BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Sihem Boudina

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

POSITION TITLE: Associate Professor

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
University of Science and Technology, Algeria	BS	1991	1996	Animal Physiology
Université Bordeaux 2, Bordeaux, France	MS	1997	1998	Neuroscience and Neuropharmacology
Université Bordeaux 2, Bordeaux, France	PhD	1998	2002	Biological and Medical Sciences
University of Utah	Postdoctoral	2002	2008	Cardiac Metabolism

A. Personal Statement

I am an Associate Professor in the Department of Nutrition and Integrative Physiology at the University of Utah. My research is focused on understanding the pathogenesis of obesity and the associated cardiovascular complications. I have a broad background in adipose and cardiac physiology with specific training and expertise in mitochondrial energetics and metabolism. Our work has advanced our understanding of how cardiac metabolism is regulated by insulin signaling and how insulin resistance and obesity affected mitochondrial energetics in the heart. My lab has the expertise and can provide training and advice related to the assessment of cardiac function and metabolism using the Langendorff working heart preparation, glucose uptake on isolated adult cardiomyocytes and isolation of heart mitochondrial and measurement of respiration. Aside from research, I have enjoyed mentoring students and fellows over the course of my career. Since my hiring in 2010, I mentored a total of 12 post-doctoral fellows, 6 graduate students, 7 medical students, 25 undergraduate students and 4 high school students. I continue to participate in two mentoring programs at the University of Utah: (1) The Bioscience high School Summer Research Program and (2) the Native American Summer Research Program (sponsored by University of Utah Department of Pediatrics). My laboratory provides an excellent interdisciplinary and culturally rich research environment for fostering the scientific development of the postdoctoral fellows, MD/PhD students and undergraduate students who wish to pursue scientific careers in metabolic and cardiovascular research. I currently serve as a principal mentor for Mrs. Kathryn Davis who obtained a predoctoral American Heart Association (AHA) fellowship, and who was a former trainee in my lab. I also serve as a principal mentor for Mr. Jordan Johnson who obtained a pre-doctoral fellowship from AHA, and who just graduated with a PhD degree in Nutrition. I am also a mentor for Dr. Jae Min Cho who just obtained AHA post-doctoral fellowship. I always encourage my trainees to apply for fellowships and co-author manuscripts. As an example, one of my native American trainee Ms. River Gunville co-authored a paper recently published in the journal Antioxidant and Redox Signaling in 2019 (PMID: 31088290). I continue to support my own trainees and trainees form my colleagues' labs for their fellowships applications and for providing career advice.

Ongoing projects

R01HL149870-01A1 Boudina (PI) 07/15/2020-05/31/2024
NIH/NHLBI
The Role of PRDM16 in Cardiac Development and Cardiomyopathy
This grant examines the role of PRDM16 in left ventricular non compaction both in humans and in mice.

R01DK128819-01 Mimche, Boudina, Henkemeyer (MPI) 04/01/2021-03/31/2026
NIH/NIDDK
Small molecule antagonists targeting EphB receptors for the treatment of nonalcoholic steatohepatitis (NASH)
The goal of this proposal is to optimize a small molecule antagonist of EphB receptor signaling and to test its efficacy in reducing fibrosis and metabolic alterations of NASH.
Role: Co-PI

Pending projects

1R01HL167866-01A1 Kai, Boudina, Morava-Kozicz (MPI) 12/01/2023 – 11/30/2028
NIH/NHLBI
Pathobiological mechanisms of cardiac disease in PGM1-CDG
This project examines the structural and the metabolic underpinnings of the cardiomyopathy phenotype of phosphoglucomutase I deficiency, an inborn error of metabolism.
Role: Co-PI
Received a score of 12%

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2023—Present	Tenured Professor, Department of Nutrition and Integrative Physiology, University of Utah
2017—2023	Tenured Associate Professor, Department of Nutrition and Integrative Physiology, University of Utah
2016—2017	Tenure-track Assistant Professor, Department of Nutrition and Integrative Physiology, University of Utah
2013—2016	Director, University of Utah Metabolic Phenotyping Core Facility
2011—2013	Interim Director, University of Utah Metabolic Phenotyping Core Facility
2010—2016	Tenure-track Assistant Professor, Division of Endocrinology, Diabetes and Metabolism, University of Utah
2008—2010	Research Assistant Professor, Division of Endocrinology, Diabetes and Metabolism, University of Utah
2002—2008	Postdoctoral Fellow, Division of Endocrinology, Diabetes and Metabolism, University of Utah (Mentor: E. Dale Abel)
1998—2002	Graduate Student Researcher, INSERM U 441, Athérosclérose and IFR 4, Université Bordeaux 2, Bordeaux, France

Honors

2017	New Investigator Award, College of Health, University of Utah
2016	College of Health top researcher honoree, University of Utah
2006—2008	Postdoctoral Fellowship Award, American Heart Association (AHA) – Western Affiliates
2004—2006	Postdoctoral Fellowship, Juvenile Diabetes Foundation (JDRF)
2003	Trainee Travel Award, American Heart Association Scientific Session, Orlando
2002	La Fondation pour la Recherche Médicale (FRM) Fellowship, France
2001	Groupe de Réflexion pour la Recherche Cardiovasculaire (GRRC) Fellowship, France
1997—2001	Algeria-France Exchange Scholarship, Ministry of Higher Education, Algeria

C. Contributions to Science

1. Mitochondria and Diabetic Cardiomyopathy

My interest in cardiac metabolism grew during my postdoctoral training with Dr. Dale Abel at the University of Utah. Prior to our work on mitochondrial energetics in the diabetic heart, little was known about how diabetes affected substrate metabolism and mitochondrial energetics. My work in this area has revolutionized the field and has led to discoveries by us and others demonstrating that the diabetic myocardium relies on fatty acid oxidation at the cost of reduced cardiac energetic efficiency caused in part by fatty acids-induced mitochondrial uncoupling. Furthermore, we were the first to establish a direct role for insulin signaling in the modulation of mitochondrial function in the heart.

a. **Boudina S,** Sena S, O'Neill BT, Tathireddy P, Young ME, Abel ED. Reduced mitochondrial oxidative capacity and increased mitochondrial uncoupling impair myocardial energetics in obesity. *Circulation*, *112*(17), 2686- 95, 2005. PMID: 16246967.

b. **Boudina S,** Sena S, Theobald H, Sheng X, Wright JJ, Hu XX, Aziz S, Johnson JI, Bugger H, Zaha VG, Abel ED. Mitochondrial energetics in the heart in obesity-related diabetes: direct evidence for increased uncoupled respiration and activation of uncoupling proteins. *Diabetes*, *56*(10), 2457-66, 2007. PMID: 17623815.

c. **Boudina S,** Bugger H, Sena S, O'Neill BT, Zaha VG, Ilkun O, Wright JJ, Mazumder PK, Palfreyman E, Tidwell TJ, Theobald H, Khalimonchuk O, Wayment B, Sheng X, Rodnick KJ, Centini R, Chen D, Litwin SE, Weimer BE, Abel ED. Contribution of impaired myocardial insulin signaling to mitochondrial dysfunction and oxidative stress in the heart. *Circulation*, *119*(9), 1272-83, 2009. PMCID: PMC2739097.

d. **Boudina S,** Han YH, Pei S, Tidwell TJ, Henrie B, Tuinei J, Olsen C, Sena S, Abel ED. UCP3 Regulates Cardiac Efficiency and Mitochondrial Coupling in High Fat-Fed Mice but Not in Leptin-Deficient Mice. *Diabetes*, 61(12), 3260-9, 2012. PMCID: PMC3501860.

2. Growth Factors Signaling, Autophagy and Mitophagy in the Heart

As a faculty member, I continued my investigation on how mitochondrial health is compromised in the diabetic heart. Our work was among the first to show that impaired cardiac autophagy in obese diabetic mice was mediated by over-activated mTORC1, which contributed to the accumulation of dysfunctional organelles. We also showed that hyperinsulinemia can further suppress autophagy and mitochondrial clearance when insulin receptors are absent in the heart, and additional stress on the lysosomes resulted in impaired cardiac function. Our work has shed light on why autophagy is reduced in the diabetic heart despite the presence of insulin resistance (which should have increased autophagy). Finally, with my colleague Dr. Dave Symons, we showed that enhancing autophagy through exercise improves cardiac function in old mice.

a. Jae Min Cho, Seul-Ki Park, Rajeshwary Ghosh, Kellsey Ly, Caroline Ramous, Lauren Thompson, Michele Hansen, Maria Sara de Lima Coutinho Mattera, Karla Maria Pires, Maroua Ferhat, Sohom Mookherjee, Kevin J Whitehead, Kandis Carter, Marcio Buffolo, **Sihem Boudina***, J David Symons*. Late-in-life treadmill training rejuvenates autophagy, protein aggregate clearance, and function in mouse hearts. Aging Cell, 20(10):e13467, 2021. PMCID: PMC8520717. * Co-corresponding authors.

b. Fullmer TM, Pei S, Zhu Y, Sloan C, Manzanares R, Henrie B, Pires KM, Cox JE, Abel ED, **Boudina S.** Insulin suppresses ischemic preconditioning-mediated cardioprotection through Akt-dependent mechanisms. *J Mol Cell Cardiol*, 64:20-9, 2013. PMCID: PMC3835741

c. Pires KM, Buffolo M, Schaaf C, David Symons J, Cox J, Abel ED, Selzman CH, **Boudina S**. Activation of IGF-1 receptors and Akt signaling by systemic hyperinsulinemia contributes to cardiac hypertrophy but does not regulate cardiac autophagy in obese diabetic mice. *J Mol Cell Cardiol*, 113:39-50, 2017. PMCID: PMC5689477

d. Pires KM, Torres NS, Buffolo M, Gunville R, Schaaf C, Davis K, Selzman CH, Gottlieb RA, **Boudina S**. Suppression of Cardiac Autophagy by Hyperinsulinemia in Insulin Receptor-Deficient Hearts Is Mediated by Insulin-Like Growth Factor Receptor Signaling. *Antioxid Redox Signal*, 20;31(6):444-457, 2019. PMCID: PMC6653796

3. Mitochondria, Adipose Tissue Function and Metabolic Health

Because of the associated visceral obesity and cardiovascular disease, we developed a research program looking at the role of mitochondria in adipose tissue dysfunction during obesity. We first showed that mitochondrial superoxide is an inducer of mitochondrial uncoupling *in vivo* and that the activation of this uncoupling drives diet-induced thermogenesis in mice. We challenged the previous notion that autophagy reduction in adipose tissue drives thermogenesis and conferred protection against diet-induced obesity in mice.

Thus, we demonstrated that autophagy is required for mitochondrial clearance post-differentiation and failure to initiate this process led to a massive accumulation of dysfunctional organelles that leaked reactive oxygen species. Despite no difference in weight gain, mice lacking autophagy in mature adipocytes develop systemic insulin resistance.

a. Pires KM, Ilkun O, Valente M, **Boudina S**. Treatment with a SOD mimetic reduces visceral adiposity, adipocyte death, and adipose tissue inflammation in high fat-fed mice. *Obesity (Silver Spring)*, 22(1):178-87, 2014. PMCID: PMC3758415.
b. Han YH, Buffolo M, Pires KM, Pei S, Scherer PE, **Boudina S**. Adipocyte-Specific Deletion of Manganese Superoxide Dismutase Protects From Diet-Induced Obesity Through Increased Mitochondrial Uncoupling and Biogenesis. *Diabetes*, 65(9):2639-51, 2016. PMCID: PMC5001177.
c. Cai J, Pires KM, Ferhat M, Chaurasia B, Buffolo MA, Smalling R, Sargsyan A, Atkinson DL, Summers SA, Graham TE, **Boudina S**. Autophagy Ablation in Adipocytes Induces Insulin Resistance and Reveals Roles for Lipid Peroxide and Nrf2 Signaling in Adipose-Liver Crosstalk. *Cell Rep*, 25(7):1708-1717, 2018. PMCID: PMC6802939.

4. Visceral Adipose Tissue Cellular Heterogeneity and Novel Regulators of Adipogenesis

Our group and others showed that visceral fat in mice contains pro and anti-adipogenic stromal cells and the abundance of the anti- adipogenic cells promoted adipose tissue hypertrophic growth and inflammation and led to exacerbation of systemic insulin resistance in response to high fat diet. Along the same line of research and using single cell RNA sequencing of viscreal fat in humans and mice, our group recently identified BMP Binding Endothelial Regulator (BMPER) as a positive regulator of adipogenesis *in vitro*.

a. Buffolo M, Pires KM, Ferhat M, Ilkun O, Makaju A, Achenbach A, Bowman F, Atkinson DL, Holland WL, Amri EZ, Chaurasia B, Franklin S, **Boudina S**. Identification of a Paracrine Signaling Mechanism Linking CD34high Progenitors to the Regulation of Visceral Fat Expansion and Remodeling. *Cell Rep*, 29(2):270-282, 2019. PMID: 31597091.
b. Garritson JD, Zhang J, Achenbach A, Ferhat M, Eich E, Stubben CJ, Martinez PL, Ibele AR, Hilgendorf KI, **Boudina S**. BMPER is a marker of adipose progenitors and adipocytes and a positive modulator of adipogenesis. *Commun Biol, Jun 13;6(1):638*. PMID: 37311809.

5. Understanding the Basis of Genetic Cardiomyopathies

My recent interest in science grew to a broader area of research that involves team-based science. Genetic cardiomyopathies are complex and require complementary expertise to study their development, progression and the influence of systemic alterations associated with these diseases. In a recent collaboration between the University of Utah and researchers from the Mayo Clinic, we developed a novel mouse to model N-linked congenital disorders of glycosylation (CDG) caused by model phosphoglucomutase 1 (PGM1) deficiency) in humans. This model has allowed us to study mechanisms underlying cardiomyopathy in CDG patients. We utilized this model to develop novel AAV-mediated gene therapy for this devastating disease.
Relevant to this application and in collaboration with Duke University scientist Dr. Landstrom, we were among the first labs to establish a role for PRDM16 in the heart (Abstract N 100, Circ Res Vol 123 Suppl 1). We demonstrated that PRDM16 is causal for non-compaction cardiomyopathy and dilated cardiomyopathy in humans and mice. We also showed recently that female patients that have PRDM16 deleted have higher incidence and severity of cardiomyopathy when compared to male patients with PRDM16 deleted. These findings were further confirmed in a mouse model of cardiac-specific Prdm16 deletion.

a. Balakrishnan B, Altassan R, Budhraja R, Liou W, Lupo A, Bryant S, Mankouski A, Radenkovic S, Preston GJ, Pandey A, **Boudina S**, Kozicz T, Morava-Kozicz E, Lai K. AAV-based gene therapy prevents and halts progression of dilated cardiomyopathy in a mouse model of phosphoglucomutase 1 deficiency (PGM1-CDG).

b. Ryan J. Kramer, Amir Nima Fatahian, Alice Chan, Jeffery Mortenson, Jennifer Osher, Bo Sun, Lauren E. Parker, Michael B. Rosamilia, Kyra B. Potter, Kaila Moore, Sage L. Atkins, Jill A. Rosenfeld, Alona Birjiniuk, Edward Jones, Taylor S. Howard, Jeffrey J. Kim, Daryl A. Scott, Seema Lalani, Omid MT. Rouzbehani, Samantha Kaplan, Marissa A. Hathaway, Jennifer L. Cohen, S. Yukiko Asaki, Hugo R. Martinez, **Sihem Boudina*** and Andrew P. Landstrom*. RDM16 deletion is associated with sex-

dependent cardiomyopathy and cardiac mortality: a translational, multi-institutional cohort study. *Circ Genom Precis Med, July 3:e003912, 2023.* PMID: 37395136. * Co-Corresponding Co-Senior authors.

c. Bo Sun, Omid MT Rouzbehani, Ryan Kramer, Rajeshwary Ghosh, Robin Perelli, Sage Atkins, Amir Fatahian, Kathryn Davis, Marta Szulik, Michael Goodman, Marissa Hathaway, Ellenor Chi, Tarah Word, Hari Tunuguntla, Susan Denfield, Xander Wehrens, Kevin Whitehead, Hala Abdelnasser, Junco Warren, Mingfu Wu, Sarah Franklin, **Sihem Boudina*** and Andrew Landstrom*. Nonsense variant PRDM16-Q187X causes impaired myocardial development and TGF-beta signaling resulting in noncompaction cardiomyopathy in humans and mice. *Circulation: Heart Failure*. Accepted. * Co-Corresponding Co-Senior Authors

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/sihem.boudina.1/bibliography/public/