BIOGRAPHICAL SKETCH

NAME: Lorena Machado Amaral, Ph.D.

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

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 Data	FIELD OF STUDY
Federal University of Juiz de Fora, MG, Brazil	Pharm.D.	12/2008	Pharmacology/ Biochemistry
Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, SP, Brazil	M.S.	11/2010	Sciences Pharmacology
Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, SP, Brazil	Ph.D.	12/2012	Pharmacology
University of Mississippi Medical Center	Postdoctoral Fellowship	04/2013-08/2016	Pharmacology/ Toxicology
University of Mississippi Medical Center	Scientist	09/2016-09/2017	Pharmacology/ Toxicology
University of Mississippi Medical Center	Instructor	10/2017-05/2019	Pharmacology/ Toxicology
University of Mississippi Medical Center	Assistant Professor	05/2019-Present	Pharmacology/ Toxicology

A. Personal Statement

As a new Assistant Professor at University of Mississippi Medical Center (UMMC), I am currently launching my independent clinical and basic research program in the pathogenesis and treatment of the pregnancy-specific hypertensive disorder, preeclampsia (PE). There is no known cure and the only effective treatment is delivery of the fetus and placenta. PE affects 5-7% of all pregnancies in the U.S., and is associated with reduced placental perfusion and fetal weight, increased inflammation, antiangiogenic factor sFlt-1, vascular endothelial dysfunction and hypertension. Despite being a leading cause of maternal death and perinatal morbidity, the mechanisms responsible for the pathogenesis of PE still are unclear. In my recent studies, my lab has shown that PE is a progesterone deficient state that is associated with an imbalance between TH1/TH2 cells, natural killer *(*NK) cells, and inflammatory cytokines which in turn lead to endothelial dysfunction, uterine growth restriction and high blood pressure. In contrast, healthy normal pregnancy (NP) is associated with elevations in progesterone and TH2/uterine NK cells favoring immunotolerance of the fetus. Activated lymphocytes during normal pregnancy express progesterone receptors, which stimulate a protein called Progesterone Induced Blocking Factor (PIBF). PIBF increases during NP and has been shown to bind IL-4 receptor and stimulate IL-4/TH2 cells, both of which are reduced during PE. The role of PIBF in PE still unknown, however I believe that levels of PIBF are low in PE patients that exhibit lower circulating progesterone compared to normal pregnant patients. Over the past few years, I have mentored graduate students and served as PI or Co-investigator on a number of clinical projects that have investigated preeclampsia and gestational hypertension. As a Women's Heath researcher, with the experience in translational studies I have worked with physicians and scientist on various research studies, which resulted in several publications as documented below.

- Jesse N, Cottrell , Alexis Witcher , Kyleigh M Comley , Mark W Cunningham Jr ,Tarek Ibrahim , Denise Cornelius , Babbette D LaMarca , **Lorena M Amaral.** Progesterone induced blocking factor improves blood pressure, inflammation and pup weight in response to reduced uterine perfusion pressure (RUPP). Am J Physiol Regul Integr Comp Physiol 2021.
- Cornelius DC, Cottrell J, **Amaral LM,** LaMarca B. Inflammatory Mediators: A causal link to hypertension during pregnancy- Studies in Preeclampsia. Br J Pharmacol. 2018 Aug 10.

- **Amaral LM**, Wallace K, Owens M, LaMarca B. Pathophysiology and Current Clinical Management of Preeclampsia. Curr Hypertens Rep. 2017 Aug; 19(8):61.
- Elfarra J, **Amaral LM,** McCalmon M, Scott JD, Cunningham MW Jr, Gnam A, Ibrahim T, LaMarca B, Cornelius DC.Natural Killer Cells Mediate Pathophysiology in Response to Reduced Uterine Perfusion Pressure. Clin Sci (Lond). 2017 Oct 17. pii: CS20171118.
- LaMarca BD, Cornelius DC, Harmon AC, **Amaral LM**, Cunningham MW Jr, Faulkner JL, Wallace K. Identifying Immune Mechanisms Mediating the Hypertension During Preeclampsia. Am J Physiol Regul Integr Comp Physiol. 2016 Jul 1;311(1):R1-9.
- **Amaral LM,** Cunningham MW Jr, Cornelius DC, LaMarca B. Preeclampsia: long-term consequences for vascular health. Vasc Health Risk Manag. 2015:11:403-415.
- **Amaral LM**, LaMarca B (2015).17-Hydroxyprogesterone Caproate as a Potential Therapeutic to Add to the Management of Preeclampsia. J Pharmacol Clin Toxicol 3(4):1059

B. Positions and Honors

Professional Experience:

2007-08 Instructor in Pharmacy course at Federal University of Juiz de Fora, MG, Brazil
2009-10 Master's degree-Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Brazil
2011-12 Instructor in Chemistry course at Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Brazil
2010-12 Doctorate (Ph.D.)- Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Brazil
2013-2016 Postdoctoral Research Fellow – Department of Pharmacology, School of Medicine, University of Mississippi Medical Center, Jackson, USA
2016-2017 Scientist- Department of Pharmacology, School of Medicine, University of Mississippi Medical Center, Jackson, USA
2017-2019 Instructor-Department of Pharmacology, School of Medicine, University of Mississippi Medical Center, Jackson, USA
2019-Pr. Assistant Professor- Department of Pharmacology, School of Medicine, University of Mississippi Medical Center, Jackson, USA

Awards & Honors

2020: AFHRE Travel Grants Award for Support of Underrepresented Minorities. High Blood Pressure Council (HBPR) Scientific Sessions.
2019: Finalist for the Stephanie Watts Career Development Award. High Blood Pressure Council (HBPR) Scientific Sessions, New Orleans, USA.
2019: Onsite Poster Competition award at the HTN 2019 Scientific Sessions, New Orleans USA.
2018: The American Physiological Society Water and Electrolyte Homeostasis Postdoctoral Research with Distinction Award, San Diego, USA
2017: APS Minority Travel Fellowship Awards, Chicago, IL, USA.
2017: Underrepresented Postdoctoral Scientist Travel Award, Chicago, IL, USA.
2016 20th World Congress of International Society for the Study Hypertension in Pregnancy Travel Award, Sao Paulo, Brazil
2015: Annual Hypertension Conference Travel Awards for New Investigators**,** Washington, D.C., USA
2015: WEH/AJP: Regulatory, Integrative, and Comparative Trainee Abstract Award, Boston, USA
2015 Caroline tum Suden/Hellebrand Professional Opportunity Award, Boston, USA
2014 Postdoctoral Research with Distinction Award- San Diego, USA
2014 President Award: The Most Outstanding Basic Science Oral Presentation New Orleans and New Investigator Travel Award, ISSHP, New Orleans, USA

Invited Talks

2013 Progesterone supplementation attenuates hypertension and AT1-AA in response to elevated IL-6 during pregnancy". 3rd ISH New Investigators' Symposium on Hypertension and Cardiovascular Disease. New Orleans, USA

2014 Progesterone supplementation improves blood pressure and uterine artery resistance in response to placental ischemia during pregnancy. High Blood Pressure Council (HBPR) Scientific Sessions, San Francisco, USA

2014 17- Hydroxyprogesterone attenuates hypertension and uterine artery resistance in response to reduced uterine perfusion pressure (RUPP) in pregnant rats." International Society for Study of Hypertension in Pregnancy (ISSHP), New Orleans, USA

2015 Early administration of 17-hydroxyprogesterone caproate improves fetal growth restriction possibly by reducing sFlt-1 and placental cytolytic Nk cells in response to placental ischemia during pregnancy. High Blood Pressure Council (HBPR) Scientific Sessions, Washington, DC, USA

2016 17-hydroxyprogesterone caproate improves fetal growth restriction possibly by reducing sFlt-1 and placental cytolytic NK cells in the Reduced Uterine Perfusion Pressure (RUPP) rat model of Preeclampsia. 20th World Congress of International Society for the Study Hypertension in Pregnancy, Sao Paulo, Brazil

2018 Progesterone Induced Blocking Factor Improves Clinical Characteristics Of Preeclampsia In Rupp Rats. AHA Council on Hypertension 2018, Chicago-IL, USA.

2019: Inhibition of Progesterone induced blocking factor causes clinical characteristics of preeclampsia in Sprague Dawley rats. High Blood Pressure Council (HBPR) Scientific Sessions, New Orleans, USA.

2020: Progesterone induced blocking Factor attenuates hypertension and placental mitochondrial dysfunction and reactive oxygen species in response to sFlt-1 during pregnancy.

National, Institutional and Local Service

2014 Science Fair Judge for Local and District High School Science Fairs
2014 Secondary mentor for Base-Pair students
2013-14 American Physiological Society's Physiology Understand (PhUn) Week Outreach
2014-pr. Instructor in Research Tools Molecular Biology MFM Fellows courses at University of Mississippi Medical Center (Jackson, MS)
2014-pr. Instructor in Medical Pharmacology course at University of Mississippi Medical Center (Jackson, MS)
2014- Pr Secondary mentor for MFM Fellows: Collaboration with the OBG-YN that allows me to work and teach fellows to obtain their M.S degree.
2014- Pr Secondary mentor for Graduate Students- Pharmacology Department.
2017 Bruce Award judges and ASPET mentoring program for Experimental Biology 2017
2017-18 GWIMS Membership Committee
2020-Pr GWIMS Mentoring Committee Chair
2020-Pr Instructor in Perspectives in Multidisciplinary Clinic class
2020-Pr Ph.D advisory committee-UMMC
2021-Pr Graduate Committee- UMMC

Membership

2009-11 Brazilian Society for Pharmacology and Experimental Therapeutics
2013-Pr American Heart Association (AHA)
2013-Pr American Society of Physiology (APS)
2014-Pr International Society of Hypertension (ISH)
2014-Pr International Society for Study of Hypertension in Pregnancy (ISSHP)
2014-Pr American Society for Pharmacology and Experimental Therapeutics (ASPET)
2017-Pr Group of Women in Science and Medicine (GWIMS -UMMC)
2018-Pr The Society for Maternal-Fetal Medicine (SMFM)
2019-Pr Society for Reproductive Investigation (SRI)

C. Contribution to Science

1. During my graduate training, I became interested in mechanisms that mediate the hypertension during pregnancy. My Master's degree work involved the recruitment of more than 600 volunteers, as well as the study of genetic polymorphisms on nitric oxide synthase (NOS). As a Ph.D. student, I used the placental ischemic rat model of preeclampsia, induced by long-term reductions in uterine perfusion pressure (RUPP model), and to assess nitric oxide synthase (NOS) expression, nitric oxide bioavailability, oxidative stress and vascular reactivity in response to placental ischemia. I developed and optimized this important model in my lab. Another major science contribution was my Ph.D. dissertation on the role of iNOS in the pathophysiology of preeclampsia. Also, I had fundamental contributions to these studies, participating on the conception and design of the research;

performance of experiments; analysis of data; interpretation of results; preparation of figures; draft of the manuscripts; editing and revision of the manuscripts:

- **Amaral LM**, Palei AC, Sandrim VC, Luizon MR, Cavalli RC, Duarte G, Tanus-Santos JE. Maternal iNOS genetic polymorphisms and hypertensive disorders of pregnancy. *Journal of Human Hypertension.* 2012; 26 (9):547-52.
- **Amaral LM**, Pinheiro LC, Guimaraes DA, Palei AC, Sertório JT, Portella RL, Tanus-Santos JE. Antihypertensive effects of inducible nitric oxide synthase inhibition in experimental preeclampsia. *Journal of Cellular and Molecular Medicine*. 2013 Oct; 17(10):1300-7.
- Sertório JT, Lacchini R, **Amaral LM**, Palei AC, Cavalli RC, Sandrim VC, Duarte G, Tanus-Santos JE. Haptoglobin polymorphism affects nitric oxide bioavailability in preeclampsia. *J Hum Hypertens*. 2013; Jun; 27(6):349-54.

2. My mentor's laboratory has focused on immune mechanisms that mediate the altered renal function and hypertension in response to chronic placental ischemia during pregnancy. Since joining her lab, we have identified an important role for 17-OHPC to the management of preeclampsia in response to placental ischemia and in response to elevated cytokines during pregnancy. Previously, my mentor showed that administration of 17-OHPC attenuated blood pressure and decreased renal cortex prepro-ET-1 mRNA levels in response to elevated TNF-α during pregnancy. We subsequently demonstrated that 17-OHPC decreased AT1-AA and improves nitric oxide bioavailability while lowering blood pressure in response to IL-6 induced hypertension during pregnancy. Furthermore our most recent studies have shown that while 17-OHPC improves inflammation, it also significantly improves uterine artery resistance index (UARI), increased vascular endothelial nitric oxide synthase (eNOS) expression and circulating levels of nitrate-nitrite in response to placental ischemia. These studies have identified 17-OHPC as potential therapeutic for the management or treatment of preeclampsia. My role in these studies was as primary investigator in which I performed animal surgeries, molecular analysis, and tissue collection. I have received travel and research awards of distinction for work done in these studies and have given numerous poster and platform presentations of this work at national and international meetings.

- **Amaral LM**, Kiprono L, Cornelius DC, Shoemaker C, Wallace K, Moseley J, Wallukat G, Martin JN Jr, Dechend R, LaMarca B. Progesterone supplementation attenuates hypertension and the autoantibody to the angiotensin II type I receptor in response to elevated interleukin-6 during pregnancy. *American Journal of Obstetrics and Gynecology.* 2014 Aug;211(2):158.e1-6.
- **Amaral LM**, Cornelius DC, Harmon A, Moseley J, Martin JN Jr, LaMarca B. 17-Hydroxyprogesterone caproate significantly improves clinical characteristics of preeclampsia in the Reduced Uterine Perfusion Pressure Rat Model. Hypertension. 2015 Jan; 65(1):225-3.
- **Amaral LM** , Jessica L.Faulkner, Jamil Elfarra, Denise C. Cornelius,Mark W. Cunningham, Tarek Ibrahim,Venkata Ramana Vaka, Jessica McKenzie , Babbette LaMarca. Continued Investigation Into 17-OHPC: Results from the Preclinical RUPP Rat Model of Preeclampsia." Hypertension. 2017, Dec;70(6):1250-1255
- 17-Hydroxyprogesterone caproate improves T cells and NK cells in response to placental ischemia; new mechanisms of action for an old drug. Elfarra JT, Cottrell JN, Cornelius DC, Cunningham MW Jr, Faulkner JL, Ibrahim T, Lamarca B, **Amaral LM**. Pregnancy Hypertens. Dec 2019.

3. During my Ph.D. degree and postdoctoral work, I have had the chance to collaborate in different projects related to preeclampsia. One of the most interesting was dedicated to examine the role of metalloproteinases in the pathophysiology of hypertensive disorders of pregnancy. We have recently started to study the role of T cells (T helper 17, T regulatory cells) in the pathophysiology of preeclampsia. My contributions in these publications were mainly on the design of the research; performance of experiments; analysis of data; interpretation of results; draft of the manuscripts, editing and revision of the manuscripts, and approval of the final version of manuscripts:

- PALEI AC, Sandrim VC, **Amaral LM**, Machado JSR, Cavalli RC, Lacchini R, Duarte G, Tanus-Santos JE. Association of matrix metalloproteinase (MMP)-9 polymorphisms with plasma MMP-9 levels and with reponsiveness to anti-hypertensive therapy in preeclampsia and gestational hypertension. *Pharmacogemomics J.*2012; 12(6):489-98.

- Luizon MR, **Amaral LM**, Palei AC. Matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs genetic polymorphisms and plasma levels in hypertensive disorders of pregnancy.*J Hum Hypertens*. 2013; Apr;27(4):278-9.
- Luizon MR, Palei AC, Sandrim VC, **Amaral LM**, Machado JS, Lacchini R, Cavalli RC, Duarte G, Tanus-Santos JE.Tissue inhibitor of matrix metalloproteinase-1 polymorphism, plasma TIMP-1 levels, and antihypertensive therapy responsiveness in hypertensive disorders of pregnancy. *Pharmacogenomics Journal*. 2014 Dec; 14(6):535-41.
- Cornelius DC, **Amaral LM,** Harmon AC, Wallace K, Thomas AJ, Campbell N, Scott J, Herse F,Haase N, Moseley J, Wallukat G, Dechend R, LaMarca BD. An increase population of regulatory T Cells improves the pathophysiology of placental ischemia in a rat model of preeclampsia. *Am J Physiol Regul Integr Comp Physiol*. 2015 Oct 15;309(8):R884-91
- Cornelius DC, Castillo J, Porter J, **Amaral LM**, Campbell N, Paige A, Thomas AJ, Harmon AC, Cunningham MW Jr, Wallace K, Herse F, Wallukat G, Dechend R, LaMarca BD. Blockade of CD40 ligand for intercellular communication reduces hypertension,placental oxidative stress, and AT1-AA in response to adoptive transfer of CD4+ T. *Am J Physiol Regul Integr Comp Physiol*. 2015 Nov 15; 309(10):R1243-50.
- Cornelius DC, **Amaral LM**, Wallace K, Campbell N, Thomas AJ, Scott J, Herse F,Wallukat G, Dechend R, LaMarca BD. Reduced Uterine Perfusion Pressure T-helper 17 cells cause Pathophysiology Associated with Preeclampsia during Pregnancy. A*m J Physiol Regul Integr Comp Physiol.* 2016 Nov 30:ajpregu.00218.2016.
- Ibrahim T, Przybyl L, Harmon AC, **Amaral LM**, Faulkner JL, Cornelius DC, Cunningham MW, Hünig T, Herse F, Wallukat G, et al. Proliferation of endogenous regulatory T cells improve the pathophysiology associated with placental ischaemia of pregnancy. Am J Reprod Immunol. 2017 Nov;78(5).
- Cottrell JN, **Amaral LM**, Harmon A, Cornelius DC, Cunningham MW Jr, Vaka VR, Ibrahim T, Herse F, Wallukat G, Dechend R, LaMarca B. Interleukin-4 supplementation improves the pathophysiology of hypertension in response to placental ischemia in RUPP rats. American journal of physiology. Regulatory, integrative and comparative physiology. 2019; 316(2):R165-R171.

To view my complete list of published work access the following weblink (MyBibliography):
https://www.ncbi.nlm.nih.gov/myncbi/14qveykmbptQ6/bibliography/public/

D. Previous and Current Research Support

Research Support

Current

April 2019- March 2022 2019 Career Development Award 19CDA34670055. Title: “Benefits of progesterone: missing in action during preeclampsia.

Dec 2020- November 2021. Mississippi Center for Clinical and Translational Research (MCCTR). Title: Progesterone and PIBF: new insights into treatment options for preeclampsia

Previous

Jun 2018 - **May 2019** NIH/ NIGMS Pilot project on grant 5P20GM121334-02. Title: “Anti-inflammatory effects of progesterone: missing in action during preeclampsia”.

Oct 2016 - Oct 2018 AMAG Pharmaceuticals. Title: “17-Hydroxyprogesterone Caproate Supplementation: A Novel Therapeutic for the Management of Preeclampsia?” Role: Amaral Co-investigator / LaMarca (PI).

Feb 2011-Nov 2012: Predoctoral fellowship from ‘Fundação de Amparo à Pesquisa de São Paulo’ (FAPESP), Sao Paulo, Brazil. Title: “Effects of inducible nitric oxide synthase inhibition in experimental pre-eclampsia.”

Feb 2009-Dec2010 Graduate fellowship from ‘Conselho Nacional de Desenvolvimento Científico e Técnológico’ (CNPq), Brazil. Tittle:"Effects of genetic polymorphisms of iNOS on the susceptibility in hypertensive disorders of pregnancy”.

Apr 2007-Aug 2008 Undergraduate fellowship from Federal University of Juiz de Fora, MG, Brazil. Title: “Pharmaceutical Care”