BIOGRAPHICAL SKETCH

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NAME: Alexandre Alves da Silva

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

POSITION TITLE: Assistant 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)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Sao Paulo, Sao Paulo, Brazil	BS	12/1996	Biological Sciences
University of Sao Paulo, Sao Paulo, Brazil	Ph.D.	04/2001	Physiology
University of Mississippi Medical Center	Postdoc	06/2002	Physiology

A. Personal Statement

My research focuses on uncovering the molecular/cellular mechanisms of central nervous system (CNS) control of glucose homeostasis and cardiovascular function. Specifically, we are examining the powerful CNS-mediated beneficial effects of the leptin-melanocortin system pathway on the heart's ability to maintain good contractile function after myocardial infarction (MI) induced by left descending coronary artery ligation. We are also examining the powerful CNS-mediated antidiabetic actions of the leptin-melanocortin system that are capable of maintaining euglycemia even in the absence of normal beta-cell function. In addition, in collaboration with Dr. do Carmo we began a series of studies to unravel the impact of parental (maternal + paternal) obesity on developmental programming of cardiac dysfunction and cognitive disorders in the offspring of obese parents. I utilize *in vitro* and *ex vivo* techniques coupled with genetic mouse and rat models for *in vivo* long-term integrative physiological studies of many metabolic and cardiovascular parameters, including cardiac function, to carry out these studies.

Ongoing and recently completed projects that I would like to highlight:

Active

NIH/NHLBI 1R01HL163076 da Silva (MPI with Dr. do Carmo) 01/09/2023-12/31/2026
"Cardiac protective mechanisms of melanocortin system activation"
The major goal of this project is to examine the mechanisms by which activation of brain melanocortin 4 receptors protects the heart against progressive heart failure in myocardial infarction.
Role: PI (4.2 calendar)

NIH P20GM104357-Supplement (Hall, PI) 07/01/2021-04/30/2023
"Cardiorenal and Metabolic Diseases Research Center"
The goal is this project is also to generate key preliminary data for R01 application aiming at determining the consequences of parental obesity on offspring cognitive disorders and cardiometabolic dysfunction, and the potential mechanisms involved.
Role: Supplement Project PI (2.4 calendar)

NIH-NIDDK - R01 DK121411 (do Carmo, PI) 09/19/2019-07/31/2023
"Long-term consequences of parental obesity on development programming of cardiorenal diseases in offspring"
The major goal of this project is to investigate the effects of parental obesity on kidney dysfunction in offspring.
Role: Investigator (1.8 calendar)

NIH 1R01HL11085-01 Chen Y (PI) 02/01/2022-01/31/2026
"Mechanism of PD1 on cardiac inflammation resolution during heart failure development"
The major goal of this project is to investigate the role of PD1 on several aspects of inflammation development and resolution in a standard model of heart failure.

Role: Investigator (0.6 calendar)

NIH P20 GM104357 Hall JE (PI) 07/01/2018 – 04/30/2023
Cardiorenal and Metabolic Diseases Research Center
The long-term goal is to develop the Cardiorenal and Metabolic Diseases Research Center and provide infrastructure for multidisciplinary, diverse group of basic, clinical and population scientists working on the common synergistic theme of obesity, cardiorenal and metabolic diseases and to facilitate their collaborations.
Role: Sub-Core Leader, Imaging Core (1.2 calendar)

Completed

NIH P20GM104357 da Silva (PI) 07/01/2019-06/30/2022
Pilot Grants Program-Center of Biomedical Research Excellence (COBRE) “Obesity, Cardiorenal and Metabolic Disease Center”
Title: “CNS mechanisms of cardiac protection in heart failure.”
The major long-term goal is to generate key preliminary data for R01 application aiming to identify the mechanisms by which activation of the brain leptin-melanocortin system protects against heart failure.
Role: PI (1.2 calendar)

NIH/NHLBI PO1 HL519717 Hall JE (PI) 08/01/2014 - 05/31/2020
"Cardiovascular dynamics and their control"
The major long-term goal of this project is to investigate the central nervous system signaling pathways that mediate the antidiabetic actions of leptin.
Role: Investigator of Project I (1.2 calendar)

JP-15440 da Silva (PI) 02/01/15-10/31/2017
CAPES-Brazil
"Protective cardiovascular effects of leptin in type-1 diabetes"
Role: PI (4.8 calendar)

Citations (* corresponding author):

1. Omoto ACM, do Carmo JM, Nelson B, Aitken N, Dai X, Moak S, Flynn E, Wang Z, Mouton AJ, Li X, Hall JE, **da Silva AA**. Central nervous system actions of leptin improve cardiac function after ischemia-reperfusion: role of sympathetic innervation and sex differences. *J Am Heart Assoc* 11(21):e027081, 2022.
2. Gava FN, **da Silva AA***, Dai X, Harmancey R, Ashraf S, Omoto ACM, Salgado MC, Moak SP, Li X, Hall JE, do Carmo JM. Restoration of cardiac function after myocardial infarction by long-term activation of the CNS leptin-melanocortin system. *JACC: Basic Transl Sci* 6(1):55-70, 2021.
3. do Carmo JM, Omoto AC, Dai X, Moak SP, Li X, Wang Z, Mouton A, Hall JE, **da Silva AA**. Sex differences in the impact of parental obesity on offspring cardiac SIRT3 expression, mitochondrial efficiency and diastolic function early in life. *Am J Physiol Heart Circ Physiol* 321(3):H485-H495, 2021.
4. **da Silva AA***, Hall JE, Dai X, Wang Z, Salgado MC, do Carmo JM. Chronic antidiabetic actions of leptin: Evidence from parabiosis studies for a CNS-derived circulating antidiabetic factor. *Diabetes 70(10):2264-74, 2021.*
5. **da Silva AA***, Pinkerton MA, Spradley FT, Palei AC, Hall JE, do Carmo JM. Chronic CNS-mediated cardiometabolic actions of leptin: potential role of sex differences. *Am J Physiol Regul Integr Comp Physiol* 320(2):R173-R181, 2021.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2001-2006	Instructor, Physiology Department, University of Mississippi Medical Center, Jackson, MS.
2006-2014	Assistant Professor, Physiology Department, Univ. of Mississippi Medical Center
2015-2017	Professor, Physiology Dept., Centro Universitario Barao de Maua, Ribeirao Preto – Brazil
2016-2017	Professor, Physiology Dept., Univ. Estadual de Minas Gerais, Passos – Brazil
2018-Present	Assistant Professor, Physiology Department, University of Mississippi Medical Center, Jackson, MS.

Honors, Other Experience and Professional Memberships

2023	Ad-Hoc grant reviewer, Swiss National Science Foundation
2022	Grant reviewer, NIH Therapeutic Develop and Pre-Clinical Studies (TDPS) study section
2022	Grant reviewer, American Heart Association – Vascular Biology study section
2021-present	Special Emphasis Guest Editor, Frontiers Endocrinology (Lausanne)
2020	Special Emphasis Guest Editor, Frontiers in Physiology
2019-present	Grant reviewer, UMMC – Mississippi Center for Clinical and Translational Research (MCCTR)
2019-present	Grant reviewer, UMMC – Center for Biomedical Research Excellence (COBRE)
2018	Fujifilm-VisualSonics Vevo® Travel Award in Cardiac Imaging. Council for High Blood Pressure/Kidney Research, American Heart Association
2017	Marcos Augusto Award, Centro Universitario Barao de Maua, Ribeirao Preto, SP – Brazil
2016-2017	Member, International Committee Board, Centro Universitario Barao de Maua, Ribeirao Preto, SP – Brazil
2016-2017	Medical Physiology Course Coordinator, Universidade Estadual de Minas Gerais, Passos, MG – Brazil.
2015-2017	Vice-Chair, Research Nucleus, Centro Universitario Barao de Maua, Ribeirao Preto, SP – Brazil
2015-2017	Medical Physiology Course Coordinator, Centro Universitario Barao de Maua, Ribeirao Preto, SP – Brazil
2015-2017	Member, Medical School Faculty Board, Centro Universitario Barao de Maua, Ribeirao Preto, SP – Brazil
2015-2017	Member, Faculty Search Committee, Centro Universitario Barao de Maua, Ribeirao Preto, SP – Brazil
2015-2017	Abstract reviewer and examiner, Medical School Research Day, Centro Universitario Barao de Maua, Ribeirao Preto, SP – Brazil
2014	Abstract reviewer, International Society of Hypertension (ISH)
2013-2014	Grant reviewer, UMMC-IRSP
2012-present	Fellow of the American Heart Association
2012-Present	Member and Associate Editor, BMC-Physiology
2011-2017	Member, Editorial Board of Hypertension
2009-2014	Study Section Grant Reviewer for the American Heart Association
2007	Excellence in Research Award Bronze Level – University of Mississippi Medical Center
2007-present	Member, Inter-American Society of Hypertension
2005	New Investigator Award from CV Therapeutics. American Heart Association - Council for High Blood Pressure Research
2005	Research Recognition Award / Cardiovascular Section of American Physiological Society, APS
2005-Present	Member, American Heart Association. Council for High Blood Pressure/Kidney Research
2003	American Heart Association Postdoctoral Fellowship (0325353B)
2003-Present	Member, American Physiological Society
2002	Young investigator Travel Award of International Society of Hypertension, ISH
1999	MERCK Young Investigator Award/Latin America – Council for High Blood Pressure. Research, American Heart Association
1998	Young investigator Travel Award of International Society of Hypertension, ISH
1997- 2001	Predoctoral Fellowship (FAPESP), Nephrology Division, University of Sao Paulo, Sao Paulo, Brazil.
1995-1996	Undergraduate (Scientific Initiation - CNPq) Fellowship, Dept. of Microbiology, University of Sao Paulo, Sao Paulo, Brazil.
1993-1995	Undergraduate (Scientific Initiation - CNPq) Fellowship, Dept. of Pharmacology, University of Sao Paulo, Sao Paulo, Brazil.

Scientific review service:

Ad hoc reviewer for over 42 peer-reviewed scientific journals: JACC-Heart Failure, Hypertension; Diabetes; Circulation Research; American Journal of Physiology – RICP; PlosOne; Peptides; American Journal of Hypertension; Journal of Molecular Endocrinology; Brain Research Bulletin; European Journal of Internal Medicine; Gender Medicine; Journal of Pharmacological and Toxicological Methods; Experimental Biology and Medicine; Future Medicine; Diabetes &

Metabolic Syndrome: Clinical Research & Reviews; Acta Diabetologica; several Frontiers Journals, etc.

C. Contributions to Science

(Selected from over 86 publications and 8 book chapters)
https://www.ncbi.nlm.nih.gov/myncbi/alexandre.silva.1/bibliography/public/

Mission Statement: My laboratory aims at uncovering the cellular/molecular mechanisms by which activation of the brain leptin-melanocortin system improves metabolic and cardiac function in situations of severe stress (i.e., type-1 diabetes and heart failure) with the ultimate goal of developing better strategies to treat cardiometabolic diseases. This is achieved by generating and sharing novel critical data, animal models and new techniques.

Role of the leptin-brain MC4R axis in ameliorating cardiovascular function during metabolic stress:

We demonstrated that activation of the brain leptin-MC4R axis restores cardiovascular function (e.g., heart rate, baroreflex sensitivity, intrinsic heart rate control, and blood pressure) in insulin-deficient diabetic animals. Even more surprinsing, we recently observed that leptin markedly improves heart function in non-diabetic and insulin-deficient diabetic rats with heart failure induced by ligation of the left anterior descending coronary artery. These findings highlight a novel mechanism for an important new effect of leptin mediatied by its action on the CNS.

1. do Carmo JM, Hall JE, **da Silva AA**. Chronic central leptin infusion restores cardiac sympathetic-vagal balance and baroreflex activity in diabetic rats. *Am J Physiol Heart Circ Physiol* 295: H1974-81, 2008. PMID: 1879083.

2. **da Silva AA***, do Carmo JM, Wang Z, Hall JE. The brain melanocortin system, sympathetic control and obesity hypertension. *Physiology (Bethesda)* 29:196-202, 2014. (* corresponding author)

3. **da Silva AA***, Gava FN, Lataro, RM, Silva CMA, Salgado HC. Chronic central leptin infusion improves cardiac function in STZ-diabetic rats with heart failure. FASEB J 31:853, 2017.

4. Gava FN, **da Silva AA***, Dai X, Harmancey R, Ashraf S, Omoto ACM, Salgado MC, Moak SP, Hall JE, do Carmo JM. Restoration of cardiac function after myocardial infarction by chronic activation of the CNS leptin-melanocortin system. *JACC Basic Transl Sci* 6(1):55-70, 2021. (* corresponding author)

5. Omoto ACM, do Carmo JM, Nelson B, Aitken N, Dai X, Moak S, Flynn E, Wang Z, Mouton AJ, Li X, Hall JE, **da Silva AA**. Central nervous system actions of leptin improve cardiac function after ischemia-reperfusion: role of sympathetic innervation and sex differences. *J Am Heart Assoc* 11(21):e027081, 2022

Impact of parental obesity on developmental origins of obesity and cardiometabolic dysfunction; and impact of obesity on the brain melanocortin system.

We recently observed that offspring from obese parents develop signs of diastolic dysfunction starting very early in life (i.e., 3 weeks of age). In preliminary studies we also observed that these ealy signs of diastolic dysfunction worsen as the offspring get older. In addition, we found that obesity, which is commonly associated with resistance to many of the metabolic effects of leptin, does not induce resistance to the metabolic and cardiovascualr actions of activating the bain melanocortin system.

1. do Carmo JM, Omoto AC, Dai X, Moak SP, Li X, Wang Z, Mouton A, Hall JE, **da Silva AA**. Sex differences in the impact of parental obesity on offspring cardiac SIRT3 expression, mitochondrial efficiency and diastolic function early in life. *Am J Physiol Heart Circ Physiol* 321(3):H485-H495, 2021.

2. **da Silva AA**, Gava FN, Omoto ACM, Moak SP, Dai X, Hall JE, do Carmo JM. Intergenerational inheritance of obesity-induced diastolic dysfunction with preserved ejection fraction. *Hypertension* 74(suppl 1):A090, 2019 (oral presentation at the AHA/Council for High Blood Pressure)

3. da Silva AA*, Kuo JJ, Tallam, Liu J, Hall JE. Chronic cardiovascular and dietary responses to activation of melanocortin 3/4 receptors in a model of visceral adiposity. J *Hypertens* 22:S202, 2004 (* corresponding author)

Role of the leptin-brain MC4R axis in regulating whole body glucose homeostasis:

We demonstrated that activation of the leptin-MC4R axis has powerfull antidiabetic actions that are capable of sustaining euglycemia even in animals that lack normal insulin production due to failure of pancreatic beta cells. We also discovered that contrary to pre-existing concensus that the CNS actions of leptin and MC4R activation of peripheral glucose regularion were mediated via the autonomic nervous system, the antidiabetic effects of the leptin-MC4R axis are independent of changes in autonomic activity or pituitary function.

1. **da Silva AA***, Spradley FT, Granger JP, Hall JE, do Carmo JM. Brain-mediated antidiabetic, anorexic, and cardiovascular actions of leptin require melanocortin-4 receptor signaling. *J Neurophysiol* 113: 2786-91, 2015. PMID: 25717164. (* Corresponding author)

2. **da Silva AA***, Freeman JN, Hall JE, do Carmo JM. Control of appetite, blood glucose ad blood pressure during melanocortin-4 activation in normoglycemic and diabetic NPY deficient mice. *Am J Physiol Integr Comp Physiol* 314: R533-R539, 2017. PMID: 29351428. (* Corresponding author)

3. **da Silva AA***, Hall JE, Moak SP, Browning J, Houghton HJ, Micheloni GC, do Carmo JM. Role of autonomic nervous system in chronic CNS-mediated antidiabetic action of leptin. *Am J Physiol Endocrinol Metab* 312:E420-E428, 2016. PIMD: 27923809 (* Corresponding author)

4. **da Silva AA***, Hall JE, do Carmo JM. Leptin reverses hyperglycemia and hyperphagia in insulin deficient diabetic rats by pituitary-independent central nervous system actions. *PLoS One* 30:12:e0184805, 2017. PMID: 29190687. (* Corresponding author)

5. **da Silva AA***, do Carmo JM, Hall JE. CNS Regulation of Glucose Homeostasis: Role of the Leptin-Melanocortin System. *Curr Diab Rep* 20(7):29, 2020. PMID: 32451760. (* Corresponding author)

Role of the central nervous system melanocortin system in long-term control of blood pressure and in mediating leptin's dietary and metabolic effects:

We demonstrated that the brain melanocortin system plays an important role in long-term regulation of blood pressure and heart rate. For instance, blockade of MC4R markedly increases food intake leading to rapid weight gain and morbid obesity while causing bradycardia and small reductions in blood pressure. In addition, we demonstrated that the long-term effects of leptin to induce hypertension, anorexia and weight loss are completely blocked by pharmacological blockade or genetic disruption of MC4R.

1. **da Silva AA***, Kuo JJ, Hall JE. Role of hypothalamic melanocortin 3/4-receptors in mediating chronic cardiovascular, renal, and metabolic actions of leptin. *Hypertension* 43:1312-7, 2004 (* Corresponding author)

2. **da Silva AA***, do Carmo JM, Kanyicska B, Dubinion J, Brandon E, Hall JE. Endogenous melanocortin system activity contributes to the elevated arterial pressure in spontaneously hypertensive rats. *Hypertension* 51(4):884-90, 2008. (* Corresponding author)

3. do Carmo JM, **da Silva AA**, Rushing JS, Hall JE. Activation of the central melanocortin system contributes to the increased arterial pressure in obese Zucker rats. *Am J Physiol Regul Integr Comp Physiol* 302(5):R561-7, 2012.

4. **da Silva AA***, do Carmo JM, Wang Z, Hall JE. Melanocortin-4 receptors and sympathetic nervous system activation in hypertension. *Curr Hypertens Rep* 21(6):46, 2019. (* Corresponding author)

5. do Carmo JM, **da Silva AA**, Gava FN, Moak SP, Dai X, Hall JE. Impact of leptin deficiency compared with neuronal-specific leptin receptor deletion on cardiometabolic regulation. *Am J Physiol Regul Integr Comp Physiol* 317(4):R552-62, 2019. PMID: 31411897

6. **da Silva AA***, do Carmo JM, Li X, Wang Z, Mouton AJ, Hall JE. Role of hyperinsulinemia and insulin resistance in hypertension: metabolic syndrome revisited. *Can J Cardio* 36(5):671-82, 2020. PMID: 32389340. (* Corresponding author)