BIOGRAPHICAL SKETCH

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NAME: Kenneth Walsh, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): kxwalsh@bu.edu

POSITION TITLE: Professor, BUSM / Director, Whitaker Cardiovascular Institute

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Bowling Green State University	BS	08/1978	Chemistry
University of California, Berkeley	PhD	05/1984	Biochemistry

A. Personal Statement

I am the Aram V. Chobanian Distinguished Professor of Medicine and Director of the Whitaker Cardiovascular Institute in the Department of Medicine at Boston University School of Medicine. My laboratory broadly examines the molecular events that drive cardiovascular cell growth, differentiation and cell death. A major focus is to elucidate mechanisms of inter-tissue communication and understand how these systems contribute to physiological versus pathological tissue growth in the cardiovascular system, particularly as they relate to systemic metabolic dysfunction and cardiovascular disease. The laboratory has successfully changed focus on multiple occasions. The chronological order of the laboratory's research track over the past 2 decades can be summarized as follows: cell cycle/death ➔ Akt-signaling survival/growth pathways ➔ growth-related tissue communication ➔ metabolism/adipokines. These studies have led to the publication of more than 350 scientific articles, some of which have been cited more than 1000 times.

Recently, large exome sequencing studies in humans have shown that aging is associated with an increased frequency of somatic mutations in the hematopoietic system which provide a competitive growth advantage to the mutant cell and therefore allow its clonal expansion (i.e. clonal hematopoiesis). Unexpectedly, these somatic mutations have been found to be associated with greater risk of cardio-metabolic disease, suggesting a previously unrecognized link between somatic mutations in the hematopoietic system and inflammation-mediated diseases. However, whether there is a causal connection between these somatic mutations in hematopoietic cells and cardio-metabolic dysfunction remains unclear and the potential underlying mechanisms are unknown.

Using the epigenetic regulator Tet2 as a test case, a new line of investigation in my lab is aimed at providing the first mechanistic framework in support of the hypothesis that somatic mutations in hematopoietic progenitor and stem cells (HSPC) represent a causal risk factor for metabolic disease. This new line of investigation will make the following novel observations:

- Progressive expansion of Tet2-deficient hematopoietic cells (i.e. clonal hematopoiesis), as occurs in human individuals carrying somatic mutations in this gene, promotes metabolic disease.
- Tet2 inhibits pro-inflammatory IL-1β signaling at multiple levels, suggesting that IL-1β blockade or NLRP3 inflammasome inhibition may be particularly effective for the prevention/treatment of metabolic disease in individuals carrying somatic mutations in TET2 and potentially other related genes in hematopoietic cells.

Collectively, this new line of investigation will support a new paradigm of inflammation-mediated, metabolic disease. Our recent paper, "Clonal hematopoiesis associated with Tet2 deficiency accelerates atherosclerosis development in mice" (J. J. Fuster, et al. (2017). *Science* **355**:842-847. PMCID: PMC5542057) supports this premise.

B. Positions and Honors

Positions and Employment

1979- 1985 Graduate Student, Department of Biochemistry, University of California, Berkeley. Advisor: DE Koshland.
1985-1988 Postdoctoral Fellow, Department of Biology, Massachusetts Institute of Technology. Advisor: P Schimmel.
1989-1993 Assistant Professor, Department of Physiology and Biophysics, Case Western Reserve University.
1990-1995 Established Investigator of the American Heart Association.
1993 Irvine F. Page Young Investigator Award, AHA Council on Arteriosclerosis.
1993-2001 Program Director, Division of Cardiovascular Research, St Elizabeth's Medical Center, Associate Professor, Department of Medicine; Department of Anatomy and Cell Biology; Department of Physiology; Graduate Program in Cell, Molecular and Developmental Biology; Tufts University SOM.
2000-2001 Professor of Medicine, Tufts University School of Medicine.
2001- Head, Molecular Cardiology, Whitaker Cardiovascular Institute, Boston University School of Medicine. Professor of Medicine, Boston University School of Medicine.
2004-2016 Associate Editor, *Circulation*.
2008- Director, Whitaker Cardiovascular Institute, Boston University School of Medicine.
2008- Aram V. Chobanian Distinguished Professor of Cardiovascular Medicine, Boston University School of Medicine.
2009-2015 Charter Member, CCHF Study Section, National Institutes of Health.
2011 Distinguished Investigator of the American Heart Association.

Editorial Board Memberships

Circulation (Associate Editor, 2004-2016); *Atherosclerosis, Thrombosis and Vascular Biology*; *Hypertension Research* (International Advisory Board, Assistant Editor); *Journal of Molecular and Cellular Cardiology*; *Circulation Research*; *Circulation Journal* (International Advisory Board); *Skeletal Muscle; Science Signaling* (Editorial Board and Board of Reviewing Editors); *Annual Review of Physiology.*

C. Contributions to Science

1. Non-canonical Wnt signaling in cardio-metabolic disease: Obesity is the major worldwide epidemic of the 21st century, and cardiovascular disease is the predominant cause of mortality in obese individuals. However, the mechanisms that link adipose tissue dysfunction to cardiovascular disease remain incompletely understood. A growing body of evidence shows that adipose tissue secretes bioactive molecules called "adipokines", and that obesity contributes to CVD due to unbalanced adipokine secretion, creating a chronic low-grade inflammatory state. Past research in the Walsh laboratory has analyzed how an anti-inflammatory adipokine, termed adiponectin, functions to protect the cardiovascular system, and we published the first papers documenting its cardio-protective actions. More recently, our laboratory has identified Sfrp5 as a new anti-inflammatory adipokine, which antagonizes the pro-inflammatory activity of Wnt5a, a regulator of non-canonical Wnt signaling. We have shown that non-canonical Wnt5a signaling and its downstream signaling components are markedly upregulated in obese patients, particularly the visceral fat depot that is most highly associated with the development of cardio-metabolic disease. We have also utilized novel genetic models to show that Sfrp5/Wnt5a signaling is a regulator of adipose tissue inflammation and systemic metabolic health. Recently, we have shown that this regulatory pathway affects revascularization in peripheral artery disease and mediates the contribution of metabolic dysfunction to vascular disease processes.

a. N. Ouchi, A. Higuchi, K. Ohashi, Y. Oshima, N. Gokce, R. Shibata, Y. Akasaki, A. Shimono, K. Walsh (2010). Sfrp5 is an anti-inflammatory adipokine that modulates metabolic dysfunction in obesity. ***Science*** 329:454-457. *Accompanied by editorial.* PMCID: PMC3132938.
b. D. T. Ngo, M.G. Farb, R. Kikuchi, S. Karki, S. Tiwari, S. J. Bigornia, D. O. Bates, M. P. LaValley, N. M. Hamburg, J. A. Vita, D. T. Hess, K. Walsh, N. Gokce (2014) Anti-angiogenic actions of VEGF-A_{165}b, an inhibitory isoform of VEGF-A, in human obesity. ***Circulation*** 130:1072-1080. PMCID: PMC4175289.
c. R. Kikuchi, K. Nakamura, S. MacLauchlan, D. T. Ngo, I. Shimizu, J. J. Fuster, Y. Katanasaka, S. Yoshida, Y. Qiu, T. P. Yamaguchi, T. Matsushita, T. Murohara, N. Gokce, D. O. Bates, N. M. Hamburg, K. Walsh

(2014). An anti-angiogenic isoform of VEGF-A contributes to impaired vascularization in peripheral artery disease. ***Nature Medicine*** 20:1464-1471. *Accompanied by editorial.* PMCID: PMC4257756.

d. J. J. Fuster, M. A. Zuriaga, D. T.-M. Ngo, M. G. Farb, T. Aprahamian, T. P. Yamaguchi, N. Gokce, K. Walsh (2015). Non-canonical Wnt signaling promotes obesity-induced adipose tissue inflammation and metabolic dysfunction. ***Diabetes*** 64:1235-1248. PMCID: PMC4375084.

2. Cardio-metabolic disease and general metabolism: In view of the growing obesity epidemic and its devastating impact on the cardiovascular system, I undertook a self-tutorial approximately 14 years ago to develop expertise in metabolism research. By reading scientific papers and reviews and by attending obesity and diabetes meetings, it became clear to me that a major driving force behind cardio-metabolic disease was the chronic, low-grade inflammatory state that develops from adipose tissue inflammation and the subsequent collateral damage of cytokine release. Thus, my laboratory's first foray into the metabolism field involved the study of adiponectin, an adipocyte-derived cytokine (or "**adipokine**"). Unlike most adipokines, adiponectin is anti-inflammatory and down-regulated in obesity. Studies by my laboratory were the first to show that adiponectin directly acts on the heart and vasculature as a protective factor. Since that time, we have published more than 58 papers on adiponectin. More recently we have studied the role of vascular rarefaction in adipose tissue and its consequences on systemic metabolism. We also created a unique mouse model that documented the profound importance of glycolytic, fast-twitch muscle in the control of systemic metabolic function. This work is of particular significance because aging is associated with the loss of glycolytic muscle, whereas oxidative muscle tends to be preserved. As we have become increasing adept in the area of metabolic research, some of our highest visibility papers have been entirely on the topic of metabolism (sans cardiovascular):

a. R. Shibata, N. Ouchi, M. Ito, S. Kihara, I. Shiojima, D.R. Pimentel, M. Kumada, K. Sato, S. Schiekofer, K. Ohashi, T. Funahashi, W.S. Colucci, K. Walsh (2004). Adiponectin-mediated modulation of hypertrophic signals in the heart. ***Nature Medicine*** 10:1384-1389. PMCID: PMC2828675.

b. R. Shibata, K. Sato, D.R. Pimentel, Y. Takemura, S. Kihara, K. Ohashi, T. Funahashi, N. Ouchi, K. Walsh (2005). Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. ***Nature Medicine*** 10: 1096-1103. *Accompanied by editorial.* PMCID: PMC2828682.

c. Y. Izumiya, T. Hopkins, C. Morris, K. Sato, L. Zeng, J. Viereck, J.A. Hamilton, N. Ouchi, N.K. LeBrasseur, K. Walsh (2008). Fast/glycolytic muscle fiber growth reduces fat mass and improves metabolic parameters in obese mice. ***Cell Metabolism*** 7:159-172. *Accompanied by editorial.* PMCID: PMC2828690.

d. I. Shimizu, T. Aprahamian, R. Kikuchi, A. Shimizu, K.N. Papanicolaou, S. Maclauchlan, S. Maruyama, K. Walsh (2014). Vascular rarefaction mediates whitening of brown fat in obesity. ***Journal of Clinical Investigation*** 124:2099-2112. PMCID: PMC4001539.

3. Growth-related tissue communication: Related to our studies on "adipokines", we have examined how alterations in cellular crosstalk mechanisms between cardiac myocytes and vascular endothelial cells contribute to the transitions from compensated hypertrophy to heart failure. Factors involved in this regulation, termed "**cardiokines**", include Fstl1, Fstl3 and Activin-A. Subsequent studies in patient populations have shown that at least one of these factors is upregulated in clinical heart failure and is predictive of mortality in patients with acute coronary syndrome. My laboratory also examines how age-associated loss of skeletal muscle mass affects metabolic and cardiovascular function, and is exploring the possibility that muscle-secreted factors ("**myokines**") confer some of the benefits of exercise training on cardiovascular and metabolic diseases. To date, we have published approximately 20 papers on putative cardiokines and myokines. Representative publications are listed below.

a. Y. Oshima, N. Ouchi, K. Sato, Y. Izumiya, D.R. Pimentel, **K. Walsh** (2008). Follistatin-like 1 is an Akt-regulated cardioprotective factor that is secreted by the heart. ***Circulation*** 117:3099-3108. PMCID: PMC2679251.

b. M. Shimano, N. Ouchi, K. Nakamura, Y. Oshima, A. Higuchi, D.R. Pimentel, K.D. Panse, E. Lara-Pezzi, S.J. Lee, F. Sam, K. Walsh (2011). Cardiac myocyte-specific ablation of Follistatin-like 3 attenuates stress-induced myocardial hypertrophy. ***Journal of Biological Chemistry*** 286:9840-9848. *Editor's Choice feature in Science Signaling.* PMCID: PMC3058981.

c. K. Wei, V. Serpooshan, C. Hurtado, M. Diez-Cuñado, M. Zhao, S. Maruyama, W. Zhu, M. Noseda, K. Nakamura, X. Tian, Q. Liu, Y. Matsuura, W. Cai, A. Savtchenko, M. Mahmoudi, M.D. Schneider, M.

vandenHoff, M.J. Butte, P.C. Yang, K. Walsh, B. Zhou, D. Bernstein, M. Mercola and P. Ruiz-Lozano (2015). Epicardial FSTL1 reconstitution regenerates the adult mammalian heart. ***Nature*** 525:479-485. PMCID: PMC4762253.

d. S. Maruyama, K. Nakamura, K. N. Papanicolaou, S. Sano, I. Shimizu, Y. Asaumi, M. J. van den Hoff, N. Ouchi, F. A. Recchia, K. Walsh (2016). Follistatin-like 1 promotes cardiac fibroblast activation and protects the heart from rupture. ***EMBO Molecular Medicine*** 8:949-966. PMCID: PMC4967946.

4. Akt-signaling growth/survival pathways: A long-term theme in my laboratory involves the analysis of signaling- and transcriptional-regulatory mechanisms that control both normal and pathological tissue growth in the cardiovascular system. Many of these studies involve analyses of the Akt/PI3K/GSK/Forkhead signaling axis. Our original publication in this area was on the initial cloning and description of the Akt2 isoform in 1995. Despite deep skepticism of the importance of this pathway at the time, we were the first, or among the first, to report that the Akt-signaling pathway controls cellular enlargement (hypertrophy), cell survival (apoptosis), and blood vessel growth (angiogenesis) and function (NO production) in the cardiovascular and/or skeletal muscle systems (due to space limitations these papers are not listed). We have shown that the Akt/PI3K/GSK/Forkhead signaling axis regulates multiple steps critical in blood vessel recruitment, cardiac hypertrophy during normal postnatal development, and myocyte survival in models of heart disease. The analysis of inducible mouse genetic models that conditionally overexpress Akt in cardiac myocytes, skeletal muscle and vascular endothelial cells ultimately led to our studies on cellular crosstalk mechanisms in growing tissues, leading to the isolation and characterization of “cardiokine” and “myokine” candidates. In the context of understanding inter-tissue communication, we continue to work on some these mouse genetic models today.

a. D. Fulton, J.P. Gratton, T. McCabe, J. Fontana, Y. Fujio, K. Walsh, T. Franke, A. Papapetropoulos, W.C. Sessa (1999). Regulation of endothelium-derived nitric oxide production by the protein kinase Akt. ***Nature*** 399:597-601. PMCID: PMC3637917.

b. Y. Kureishi, Z. Luo, I. Shiojima, A. Bialik, D. Fulton, D.J. Lefer, W.C. Sessa, K. Walsh (2000) The HMG-CoA reductase inhibitor simvastatin activates the protein kinase Akt and promotes angiogenesis in normocholesterolemic animals. ***Nature Medicine*** 6:1004-1010. *Accompanied by editorial.* PMCID: PMC2828689.

c. M. Sandri, C. Sandri, A. Gilbert, C. Skurk, E. Calabria, A. Picard, K. Walsh, S. Schiaffino, S.H. Lecker, A.L. Goldberg (2004). Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. ***Cell*** 117:399-412. PMCID: PMC3619734.

d. Shiojima, K. Sato, Y. Izumiya, S. Schiekofer, M. Ito, R. Liao, W.S. Colucci, K. Walsh (2005). Disruption of coordinated cardiac hypertrophy and angiogenesis contributes to the transition to heart failure. ***Journal of Clinical Investigation*** 115:2108-2118. *Accompanied by editorial.* PMCID: PMC1180541.

5. Cell death and cell cycle: The early studies that led to our early work on the Akt signaling pathway (and ultimately to inter-tissue communication and adipokines) developed from our initial focus on the mechanisms that controlled cell death and cell in the cardiovascular system. The paper listed below led us to embark upon the analysis of Akt signaling, genetic models of tissue growth and metabolism:

a. V. Andrés and K. Walsh (1996). Myogenin expression, cell cycle withdrawal and phenotypic differentiation are temporally separable events that precede cell fusion upon myogenesis. ***Journal of Cell Biology*** 132:657-666. PMCID: PMC2199863.

b. J. Wang and K. Walsh (1996). Resistance to apoptosis conferred by Cdk inhibitors during myocyte differentiation. ***Science*** 273:359-361. PMCID: PMC3641673.

c. R.C. Smith, D. Branellec, D.H. Gorski, K. Guo, H. Perlman J.F. Dedieu, C. Pastore, A. Mahfoudi, P. Denèfle, J.M. Isner, K. Walsh (1997). p21CIP1-mediated inhibition of cell proliferation by overexpression of the *gax* homeodomain gene. ***Genes & Development*** 11:1674-1689. PMCID: PMC not applicable.

d. M. Sata and K. Walsh (1998). TNFα-regulation of Fas ligand expression on the vascular endothelium modulates leukocyte extravasation. ***Nature Medicine*** 4:415-420. PMCID: PMC2828686.

A partial list of published work listed in MyBibliography (380 publications; h-index 112: 53,356 citations): https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40321655/?sort=date&direction=descending

Training: I have trained numerous graduate students and post-doctoral fellows, and many have gone on to establish their own successful laboratories (and at least one company (Vector Biolabs, founded in 2004)). Many

of my previous fellows have now been appointed to the rank of Professor at academic institutions. Eight of these former trainees are currently department chairs, section chiefs or institute directors. In addition, many of my prior trainees are Assistant or Associate Professors in academia or employees at major pharmaceutical firms.

D. Additional Information: Research Support

Ongoing Research Support

R01 HL126141 Gokce, Walsh (Co-PI) 12/01/14-11/30/19
"Anti-Angiogenic Mechanisms in Human Obesity"
This project investigates the role of VEGF isoforms in metabolic disease of bariatric surgery patients.
Role: Co-PI

R01 HL131006 Walsh (PI) 01/01/16-12/31/19
"Inflammatory Wnt Signaling in Ischemic Myocardium"
To investigate the roles of adipokines in the development of post-myocardial infarction remodeling.
Role: PI

R01 HL129120 Recchia/Walsh (Co-PI) 04/01/16-03/31/20
"Follistatin-like Protein 1 in Cardiac and Systemic Metabolism"
This project tests the metabolic crosstalk between skeletal muscle and the heart via Fstl1.
Role: Co-PI

R01 HL132564 Walsh (PI) 04/01/16-03/31/20
"Inflammatory Pathways in Aortic Aneurysms"
To investigate the role and therapeutic potential of a new non-canonical Wnt signaling axis in the setting of abdominal aortic aneurysm.
Role: PI

R21 AG052160 Walsh (PI) 09/15/16-05/31/18
"Myokine Control of Hepatic Steatosis"
To examine the effects of Fstl1 in the development of hepatic steatosis and insulin resistance and investigate the role of AMPK signaling in the protective effects of Fstl1 against hepatic steatosis.
Role: PI

R01 HL138014 Walsh (PI) 07/15/17-06/30/21
"Somatic TET2 mutations in cardiac remodeling"
To determine if there is a causal connection between somatic mutations in the hematopoietic system and cardiovascular disease, and to ascertain the potential underlying mechanisms.
Role: PI

Completed Research Support

P01 HL081587 Walsh (PD) 09/30/05-02/28/17
"Program Project: Metabolic Control of Endothelial Cell Phenotype" (No cost extension)
Project 1: Adipose Tissue Inflammation and Vascularity/Administrative Core Leader/Scientific Core Leader
To assess the actions of adiponectin adipose tissue vascularity and macrophage polarization, and utilize mouse genetic models to assess the contribution of adiponectin receptor candidates.
Role: Program Director, Leader Project 1

R01 HL116591 Walsh (PI) 09/01/13-6/30/17
"Paracrine Regulation of Heart Failure"
To investigate the role of Fstl1 in post-MI heart failure using genetic models.
Role: PI

R01 HL120160 Walsh (PI) 09/01/13-5/31/17
"Mitochondrial Dynamics and Cardiac Remodeling"
To analyze the roles of mitochondrial fusion genes (Mfn1 and Mfn2) in the heart.
Role: PI