphism of the *SULF2* gene that strongly associates with fasting plasma triglyceride levels and especially postprandial lipid excursions. These findings support *SULF2* inhibition as an attractive strategy to improve metabolic dyslipoproteinemia.

Third is our work on insulin signaling. We recently discovered a new pathway of insulin signaling that we named the 'NSAPP' oxide transport chain after its five major protein components. We showed that the new pathway is essential for normal, balanced insulin action via the canonical MAP kinase (ERK) and metabolic (PI3K-AKT) signaling limbs. Our newly published findings on dysfunction of the NSAPP oxide transport chain in states of chronic overnutrition indicate a unified molecular explanation for why the seemingly unrelated components of the atherometabolic syndrome and type 2 diabetes mellitus (T2DM) occur together, such as fatty liver, hypertension, atherogenic dyslipoproteinemia, hyperglycemia, and hence accelerated atherosclerosis and microvascular disease.

Dr. Williams is the sole or coinventor of over a dozen US patents to date. He was also instrumental in the conversion of computerized residency matches in North America from hospital-optimal to student-optimal algorithms.

Dr. Williams is currently Professor of Medicine and Chief of the Section of Endocrinology, Diabetes, & Metabolism at the Lewis Katz School of Medicine at Temple University in Philadelphia (USA) and Gästprofessor (visiting professor) at Göteborgs universitet in Gothenburg (Sweden).