FVSP Faculty Application Checklist-DUE 1/19/2024 5PM EST

_____Completed cover page with prior mentorship history

_____Training/Registration requirements needed

_____Abstract of proposed work

_____NIH-format biosketch

Submission Instructions

Convert the application to ***one .pdf document.*** Name the file using your last name, followed by an underscore, and your first initial. For example: Martyniuk_C.pdf

Submit the following pages, via email attachment, to Dr. Chris Martyniuk (cmartyn@ufl.edu). The subject line should read "FVSP Faculty Application".

The FVSP Research Program runs 5/27/2024 to 8/07/2024 with final research presentations prior to the national symposium.

2024 Linda F. Hayward Florida Veterinary Scholars Program Faculty Application

Name	Julie M. Moore
Email address	juliemoore@ufl.edu
Proposed project title	Visualization of uteroplacental circulation in the pregnant mouse for studies of oxidative stress
Will you provide matching student stipend funding ($3250)?	yes
Source of project/research funding	NIH and/or departmental

Prior student research mentees (last 5 years, if applicable):

CLASS	STUDENT	PROJECT TITLE	STATUS
2025	Marie Rivera	Understanding the Relationship Between Placental Malaria Infection, Intestinal Permeability, and Inflammation in Post-Partum Kenyan Women	In progress
2026	Marc Rivas	Influence of *Tnf* deficiency on inflammation, coagulation, and oxidative stress in malaria during pregnancy	In progress

If project qualifies for Morris Animal Foundation Student Scholarship Funding and you have identified a specific interested student, please provide their name and email address

LAST NAME	FIRST NAME	EMAIL ADDRESS

I agree to obtaining all necessary approvals (e.g. IACUC/IRB/EH&S/VHRRC – see below for specifics) to conduct the project with the student PRIOR to the commencement of the summer program, as well as submitting documentation of these approvals to the FVSP board by 5/11/2024

YES/NO

I agree to assisting my student prepare for the summer program during the Spring semester, which will include preparation of a study outline, and training in relevant laboratory techniques

YES/NO

I agree to plan for commencing the experiment/data collection by the beginning of the summer program (5/22/24)

YES/NO

I agree to be available to the student throughout the summer to assist with the experiment/data collection, preparation of the manuscript and poster.

YES/NO

	Needed (Yes/No)	Approval by 5/11/24 (Yes/No)?
IACUC Approval and Training	Yes	Yes
IRB Registration and Training	No	NA
Biological Agent Registration	No	NA
Biopath Registration	No	NA
Veterinary Hospital Research	No	NA
FERPA Training	No	NA
Biohazardous Waste Training	Yes	Yes
Laboratory Safety Training	Yes	Yes

Abstract of proposed student project (1 page limit. This should mirror the aims page of a grant and CLEARLY indicate the student's role.)

Despite recent concerted efforts to reduce the global burden of malaria, this disease persists as a significant international public health problem. Particularly vulnerable are pregnant women and their fetuses, who suffer the consequences of placental malaria (PM). PM is characterized by sequestration of *Plasmodium falciparum*-infected erythrocytes in the maternal blood space of the placenta, often accompanied by a maternal inflammatory response, culminating in placental damage and insufficiency. Poor birth outcomes associated with PM (fetal growth restriction, preterm delivery, abortion or stillbirth) impact hundreds of thousands of pregnancies annually. Thus, PM is a highly significant problem for maternal-fetal health. More broadly, inflammatory processes at the uteroplacental level are a significant health threat and problem for reproductive success in many Eutheria, making advances in our mechanistic understanding of key drivers of these processes a highly significant endeavor.

Understanding of the critical mechanisms that drive placental damage and dysfunction in PM is incomplete. Infection-induced maternal inflammatory cell infiltrate has been widely implicated, with focus centered on monocytes. A role for neutrophils has not been comprehensively addressed. This represents a significant gap in knowledge given that neutrophils are implicated in severe malaria in non-pregnant patients and disorders of pregnancy, including preeclampsia and anti-phospholipid syndrome. As a first line of defense, neutrophils utilize strategies such as production of reactive oxygen species (ROS) that ensure rapid but non-specific killing of invading pathogens but can also mediate bystander cell damage and precipitate cell death. In malaria, monocytes are another potentially potent source of ROS, but their importance in PM in this regard is unknown. We have observed neutrophil activity and elevated myeloperoxidase, a key mediator of oxidative activity, together with accumulation of monocytes, in placenta of *P. falciparum*-infected women. Lipid peroxidation, an indicator of oxidative damage, features prominently in human and murine PM. Necroptotic death is also observed in syncytiotrophoblast (ST) in human PM and inversely relates to infant birth weight. Cumulatively, these preliminary data compel us to hypothesize that *activated maternal innate immune cells, through oxidative mechanisms, directly contribute to ST dysfunction and death, thereby precipitating poor birth outcomes in PM.*

The *objective* of this project, which is part of the larger Aims of an NIH-funded grant targeting this central hypothesis, is to use a mouse model to explore the role of activated innate immune cells in driving ST oxidative stress and cell death in PM.

SPECIFIC AIM: Establish the relative roles of innate immune cells and malarial hemozoin in mediating placental oxidative damage and cell death in an *in vivo* model.

A mouse model for PM will be used to assess the oxidative activity of monocytes and neutrophils and, through ablation experiments, identify roles played by these cells in malaria-induced placental oxidative stress and trophoblast death. The parasite pro-oxidant molecule hemozoin will be independently assessed in this context to discern the relative roles of exogenous and endogenous sources of oxidative stress in PM pathogenesis.

STUDENT PROJECT: The student engaged in this research will, after completing all of the necessary regulatory and technical training, learn how to initiate pregnancy in laboratory mice and perform terminal surgeries of pregnant animals. The student will also learn how to isolate immune cells (neutrophils and monocytes) from mice, label them with fluorescent markers and dyes, and inject them into pregnant animals. The main goal of the project is to develop and standardize the techniques required to visualize, in the anesthetized animal, uteroplacental circulation, including intravenously-injected, labeled neutrophils and/or monocytes, with a specialized fluorescence microscope. The student will work alongside an advanced PhD student who is well-versed in mouse model work.

NAME: Julie M. Moore

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

POSITION TITLE: Professor and Chair

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
St. Lawrence University	BS	06/1987	Biology/Physics
University of Connecticut Health Center	PhD	09/1995	Mol. Biol./Immunology
Centers for Disease Control and Prevention	postdoctoral	09/1999	Immunology

A. Personal Statement

My 23 year career as an academic researcher has focused primarily on pathogenesis of infections during pregnancy, with a specific focus on the placenta. The majority of my contributions have been centered on malaria pathogenesis, as well as co-infections with HIV and malaria. I have broad, well-rounded experience, ranging from conducting field studies of malaria during pregnancy in Africa, to *in vitro* cell culture systems to understand the host-pathogen interaction in placental malaria, to development and use of several mouse models to understand malaria pathogenesis in pregnancy. My group has also studied commonalities in pathogenesis of placental malaria and cerebral malaria in mouse models, with a growing interest in how both also manifest in lung pathology. Our motivation to understand pathogenesis has been primarily motivated by the desire to identify pathways that can be leveraged as targets for therapeutics that could, with anti-malarial drugs, mitigate pathology. We have also ventured into study of how the gut microbiome influences outcomes in malaria, with an internally funded project looking at maternal influences on development of the infant gut microbiome, and how the latter impacts susceptibility to malaria in Goma, Democratic Republic of Congo. We previously also published a study of the impact of the gut microbiota on maternal and fetal outcomes in a mouse model for malaria in pregnancy. This interest is also primarily driven by the desire to identify opportunities to intervene to improve outcomes of malaria infection. The citations below provide evidence for these interests. Our many years of experience in mouse models for malaria, our particular focus on immunopathogenesis and potential therapeutics, and, more globally the technical and intellectual expertise that I have accumulated over the years in malaria and the important contributions my work overall have made to the field, make me well suited to lead the proposed work.

Current funding relevant to this proposal:

R01AI168923
Moore (PI)
9/20/22-7/31/27
Exploring the etiology of oxidative damage and cell death in placental malaria

Citations:

a. Avery JW, Smith GM, Owino SO, Sarr D, Nagy T, Mwalimu S, Matthias J, Kelly LF, Poovassery JS, Middii J, Abramowsky C, **Moore J.M.** *Maternal malaria induces a procoagulant and antifibrinolytic state that is embryotoxic but responsive to anticoagulant therapy.* PLoS One, 2012. **7**(2): p. e31090. doi:10.1371/journal.pone.0031090. [PMCID: PMC3274552]

b. Sarr, D., Cooper, C., Bracken, T., Martinez-Uribe, O., Nagy, T., and **Moore, J.M.** Oxidative stress: a potential therapeutic target in placental malaria. ImmunoHorizons, 2017. 1(4):29-41. doi: 10.4049/immunohorizons.1700002. [PMCID: PMC5589203]

B. Positions, Scientific Appointments, and Honors

Current Positions and Scientific Appointments and Memberships

2018 – present Professor and Chair, Infectious Diseases and Immunology, University of Florida (UF), Gainesville, FL
2018 – present Adjunct Professor, Center for Tropical and Emerging Global Diseases *and* Department of Infectious Diseases, University of Georgia (UGA)
2009 – present Member, American Association of Immunologists
2006 – present Member, American Society for Microbiology
1993 – present Member, American Society of Tropical Medicine and Hygiene

Honors

2021 – 2022 UF Advanced Leadership for Academic Professionals Program
2016 – 2017 UGA Women's Leadership Fellow
2006 Pfizer Award for Excellence in Research, UGA
2002 John M. Bowen Award for Excellence in Animal/Biomedical Research, UGA
1995 Young Investigator Award, American Society of Tropical Medicine and Hygiene

C. Contributions to Science

1. As a postdoctoral fellow, I pioneered studies of placental immunology in the context of malaria infection. I developed and validated novel techniques for studying the maternal contribution to antimalarial immunity in the placenta. These techniques have been widely accepted in the field as optimal approaches for studies of placental malaria. These methodologies continue to be central to the work in my laboratory, which aims to characterize how the placental immune environment differs from that in the peripheral blood and the cellular and molecular events at the placental level that are associated with malaria pathogenesis.
   e. **Moore, J.M.**, Nahlen, B. Ofulla, A.V.O., Caba, J., Ayisi, J., Oloo, A., Misore, A., Nahmias, A.J., Lal, A.A. and Udhayakumar, V. *A simple perfusion technique for isolation of maternal intervillous blood mononuclear cells from human placentae.* Journal of Immunological Methods, 1997. 209(1): p. 93-104. [PMID: 9448038]
   f. **Moore, J.M.**, Nahlen, B., Misore, A., A.A. and Udhayakumar, V. *Immunity to placental malaria. I. Elevated production of interferon-gamma by placental blood mononuclear cells is associated with protection in an area with high transmission of malaria.* J Infect Dis, 1999. 179(5): p. 1218-25. [PMID: 10191226]
   g. **Moore, J.M.**, Shi, Y.P, Othoro, C., Nahlen, B.L., Lal, A.A, and Udhayakumar, V. *Comparative flow cytometric analysis of term placental intervillous and peripheral blood from immediate postpartum women in western Kenya.* Placenta, 2003. 24(7): p. 779-85. [PMID: 12852869]
   h. Othoro C., **Moore J.M.**, Wannemuehler K., Nahlen B.L., Otieno J., Slutsker L., Lal A.A., Shi YP. *Evaluation of various methods of maternal placental blood collection for immunology studies.* Clin Vaccine Immunol, 2006. 13(5): p. 568-74. [PMCID: PMC1459646]

2. As both a postdoctoral fellow and an independent academic researcher, I participated in some of the first studies of immunological interactions between malaria and HIV during pregnancy. This work showed that HIV infection (pre-AIDS) is associated with significant alterations in anti-malarial immune responses at the placental level, and helped to galvanized significant, ongoing interest in this co-infection in the scientific community.
   a. **Moore, J.M.**, Nahlen, B., A.A. and Udhayakumar, V. *Immunity to placental malaria. II. Placental antigen-specific cytokine responses are impaired in human immunodeficiency virus-infected women.* J Infect Dis, 2000. 182(3): p. 960-4. [PMID: 10950798]

b. **Moore, J.M.**, Chaisavanneyakorn, S., Perkins, D.J., Otieno, J., Nahlen, B.L., Shi, Y.P., Udhayakumar, V. *Hemozoin differentially regulates proinflammatory cytokine production in human immunodeficiency virus-seropositive and -seronegative women with placental malaria.* Infect Immun, 2004. 72(12): p. 7022-9. [PMCID: PMC529128]

c. Perrault, S.D., Hajek, J., Zhong, K., Owino, S.O., Sichangi, M., Smith, G., Shi, Y.P., **Moore, J.M.**, Kain, K.C. *Human immunodeficiency virus co-infection increases placental parasite density and transplacental malaria transmission in Western Kenya.* Am J Trop Med Hyg, 2009. 80(1): p. 119-25. [PMCID: PMC2752680]

d. Sarr, D., Oliveira, L.J., Russ, B.N., Owino, S.O., Middii, J.D., Mwalimu, S., Ambasa, L., Almutairi, F., Vulule, J., Rada, B., and **Moore, J.M.** *Myeloperoxidase and other markers of neutrophil activation associate with malaria and malaria/HIV coinfection in the human placenta.* Front. Immunol., 2021. 12:682668 doi: 10.3389/fimmu.2021.682668. [PMCID: PMC8562302]

3. After establishing field-based malaria research expertise, I was motivated to develop mouse models for malaria during pregnancy that could be used as adjunct to our human-based studies. Mouse models had historically used virulent parasite species which precluded their utility to study malaria pathogenesis during early pregnancy (since embryos cannot implant under these conditions). We successfully developed a system that has allowed us to make significant contributions to understanding the role of inflammatory responses, oxidative stress and coagulation in malaria-induced pregnancy loss, as well as mechanisms of malaria-induced placental dysfunction and destruction, work that is ongoing as evidenced by our recent *Frontiers in Immunology* paper cited above in (2d). We have continued to innovate in this space as evidenced by our recent paper (d, below) introducing a new model for malaria-induced preterm labor. The following work, in addition to the papers cited above under Personal Statement, also highlights our interest in development of adjunctive therapies for malaria pathogenesis, which is relevant to the current proposal.
   a. Poovassery, J., Sarr, D., Smith, G., Nagy, T. and **Moore, J.M.** *Malaria-induced murine pregnancy failure: distinct roles for IFN-gamma and TNF.* J Immunol, 2009. 183(8): p. 5342-9. J Immunol. 2009 Oct 15; 183(8):5342-9. [PMCID: PMC2772180]
   b. Sarr, D., Smith, G., Poovassery, J., Nagy, T. and **Moore, J.M.** *Plasmodium chabaudi* AS induces pregnancy loss in association with systemic pro-inflammatory immune responses in A/J and C57BL/6 mice. Parasite Immunology. 2012, 34(4):224-35. doi: 10.1111/j.1365-3024.2012.01355.x. [PMCID: PMC3296870]
   c. Sarr, D., Bracken, B.C., Owino, S.O., Cooper, C., Smith, G.M., Nagy, T., and **Moore, J.M.** *Differential roles of inflammation and apoptosis in initiation of mid-gestational abortion in malaria-infected C57BL/6 and A/J mice*. Placenta. 2015, 36(7): 738-49. doi: 10.1016/j.placenta.2015.04.007. [PMCID: PMC4466201].
   d. Andrew, A.K., Cooper, C.A., **Moore, J.M.** *A novel murine model of post-implantation malaria-induced preterm birth*. PLoS One. 2022, 17(3):e0256060. doi: 10.1371/journal.pone.0256060. [PMCID: PMC8936457]

4. Our mouse model work has recently expanded to include a focus on studies of the impact of the gut microbiome on malaria infection and pregnancy outcome. This work was motivated by a desire to move beyond inbred mouse models, data from which cannot always be reliably translated to human biology. We developed an outbred mouse malaria for malaria during pregnancy, and then described how the maternal gut microbiota can influence malaria pathogenesis in the context of pregnancy. This work has laid the groundwork for human studies currently underway (with institutional support) to further define the importance of maternal factors, especially stress, in shaping development of the infant gut microbiome in the first six months of life (paper “c” below) and infant outcomes in the context of malaria transmission (in Democratic Republic of Congo). I further wrote a book chapter (“d” below) on the interaction of malaria, host immunity and the gut microbiome, and potential opportunities for disease intervention that these interactions may present.
   a. Morffy Smith, C.D., Russ, B.N., Andrew, A.K., Cooper, C.A., **Moore, J.M.** *A novel murine model for assessing fetal and birth outcomes following transgestational maternal malaria infection*. Scientific Reports. 2019, 9(1): 19566. doi: 10.1038/s41598-019-55588-8. [PMCID: PMC6925284]

b. Morffy Smith, C.D., Gong, M., Andrew, A.K., Russ, B.N., Ge, Y., Zadeh, M., Cooper, C.A., Mohamadzadeh, M., **Moore, J.M.** *Composition of the gut microbiota transcends genetic determinants of malaria infection severity and influences pregnancy outcome*. EBioMedicine. 2019 May 31. pii: S2352-3964(19)30360-3. doi: 10.1016/j.ebiom.2019.05.052. [PMCID: PMC6606560]
c. Dutton, C.L., Maisha, F.M., Quinn, E.B., Morales, K.L., **Moore, J.M.**, Mulligan, C.J. Maternal psychosocial stress is associated with reduced diversity in the early infant gut microbiome. Microorganisms 2023, 11, 975. https://doi.org/10.3390/microorganisms11040975. [PMCID: PMC10142543]

d. **Moore, J.M.**, Morales Aparicio, J.C., 2022. *Enhancing Pathogen Resistance: The Gut Microbiota and Malaria*. In: Glibetic, M. (Ed.), Comprehensive Gut Microbiota, vol. 1. Elsevier, pp. 143–167. https://dx.doi.org/10.1016/B978- 0-12-819265-8.00097-8. ISBN: 9780128192658.

5. As an adjunct to my field-based and mouse model studies of placental malaria, my group also established an *in vitro* trophoblast model system. The syncytiotrophoblast is a fetally-derived multinucleated epithelium that is in direct contact with maternal blood in the placenta, and is therefore exposed to malaria parasites in the context of maternal infection. After demonstrating that our *in vitro* system can appropriately model the phenomenon of placental malaria, we showed that the syncytiotrophoblast responds immunologically to malaria parasites borne in maternal blood, and therefore is an active participant, and collaborator, in the organ-specific response to malaria. This work has led to multiple other groups adopting this *in vitro* approach to understand pathogenesis of malaria in pregnancy.
   a. Chaisavanneyakorn, S., Lucchi, N., Abramowsky, C., Othoro, C., Chaiyaroj, S.C., Shi, Y.P, Nahlen, B.L., Peterson, D.S., **Moore, J.M.** and Udhayakumar, V. *Immunohistological characterization of macrophage migration inhibitory factor expression in Plasmodium falciparum-infected placentas.* Infect Immun, 2005. 73(6): p. 3287-93. [PMCID: PMC1111854]
   b. Lucchi, N., Koopman, R., Peterson, D.S. and **Moore, J.M.** *Plasmodium falciparum-infected red blood cells selected for binding to cultured syncytiotrophoblast bind to chondroitin sulfate A and induce tyrosine phosphorylation in the syncytiotrophoblast.* Placenta, 2006. 27(4-5): p. 384-94. [PMID 16009422]
   c. Lucchi, N.W., Peterson, D.S., **Moore, J.M.** *Immunologic activation of human syncytiotrophoblast by Plasmodium falciparum.* Malar J, 2008. 7: p. 42. [PMCID: PMC2268702]
   d. Lucchi, N.W., Sarr, D., Owino, S.O., Mwalimu, S.M., Peterson, D.S., and **Moore, J.M.** 2011. *Natural hemozoin stimulates syncytiotrophoblast to secrete chemokines and recruit peripheral blood mononuclear cells.* Placenta, 2011. 32(8): p. 579-85. DOI: 10.1016/j.placenta.2011.05.003 [PMCID: PMC3142316]

Complete list of published work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/julie.moore.1/bibliography/public/

E. Student request or ranking

1) Alexandria Teter
2) Brannon McKinley