

BIOGRAPHICAL SKETCH

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NAME: Marco A. P. Brotto

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

POSITION TITLE: Thompson Endowed Professor and Director of the Muscle Biology Research Group

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
National Course of Medicine, Vitoria, Brazil	Chemistry Technologist	12/1979	Chemistry
Federal University of Ceara, Fortaleza, Brazil	BSN	12/1983	Nursing & Obstetrics
Federal University of Ceara-Brazil	MS	12/1991	Pharmacology
Medical College of Georgia-USA	Fellowship	1992-96	Muscle Biophysics & Electrophysiology
Trinity College (Oxford), England	Ph.D.	05/1999	Physiology & Biophysics
Case Western Reserve University	Postdoc	2000-2001	Muscle Biochemistry

A. Personal Statement: I started my professional career as a clinician, and trained as a muscle physiologist/muscle cell biologist at the Medical College of Georgia. My research has been funded by the NIH for almost two decades and has focused on the role of EC coupling (ECC) and novel ECC genes on sarcopenia and muscle fatigue, and more recently on bone-muscle crosstalk with an emphasis on osteocyte signaling to muscle. On the clinical-translational front, my studies have led to the identification of a novel serum biomarker, skeletal muscle specific Troponin T for muscle weakness/risk of falls and balance impairment in older adults, I have served as the President of the Missouri American Physiological Society, Council Member for the AHA Midwest and now the Southwest Research Committee and I am a permanent reviewer for the NIH Skeletal Muscle Biology and Exercise (SMEP) study section. The AHA, the Industry and several foundations and two Endowments have also funded my research. Successful long-term collaborations and very successful mentoring of students and postdocs that have advanced in their careers and are now collaborators have distinguished my career. UTA has given me expanded resources, the ability to further recruit for my lab and to establish a new and larger Bone-Muscle research group. As an example, we have developed a new Lipidomics method with support the UTA Shimadzu Research Institute and the Shimadzu Analytical Center to be directly applied to our research and beyond. I am already successfully collaborating with Dr. Christopher Cardozo as shown by our joint preliminary data and recent presentations, abstracts. I will devote my expertise and vast resources to insure that all the goals of this R01 are completed.

B. Positions and Honors**Positions and Employment**

2000-2003 Instructor of Physiology and Biophysics, School of Medicine, Dept. of Physiology and Biophysics, Case Western Reserve University, Cleveland - Ohio, USA

2003-2007 Assistant Professor, Dept. of Physiology and Biophysics, Robert Wood Johnson Medical School

08/2007- Associate Professor of Nursing and Medicine, University of Missouri at Kansas City (UMKC), Kansas City, Missouri, USA.

02/2009- Director, UMKC Muscle Biology Research Group-MUBIG.

02/2010 Director, FTC Biomedicine Center, Salvador, Brazil
09/2011 Tenured Professor of Nursing and Medicine and Director of MUBIG
09/2012-08/2015 Dale & Dorothy Thompson Missouri Endowed Professor of Nursing Research
And Professor of Nursing, Medicine, and Pharmacology; Director of MUBIG, UMKC.
08/2015 Hazel Jay Endowed Professor, Director of the Bone-Muscle Collaborative Sciences,
Director of the PHD in Nursing Program, College of Nursing & Health Innovation,
University of Texas at Arlington.

Frequent Reviewer

Permanent Reviewer National Institutes of Health Skeletal Muscle and Exercise Physiology Study Section since 2014

Ad-Hoc Reviewer for the National Institutes of Health since 2009

Regular Reviewer for the American Federation of Aging Research since 2010

Regular Reviewer for the American Heart Association since 2007

Reviewer for the Canada Foundation for Innovation since 2013

Reviewer for the Austrian Science Fund since 2014

Reviewer for the Sweden Ministry of Education and Research since 2014

Regular Reviewer for University of Missouri Research Board Grants since 2010

Reviewer Italian Telethon Foundation since 2015

Editorial Board Member:

Journal of Pharmacology and Experimental Therapeutics (JPET)

Journal of Bone and Mineral Research (JBMR)

Journal of Open Letters in Cell Biology

Journal of Open Letters in Biology

Dialogos em Ciencia (Brazil)

Journal Reviewer:

American Journal of Physiology: Cell

American Journal of Physiology: Heart, Lung and Blood

American Journal of Physiology: Integrative and Regulatory

Biochemical Pharmacology (France)

Brain Research Bulletin

Cell Calcium

Journal of Applied Physiology

Journal of Biological Chemistry

Journal of Gerontology

Journal of Pharmacology and Experimental Therapeutics

Journal of Physiology (London)

Muscle & Nerve

Physiological Genomics

Rejuvenation Research

Biotechnology Progress

Recent Patents on Biotechnology

Honors

Sept 2015 Appointed as the Hazel Jay Endowed Chair and Director of Bone-Muscle Director (UTA)

Sept 2012 Appointed as the Dale & Dorothy Thompson Missouri Endowed Professor

Sept 2012 Invited Speaker to the 1st International Meeting on Calcium Regulation and Muscle Diseases,
University of Barcelona, Spain, 09/15-08/19, 2012

2012 Guest Editor of Special Edition on Muscle Diseases in Recent Patents on Biotechnology

2011 Promoted to Full Professor with Tenure

2010 UMKC School of Nursing Outstanding Scholar Award

2010 International Visiting Scholar, Brazilian Council of Research and University of Sciences and
Technology, Salvador, Bahia, Brazil

2010 Director of the Biomedicine Center, University of Sciences and Technology, Salvador, Bahia,
Brazil

2009- Director of the UMKC-Muscle Biology Research Group-MUBIG
2009 Chair and Organizer, APS, Muscle Biology Symposium, Experimental Biology 2009, New Orleans, LA.

C. Contribution to Science

Summary of Key Contributions:

We have been studying skeletal muscle aging and fatigue for many years, always with a focus on the Excitation-Contraction Coupling process, particularly new modulatory genes of the EC coupling process, such as MG29, MIP/MTMR14, MG53, MG33, etc. Our lab has pioneered in mammalian skeletal muscles, the confocal methodology for the monitoring of store-operated calcium entry (SOCE) in sealed T-tubules of single skinned muscle fibers and used this approach to demonstrate for the first time along with muscle contractility studies that SOCE played a role in muscle fatigue. Later, we demonstrated that muscle aging was associated with segregated intracellular Ca^{2+} release, compromised in aged skeletal muscle fibers, and contributes to sarcopenia. More recently, our studies have led to paradigm shifting ideas about how bone and muscles crosstalk to each other biochemically and influence each other optimal function through secreted myokines and "osteokines". On the clinical-translational front, we were the first group to propose the identification of serum biomarkers for the risk of falls and exercise efficiency in older adults and have linked serum elevations in skeletal muscle specific Troponin with the risk of falls and impaired balance in older adults. Our major goal is to advance the science of skeletal muscle physiology and contribute to knowledge that will lead to new treatments for muscle and bone diseases.

1. Earlier in my career when a Research Fellow at the Medical College of Georgia, I made some significant contributions to cardiac physiology in the field of heart development and E-C coupling.
 - a. Brotto, M.; Fogaca, R.T.H.; Creazzo, T.L.; Godt, R.E.; & Nosek, T.M. The effect of 2,3- Butanedione 2-monoxime (BDM) on Ventricular Trabeculae from the Avian Heart. *Journal of Muscle Research and Cell Motility*. 16:1-10, 1995
 - b. Brotto, M. and Creazzo, T.L, The Excitation-Contraction coupling in the Embryonic Chick Heart. *American Journal of Physiology*: 270 (Heart Circ. Physiol. 39):H518-H525, 1996.
 - c. Creazzo, T.L, Burch, J.L., and Brotto, M. The Excitation-Contraction Coupling in Cardiac Dysmorphogenesis. In: *The Developing Heart*, Chapter 23: pp. 313-324. Lippincott-Raven Publishers, Philadelphia/New York, 1997.
 - d. Nosek, T.M., Fogaca, R.T.H., Brotto, M., Hatcher, C.G., and Godt, R.E. Effect of Cardiac Neural Crest Ablation on Contractile Force and Calcium Uptake and release in Chick Heart. *American Journal of Physiology* 273:H1464-H1471, 1997.
2. I perceived a relative lack of knowledge of the fate of muscle fatigued ex vivo under hypoxia and attempted to contribute to this field of research (11-12) by demonstrating that the TnT underwent significant degradation under fatigue-hypoxia, almost mimicking the situation of a heart attack, when Troponins are degraded and can be detected in the serum. Later, we were able to demonstrate that skeletal muscle Troponin when expressed in the heart was more sensitive to acidity (13). I was also part of a highly translational study led by Drs. J-P Jin and Thomas Nosek. We found that it was a truncation by Glu180 nonsense mutation that resulted in the complete loss of the slow skeletal muscle Troponin T in a Lethal Nematode Myopathy among the Amish population, and ensuing phenotypic changes that occur in the babies that inherit this disease (14). I am very proud of having participated of these studies since they led to genetic tests to this lethal disease. Genetic counseling and a test is now available because we conducted these studies back in 2003.
 - a. Brotto, M., Nosek, C.M., Brotto, L.S., van Leyen, S.A., and Nosek, T.M. Hypoxia and fatigue- induced modification of function and proteins in intact and skinned murine diaphragm muscle. *Pflugers Arch* 440:727-734, 2000.
 - b. Brotto, M., van Leyen, S.A., Brotto, L.S., Nosek, C.M., Jin, J.-P., and Nosek, T.M. Hypoxia/Fatigue- Induced Degradation of Troponin I and Troponin C: New Insights into Physiologic Muscle Fatigue, *Pflugers Arch*. 442:738-44, 2001.
 - c. Thomas M. Nosek, Brotto, M., Jin, J-P, TroponinT isoforms alters the tolerance transgenic mouse cardiac muscle to acidosis, *Archives of Biochem. & Biophysics*, 15;430(2):178-84, 2004.
 - d. Jin, J.-P., Brotto, M., Hossain, M.M., Huang, Q.-Q., Brotto, L.S., Nosek, T.M., Morton, D.H., and

Crawford, T.O. Truncation by Glu¹⁸⁰ Nonsense Mutation Results in Complete Loss of Slow Skeletal Muscle Troponin T in a Lethal Nemaline Myopathy. *Journal of Biological Chemistry (JBC)*, Jul 11;278(28):26159-65, 2003

3. In addition to these contributions described above, with four other laboratories, including the Weisleder Lab, my lab has played a major part in helping define the roles of new genes in the fundamental process of Excitation-contraction coupling (ECC). In the case of Mg29, Mg33, Mg53, and MIP/MTMR14, these genes were previously unknown and we discovered and were the first to show their functions.
 - a. Brotto, M.*, Nagaraj, R.Y., Brotto, L.S., Nosek, C.M., Takeshima, H., Nosek, T.M., and Ma, J. Defective maintenance of intracellular Ca²⁺ homeostasis is linked to increased muscle fatigability in the MG29 null mice, *Cell Research*, 14(5):373-8, 2004
 - b. Zhao X, Yoshida M, Brotto L, Takeshima H, Weisleder N, Hirata Y, Nosek TM, Ma J, Brotto M. Enhanced resistance to fatigue and altered calcium handling properties of sarcalumenin knockout mice. *Physiol Genomics*. 23(1):72-8, 2005
 - c. Brotto, M.*, Noah Weisleder*, Shinji Komazaki, Zui Pan, Thomas Nosek³, Jerome Parness, Hiroshi Takeshima, Jianjie Ma. Muscle Aging is associated with compromised Ca²⁺ spark signaling and segregated intracellular Ca²⁺ release. *Journal of Cell Biology*, 28;174(5):639-45, 2007
 - d. Brotto M.*, Jinhua Shen*, Wen-Mei Yu*, Caiying Guo, Christopher Stoddard, Thomas M. Nosek, and Cheng-Kui Qu. Deficiency of MIP/MTMR14 phosphatase induces a muscle disorder by disrupting Ca²⁺ homeostasis, *Nature Cell Biology*, Jun;11(6): 769-76, 2009

4. Then, in 2007 with my lab's relocation to the University of Missouri-Kansas City (UMKC), I started interacting with the Bone Biology Group at UMKC (Drs. Bonewald, Johnson, and Dallas), one of the most accomplished groups of bone biologists in the world. From our interactions and a new initiative at NIAMS, in 2009, we were awarded a Grand Opportunities (GO) Grant to study for the first time the Biochemical Crosstalk between bone and muscle cells. This project evolved into our Project Program Grant supported by the National Institutes of Aging. Since then, we have made some important contributions to this field as evidenced by our publications, invited reviews, new invited not previously existing book chapters, webinars, and the ASBMR DVD.
 - a. K Jähn, N Lara-Castillo, L Brotto, CL Mo, ML Johnson, Brotto M, Bonewald. Skeletal muscle secreted factors prevent glucocorticoid-induced osteocyte apoptosis through activation of β -catenin. *Eur Cell Mater*. 2012 Sep 12;24:197-210
 - b. Jian Huang, Sandra Romero-Suarez, Nuria Lara, Chenglin Mo, Simon Kaja, Leticia Brotto, Sarah L. Dallas, Mark L. Johnson, Katharina Jähn, Lynda F. Bonewald, and Marco Brotto. Crosstalk between MLO-Y4 osteocytes and C2C12 muscle cells is mediated by the Wnt/ β -catenin pathway *JBMR plus* 2017 <http://onlinelibrary.wiley.com/doi/10.1002/jbm4.10015/full>
 - c. Zhiying Wang; Liangqiao Bian; Chenglin Mo; Maciej Kukula; Kevin A Schug; Marco Brotto. "Targeted quantification of lipid mediators in skeletal muscles using restricted access media-based trap-and-elute liquid chromatography-mass spectrometry" *Analytica Chimica Acta*: 2017 <https://doi.org/10.1016/j.aca.2017.07.024>
 - d. Mo C, Zhao R, Vallejo J, Igwe O, Bonewald L, Wetmore L, Brotto M. Prostaglandin E(2) promotes proliferation of skeletal muscle myoblasts via EP4 receptor activation. *Cell Cycle*. 2015; 14(10):1507-16. [PMC4615122](http://dx.doi.org/10.1080/15388619.2015.1061512)

5. I started my career as a clinician and I have never lost this connection, in fact, my research efforts in the last few years also demonstrate the translational nature of our studies, and the importance of connecting applied, basic, and clinical research, including our studies in search for biomarkers for the muscle weakness, balance, and risk of falls in older adults.
 - a. King GW, Abreu EL, Cheng AL, Chertoff KK, Brotto L, Kelly PJ, Brotto M. A multimodal assessment of balance in elderly and young adults. *Oncotarget*. 2016 Feb 26. doi: 10.18632/oncotarget.7758. [Epub ahead of print]

- b. Chou WC, Cheng AL, Brotto M, Chuang CY. Visual gene-network analysis reveals the cancer gene co-expression in human endometrial cancer. *BMC Genomics*. 2014 Apr 23;15:300. doi: 10.1186/1471-2164-15-300. PubMed PMID: 24758163; PubMed Central PMCID: PMC4234489.
- c. Abreu EL, Cheng AL, Kelly PJ, Chertoff K, Brotto L, Griffith E, Kinder G, Uridge T, Zachow R, Brotto M. Skeletal muscle troponin as a novel biomarker to enhance assessment of the impact of strength training on fall prevention in the older adults. *Nurs Res*. 2014 Mar-Apr;63(2):75-82. doi: 10.1097/NNR.000000000000018. PubMed PMID: 24589644.
- d. Ball S, Gammon R, Kelly PJ, Cheng AL, Chertoff K, Kaume L, Abreu EL, Brotto M. Outcomes of Stay Strong, Stay Healthy in community settings. *J Aging Health*. 2013 Dec;25(8):1388-97. doi: 10.1177/0898264313507318. Epub 2013 Oct 22. PubMed PMID: 24150062.

List of Published Work in MyBibliography: Complete List of Published Work in MyBibliography: <https://www.ncbi.nlm.nih.gov/pubmed/?term=brotto+m>

D. Research Support

Ongoing Research Support

R01 HL127071 Fadel, Paul (PI) 04/01/16-03/31/20
 Targeting Sympathetic Overactivity in CKD Patients: Mechanisms & Novel Therapies
 The goal of this study is to determine the specific mechanisms leading to hyperactivity of the sympathetic system in CKD patients. Due to the participation of the musculoskeletal system and potential new biomarkers, I am contributing as a Co-Investigator as well as my laboratory.
 Role: Co-PI

P01 AG039355 Bonewald, Brotto, Dallas, Johnson (Co-PIs) 05/01/13-04/30/18
 Osteocyte Regulation of Bone/Muscle with Age
 The goal of this program project grant is to investigate the biochemical signaling mechanisms regulating specific factors that influence the health and function of each tissue vice-versa during aging using cell and via the Wnt/ β -catenin pathway during aging.
 Role: Director of Project 2 and Co-Director of the Core B (Phenotyping Core with Dr. Sarah Dallas)

R01 DK93821 Haldar, (PI) 12/15/13-11/30/18
 Role of KFL15 in skeletal muscle metabolism
 The goal of this study is to determine the specific roles of KFL15 in skeletal muscle via the establishment of global knockout and myogenin-CRE specific lines.
 Role: Co-PI

R56 AG049083 Brotto, Weisleder (PI) 09/15/15-09/14/17
 Mitsugumin 29 function in regulation of Store-Operated Calcium Entry during Muscle Aging
 The goal of this study is to determine the specific roles of MG29 in muscle aging. The specific role of the R56 funding mechanism is to fund highly promising grant proposals with gap funding to obtain additional preliminary data in preparation for resubmission of the R01 proposal
 Role: Co-PI

Completed Research Support

R01AR-0027581-A1 Ueki, Yasu (PIs) 07/01/10-06/30/15
 Molecular Mechanisms of Cherubism
 The goals of this proposal were to understand the pathogenesis of human known mutations that are causative for cherubism in humans by expressing them in cells and in mouse models of this human disease.
 Role: Co-Investigator (Provided expertise on intracellular calcium homeostasis, led to a publication in JBMR)