BIOGRAPHICAL SKETCH

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NAME: Wende, Adam Raymond

eRA COMMONS USER NAME (credential, e.g., agency login): ADAMWENDE

POSITION TITLE: Assistant Professor of Molecular and Cellular Pathology

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
Knox College, Galesburg, IL	B.A.	05/2000	Biochemistry and Biology (double)
Washington University, Saint Louis, MO	Ph.D.	05/2006	Molecular and Cellular Biology
University of Utah, Salt Lake City, UT	Postdoctoral Fellowship	07/2012	Endocrinology, Metabolism, and Diabetes

A. Personal Statement

Although independent for less than two years, my training and research for the past 15 years has focused on expanding our understanding of the molecular pathways in control of mitochondrial function. During my thesis training I focused on how exercise or hypertension alter cardiometabolic function in opposing directions through the regulation of gene expression by the transcriptional co-activator PGC-1α. My postdoctoral training expanded these interests to include studies of how heart function, directly related to diabetic complications, is influenced by insulin signaling and glucose utilization. By combining the gained expertise in transcriptional biology and cellular signaling I have begun my independent faculty career with a mission to decipher the cardiometabolic control of cellular function in normal physiology and disease. This work has two primary goals: 1) to determine the role of metabolic substrate switching in individuals with diabetes, and 2) to define the post-translational regulation of mitochondrial enzyme activity and epigenetic regulation of gene expression that together may lead to the development of diabetic complications. I have begun to explore multiple aspects of metabolic control in a systems biology approach. Current animal model work in the laboratory, supported by an NIH R00 Pathway to Independence award (R00 HL111322), is focused on changes in DNA methylation and protein *O*-GlcNAcylation that may impact gene expression, protein function, and mitochondrial capacity in the hearts of diabetics. One of my primary reasons for starting my independent career at the University of Alabama at Birmingham (UAB) is the strength of their Nutrition Obesity Research Center, Center for Exercise Medicine, Diabetes Center, and Cardiovascular Center. As an investigator at the intersection of these various fields the environment is perfect. In my short time at UAB I have taken on a number of collaborations while increasing the funding for my independent work. Specifically, we have obtained NIH funding to explore DNA methylation in human heart failure samples (U24 DK076169) and the role of circadian rhythm in regulating insulin signaling with Dr. Martin Young (R01 HL123574). The current R01 proposal seeks to build on these successes and gained knowledge by being one of the first to define the contribution of glucose delivery to epigenetic programming in the heart.

Most relevant 4 publications (from 35) for current proposal showing successful collaborations with other laboratories, specific personal contributions described in Section C.
Expanded profile at: https://services.medicine.uab.edu/facultydirectory/FacultyData.asp?ID=arwende

1. Kim J, **Wende AR**, Sena S, Theobald HA, Soto J, Sloan C, Wayment BE, Litwin SE, Holzenberger M, LeRoith D and Abel ED. Insulin-like growth factor-1 (IGF-1) receptor signaling is required for exercise-induced cardiac hypertrophy. *Molecular Endocrinology*, 22(11):2531-2543, 2008. *Cited > 50 times.* PMCID: PMC2582541

2. Marcus RL, Addison O, LaStayo PC, Hungerford R, **Wende AR**, Hoffman JM, Abel ED and McClain DA. Regional muscle glucose uptake remains elevated 1 week after cessation of resistance training independent of altered insulin sensitivity response in older adults with type 2 diabetes. *The Journal of Endocrinological Investigation*, 36:111-117, 2013. PMID: 22522495

3. Addison O, Drummond MJ, LaStayo PC, Dibble LE, **Wende AR**, McClain DA and Marcus RL. Intramuscular fat and inflammation differ in older adults: The impact of frailty and inactivity. *The Journal of Nutrition, Health and Aging,* 18(5):532-538, 2014. PMID: 24886741

4. Riehle C, **Wende AR**, Zhu Y, Oliveira KJ, Pereira RO, Jaishy BP, Bevins J, Valdez S, Noh J, Kim BJ, Moreira AB, Weatherford ET, Manivel R, Rawlings TA, Rech M, White MF and Abel ED. Insulin receptor substrates (IRS) are essential for the bioenergetic and hypertrophic response of the heart to exercise training. *Molecular and Cellular Biology*, 34(18):3450-3460, 2014. PMCID: PMC4135616

B. Positions and Honors

Positions and Employment

1997-2000 Undergraduate thesis student with Mark R. Brodl, Ph.D., Knox College, Galesburg IL
2000-2006 Graduate student with Daniel P. Kelly, M.D., Washington University, St. Louis MO
2006-2012 Postdoctoral Fellow with E. Dale Abel, M.D., Ph.D., University of Utah, Salt Lake City UT
2012-2013 Research Instructor with E. Dale Abel, M.D., Ph.D., University of Utah, Salt Lake City UT
2013-Pres. Assistant Professor, University of Alabama at Birmingham, Birmingham AL

Other Experience and Professional Memberships

2003-Pres. Member, American Heart Association (AHA)
2008-Pres. Member, American Diabetes Association (ADA)
2013-Pres. Member, American Physiological Society (APS)
2014-Pres. Member, American Society for Biochemistry and Molecular Biology (ASBMB)
2014-Pres. Study Section Member, AHA Cardiac Biology / Regulation - Basic Science 4

Honors

1996-2000 Muelder Scholar, Knox College
1998 Howard Hughes Medical Institute Undergraduate Fellowship, Knox College
2001-2003 Molecular Cell Biology Training Grant, Washington University (T32 GM007067)
2001 AHA Trainee Abstract Award
2002 Keystone Symposium Travel Grant Award
2003-2005 Cardiovascular Biology Training Grant, Washington University (T32 HL007275)
2006-2007 Cardiovascular Biology Training Grant, University of Utah (T32 HL007576)
2007 FASEB Symposium Travel Grant Award
2007-2009 AHA Western States Affiliate Postdoctoral Fellowship
2009-2012 JDRF Advanced Postdoctoral Fellowship
2010 AHA Trainee Abstract Award
2011 Society for Heart and Vascular Metabolism (SHVM) Early Investigator Commendation
2012 Keystone Symposium Scholarship NIH-NIDDK & NIA 5R13DK084688-03
2015-Pres. Inaugural Pittman Scholar, UAB

C. Contribution to Science

Current h-index = 15, i10-index = 20, and Google Scholar citations 2,493 (April 2015)

1. I was fortunate to start my career around the same time as the discovery of the transcriptional co-activator PGC-1α. At that time little was known about this factor other than its induction in response to cold, a role in mitochondrial biogenesis, and control of fatty acid oxidation. Under the guidance of a number of great mentors, including my thesis advisor Dr. Daniel P. Kelly, I contributed to a number of publications defining new roles of this now widely accepted master regulator of mitochondrial function. In my first collaborative study we found that *Ppargc1a*, the gene encoding PGC-1α, is robustly induced following exercise and alternate transcripts are formed. We next defined a critical role for PGC-1α in overall energy metabolic maintenance using a null mouse model. However, the primary contribution of my early career is captured in two publications expanding the role of PGC-1α to the regulation of glucose utilization by direct transcriptional regulation of ERRα to induce expression of the *Pdk4* gene resulting in reduced glucose oxidation and enhanced glucose storage in the form of glycogen replenishment following acute exercise.
    a. Baar K, **Wende AR**, Jones TE, Marison M, Nolte LA, Chen M, Kelly DP and Holloszy JO. Adaptations of muscle to exercise: rapid increase in the transcriptional coactivator PGC-1. *The FASEB Journal*, 16(14):1879-1886, 2002. *Cited > 650 times.* PMID: 12468452

b. Leone TC, Lehman JL, Finck BN, Schaeffer PJ, **Wende AR**, Boudina S, Courtois M, Wozniak DF, Sambandam N, Bernal-Mizrachi C, Chen Z, Holloszy JO, Medeiros DM, Schmidt RE, Saffitz JE, Abel ED, Semenkovich CF and Kelly DP. PGC-1α deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis. *PLoS Biology*, 3(4):e101, 2005. *Cited > 650 times.* PMCID: PMC1064854

c. **Wende AR**, Huss JM, Schaeffer PJ, Giguère V and Kelly DP. PGC-1α coactivates PDK4 gene expression via the orphan nuclear receptor ERRα: A mechanism for transcriptional control of muscle glucose metabolism. *Molecular and Cellular Biology*, 25(24):10684-10694, 2005. *Cited > 250 times.* PMCID: PMC1316952

d. **Wende AR**, Schaeffer PJ, Parker GL, Zechner C, Han DH, Chen MM, Hancock CR, Lehman JJ, Huss JH, McClain DA, Holloszy JO and Kelly DP. A role for the transcriptional coactivator PGC-1α in muscle refueling. *The Journal of Biological Chemistry*, 282(50):36642-36651, 2007. *Cited > 150 times.* PMID: 17932032

2. In addition to these contributions looking at PGC-1α in skeletal muscle, I have explored metabolic function and focused on studies in the heart. During this time I also transitioned to a new institute and a new team of excellent mentors, led primarily by my postdoctoral advisor Dr. E. Dale Abel. By this time a family of related PGC factors were discovered and one of my first major contributions was showing that PGC-1β is required to maintain cardiac function in response to pressure overload induced hypertrophy. However, we also found that PGC-1α is not sufficient to provide complete protection from progression to heart failure, suggesting distinct roles for these related factors. My contributions to these studies included developing the surgical expertise to perform aortic constriction, a skill I have trained a number of investigators to use. The understanding that the response to pressure overload is much more than just regulation of PGC led me to expand my exploration well beyond this single family of molecules and through a series of collaborations we also looked at the requirement of glucose delivery to the heart via the glucose transporter GLUT1 finding that substrate supply can be just as important as mitochondrial integrity to heart function.

   a. Riehle C*, **Wende AR***, Zaha VG, Pires KM, Wayment B, Olsen C, Bugger H, Buchanan J, Wang X, Moura AB, Doenst T, Medina-Gomez G, Litwin SE, Lelliott CJ, Vidal-Puig A and Abel ED. PGC-1β deficiency accelerates the transition to heart failure in pressure overload hypertrophy. *Circulation Research*, 109(7):783-793, 2011. PMCID: PMC3175248 (* denotes equal contributions)

   b. Pereira RO, **Wende AR**, Crum A, Hunter D, Olsen CD, Rawlings T, Riehle C, Ward WF and Abel ED. Maintaining PGC-1α expression following pressure overload-induced cardiac hypertrophy preserves angiogenesis but not contractile or mitochondrial function. *The FASEB Journal*, 28(8):3691-3702, 2014. PMCID: PMC4101649

   c. Pereira RO, **Wende AR**, Olsen C, Soto J, Rawlings T, Zhu Y, Anderson SM and Abel ED. Inducible overexpression of GLUT1 prevents mitochondrial dysfunction and attenuates structural remodeling in pressure overload but does not prevent left ventricular dysfunction. *Journal of the American Heart Association*, 2(5):e000301, 2013. PMCID: PMC3835233

   d. Pereira RO, **Wende AR**, Olsen C, Soto J, Rawlings T, Zhu Y, Riehle C and Abel ED. GLUT1 deficiency in cardiomyocytes does not accelerate the transition from compensated hypertrophy to heart failure. *Journal of Molecular and Cellular Cardiology*, 72:95-103, 2014. PMCID: PMC4037364

3. A major goal behind my choice of postdoctoral laboratory was to learn more about diabetes and general endocrinology. This has led to a number of publications related to upstream regulation of mitochondrial and cardiac function, centered on insulin. My primary contributions in this area have included studies showing that some but not all of phosphatidylinositol 3-kinase signaling is through the kinase Akt and this changes in response to the physiological stress of exercise. Surprisingly we also found that a key-signaling pathway in diabetes for the development of kidney dysfunction via bradykinin has relatively little effect on the heart. A recent contribution to this area is a study that brings together all the above findings showing that sustained Akt signaling produces heart failure via reduction in gene expression focused primarily on *Ppargc1a* and related transcriptional targets resulting in disruption of mitochondrial function.

   a. O'Neill BT, Kim J, **Wende AR**, Theobald HA, Tuinei J, Buchanan J, Guo A, Zaha VG, Davis DK, Schell JC, Boudina S, Wayment B, Litwin SE, Shioi T, Izumo S, Birnbaum MJ and Abel ED. A conserved role for phosphatidylinositol 3-kinase but not Akt signaling in mitochondrial adaptations that accompany physiological cardiac hypertrophy. *Cell Metabolism*, 6(4):294-306, 2007. *Cited > 50 times.* PMCID: PMC2084219

b. **Wende AR**, Soto J, Olsen CD, Pires KM, Schell JC, Larrieu-Lahargue F, Litwin SE, Kakoki M, Takahashi N, Smithies O and Abel ED. Loss of bradykinin signaling does not accelerate the development of cardiac dysfunction in type 1 diabetic Akita mice. *Endocrinology*, 151(8):3536-3542, 2010. PMCID: PMC2940524

c. **Wende AR***, O'Neill BT*, Bugger H, Riehle C, Tuinei J, Buchanan J, Tsushima K, Wang L, Caro P, Guo A, Sloan C, Kim BJ, Wang X, Pereira RO, McCrory MA, Nye BG, Benavides GA, Darley-Usmar VM, Shioi T, Weimer B and Abel ED. Akt/PKB signaling induces mitochondrial dysfunction in pathological cardiac hypertrophy via transcriptional repression of nuclear-encoded mitochondrial genes. *Molecular and Cellular Biology*, 35(5):831-846, 2015. PMCID: PMC4323486

4. My independent career is just at its beginning. My choice to start it at The University of Alabama at Birmingham has to do with a number of great centers to support my research and collaborators to increase my areas of expertise. I have already expanded beyond my formal training and have begun exploring the contribution of the circadian clock to metabolic control with my collaborator Dr. Martin Young. Most relevant to my current funding and career goals is training and contributions to the areas of the posttranslational modification *O*-GlcNAcylation and I have identified a complementary group of investigators led by Dr. John Chatham. I have also continued training in a completely independent avenue of epigenetics. This later directly builds upon my substantial training in transcriptional regulation and expands it to the intersection of environmental influences on chromatin structure and ultimately functional changes related to altered gene expression patterns. Contributions to these areas are in manuscripts currently in preparation, and have provided the foundation for a series of funded grants (see section D) and a growing number of meeting abstracts by current trainees. Together this and the previous three areas have built upon each other and helped shape my current trajectory.

   a. Young ME, Brewer RA, Peliciari-Garcia RA, Collins HE, He L, Birky TL, Peden BW, Thompson EG, Ammons BJ, Bray MS, Chatham JC, **Wende AR**, Yang Q, Chow CW, Martino TA and Gamble KL. Cardiomyocyte-specific BMAL1 plays critical roles in metabolism, signaling, and maintenance of contractile function of the heart. *Journal of Biological Rhythms*, 29(4):257-276, 2014. PMCID: PMC4260630

   b. Nye BG, Bailey TJ and **Wende AR**[#]. DNA methylation and corresponding gene expression changes in the diabetic heart. *Keystone - Mitochondria, Metabolism and Heart Failure (J5) joint with the meeting on Diabetes and Metabolic Dysfunction (J6)*, 2015. (selected workshop talk) (# denotes corresponding author)

   c. Brahma MK, McCrory MA and **Wende AR**[#]. Modulation of myocardial ketone body oxidation by increased glucose delivery. ADA Scientific Sessions. *Diabetes Supplement*, (accepted), 2015. (poster) (# denotes corresponding author)

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/adam.wende.1/bibliograpahy/40270874/public/

D. Research Support
Ongoing Research Support

NIH R00 HL111322 Wende AR (PI) 08/01/13 – 07/31/16
Mechanisms of glucose mediated cardiac mitochondrial dysfunction
Heart failure is characterized by a decline in mitochondrial oxidative capacity and is a major cause of death in individuals with diabetes. We have developed a novel mouse model for inducible cardiac specific overexpression of the glucose transporter 4 (GLUT4). These studies will determine the contribution of cellular glucose uptake in the development of mitochondrial dysfunction in the mouse heart.
Role: Principal Investigator

NIH R01 HL123574 Young ME (PI) 07/01/14 – 06/30/19
Circadian regulation of myocardial insulin signaling
The broad objective of this proposal is to test the hypothesis that hypothesize that the cardiomyocyte circadian clock modulates myocardial insulin sensitivity in a time-of-day-dependent manner (through regulation of p85α), and that dysfunction of the clock following diet-induced obesity disrupts myocardial insulin signaling, thereby contributing to contractile dysfunction.
Role: Co-Investigator

NIH U24 DK076169 McIndoe RA (PI) 08/01/14 – 07/31/15
Diabetic Complications Consortium (DiaComp)
Human DNA methylation signatures to define diabetic cardiac subtypes
Heart failure is characterized by a reprogramming of gene expression and is a major cause of death in individuals with diabetes. DNA methylation is a newly emerging focus of study for the regulation of gene expression. The relevance of this study is to define subtypes of end-organ disease between diabetic and non-diabetic heart failure patients by interrogating cardiac biopsy samples for unique genomic changes.
Role: Subcontract

NIH R00 HL111322-S1 Wende AR (PI) 08/01/14 – 07/31/15
Collaborative Activities to Promote Metabolomics Research (Admin Supp)
Mechanisms of glucose mediated cardiac mitochondrial dysfunction
Studies outlined for the proposal, will define changes in metabolites associated with the placement and maintenance of epigenetic modifications and changes in gene expression that are uniquely regulated by glucose. The initial phase of this proposal will facilitate training in aspects of metabolomics (LC-MS and NMR). Collectively, the completion of these studies, and those of the parent grant, will provide fundamental insights into the mechanistic basis for glucose in the development of diabetic cardiomyopathy and loss of metabolic substrate flexibility.
Role: Principal Investigator

UAB CFAR P&F Tse HM (PI) 03/01/15 – 02/28/16
Center For AIDS Research (CFAR)
Epigenetic & kinomic analysis of adipose inflammation from anti-retroviral therapy-treated diabetic mice
Collectively, these studies will define novel information regarding the intersection of HIV-infection, anti-retroviral therapy, inflammation, and the development of metabolic complications (i.e. diabetes and obesity). The insights gained from these studies will influence the design of novel anti-diabetic/anti-obesity therapies for the growing population of ART-treated, HIV-positive, metabolically impaired individuals.
Role: Multi-Investigator: Tse HM, Habegger KM and Wende AR

NIH R25 DK078381 Reeves WB (PI) 06/15/15 – 09/06/15
Short-Term Research Experience for Underrepresented Persons (STEP-UP)
Glucose-mediated regulation of cardiac metabolome and UQCRFS1
This study is part of an ongoing undergraduate Honors Thesis and seeks to define the contributions of GlcNAc mediated regulation of OXPHOS activity. Specifically, the trainee's project is building on data generated by the R00 funded research to examine the expression, regulation, and function of complex III subunit UQCRFS1.
Role: Sponsor/Mentor to Williams LJ

Completed Research Support (last 5 years; 4 awards prior)

10-2009-672 Wende AR (PI) 07/01/09 – 05/31/12
JDRF Advanced Postdoctoral Fellowship
In vivo identification of mechanisms mediating cardiac glucose toxicity
To determine how high blood glucose levels in diabetes affects the function and expression of proteins in the heart, which ultimately are responsible for metabolic dysfunction and other complications of type 1 diabetes.
Role: Postdoctoral Fellow (Mentor: Abel ED)

NIH K99 HL111322 Wende AR (PI) 06/01/12 – 07/31/13
Pathway to Independence Award
Mechanisms of glucose mediated cardiac mitochondrial dysfunction
The objective of these studies is to determine the contribution of cellular glucose uptake in the development of mitochondrial dysfunction in the heart.
Role: Postdoctoral Fellow (Co-mentors: Abel ED and Lane RH)

10-2006-261 Wende AR (PI) 01/01/13 – 12/31/13
JDRF Transition Award
In vivo identification of mechanisms mediating cardiac glucose toxicity
The objective of these studies is to examine regulation of DNA methylation that is associated with glucose-mediated changes in gene expression.
Role: Principle Investigator