BIOGRAPHICAL SKETCH

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NAME: Brown, Mary

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

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	START DATE MM/YYYY	END DATE MM/YYYY	FIELD OF STUDY
University of South Carolina, Columbia, SC	BS		1971	Biology
University of Florida, Gainesville, FL	MS		1974	Microbiology
University of Alabama at Birmingham, Birmingham, AL	PHD		1985	Biology

A. Personal Statement

My laboratory has a long history of developing rodent models for the impact of infectious agents on pregnancy outcome. Administration of a purified toxin like LPS is often used as a surrogate for maternal infection and can induce premature birth and/or evidence of resorption in rats and mice. LPS intoxication stimulates innate immune responses, induces prematurity, and has provided valuable insights into the specific mechanism by which LPS alone or in concert with nicotine impacts pregnancy. However, intoxication is not adequate to examine the mechanisms by which viable pathogens invade and breach the placental barrier. Therefore, we use live microbes that are capable of breaching the placental barrier, and colonizing and replicating in the fetal compartment.

B. Positions and Honors

Positions and Employment

1976 - 1978	Instructor, Allied Health Sciences Program, Santa Fe Community College, Gainesville, FL
1978 - 1985	Research Assistant, Department of Microbiology, University of Alabama at Birmingham, Birmingham, AL
1985 - 1992	Assistant Professor, Department of Infectious Diseases, University of Florida, Gainesville, FL
1992 - 1998	Associate Professor, Department of Pathobiology, University of Florida, Gainesville, FL
1998 -	Professor, Department of Infectious Diseases and Immunology, University of Florida, Gainesville, FL
2004 -	Professor, adjunct, Department of Pediatrics, University of Florida, Gainesville, FL
2011 -	Professor, adjunct, Department of Environmental and Global Health, University of Florida, Gainesville, FL

Other Experience and Professional Memberships

1978 -	Member, American Society for Microbiology
1980 -	Member, International Organization for Mycoplasmology
2007 -	Member, American Society for Reproductive Immunology
2015 -	Member, Society for the Study of Reproduction
2005 - 2017	ad hoc Study Section Member, multiple but not consecutive years, National Institutes of Health
2009 - 2017	Panel Review Member, multiple but not consecutive years, National Science Foundation

Honors

2003	Pfizer Animal Health Award for Research Excellence, College of Veterinary Medicine, University of Florida

2008 - 2011 University of Florida Research Foundation Professorship, University of Florida
2010 P.R. Edwards Award for Excellence in Microbiology, SE Branch of ASM

C. Contribution to Science. Complete List of Published Work in My Bibliography (total 99):

https://www.ncbi.nlm.nih.gov/myncbi/mary.brown.1/bibliography/48512331/public/

1. My early publications addressed development of a model for adverse pregnancy outcome using Mycoplasma pulmonis, a natural genital pathogen of rats. While causal relationships of adverse pregnancy outcomes can be inferred from retrospective and prospective epidemiological studies, animal models are essential to elucidate mechanisms of pathogenesis. The rat is a good model for studies focused on the maternal:fetal interface because, similar to that in humans, this species has both hemochorial placentation and deep trophoblast invasion of spiral arteries. The primary limitation of the rat as a model is that rats resorb fetuses rather than deliver prematurely. One of the strengths of our model system is that we used viable M. pulmonis that can replicate, establish in the placenta, and disseminate throughout the fetal unit, similar to what is likely to occur during intrauterine infection in humans. We established a dose response and reproducible pattern of colonization of maternal and fetal tissues as well as defined pathology. Experimentally-infected dams develop varying complications as well as histological lesions similar to ureaplasmal-associated reproductive disease of humans, including chorioamnionitis, fetal infection of the lung and central nervous system, low birth weight, and fetal and neonatal death.

    a. Peltier MR, Richey LJ, Brown MB. Placental lesions caused by experimental infection of Sprague-Dawley rats with Mycoplasma pulmonis. Am J Reprod Immunol. 2003 Sep;50(3):254-62. PubMed PMID: 14629031.
    b. Brown MB, Steiner DA. Experimental genital mycoplasmosis: time of infection influences pregnancy outcome. Infect Immun. 1996 Jun;64(6):2315-21. PubMed PMID: 8675343; PubMed Central PMCID: PMC174072.
    c. Steiner DA, Uhl EW, Brown MB. In utero transmission of Mycoplasma pulmonis in experimentally infected Sprague-Dawley rats. Infect Immun. 1993 Jul;61(7):2985-90. PubMed PMID: 8514404; PubMed Central PMCID: PMC280949.
    d. Steiner DA, Brown MB. Impact of experimental genital mycoplasmosis on pregnancy outcome in Sprague-Dawley rats. Infect Immun. 1993 Feb;61(2):633-9. PubMed PMID: 8423093; PubMed Central PMCID: PMC302774.

2. We further characterized the model such that timed infections during pregnancy permitted us to identify the precise timing at which the pathogen breached the placental barrier, infecting the fetal compartment. We also showed that the severity of pregnancy outcomes was influenced by the maternal genetic background, with inbred Lewis and outbred Sprague Dawley rats more susceptible to genital tract infection than inbred Fisher 344 and outbred Wistar rats. This was an unexpected finding as M. pulmonis also causes respiratory tract infection, and LEW rats are more susceptible that F344. *This suggests that the susceptibility/resistant mechanism are different between these two mucosal sites, even when the infection is initiated by the same pathogen.*

    a. Riggs MA, Maunsell FP, Reyes L, Brown MB. Hematogenous infection of Sprague-Dawley rats with Mycoplasma pulmonis: development of a model for maternal and fetal infection. Am J Obstet Gynecol. 2008 Mar;198(3):318.e1-7. PubMed PMID: 18068142.
    b. Reyes L, Shelton M, Riggs M, Brown MB. Rat strains differ in susceptibility to maternal and fetal infection with Mycoplasma pulmonis. Am J Reprod Immunol. 2004 Mar;51(3):211-9. PubMed PMID: 15209390.
    c. Brown MB, Peltier M, Hillier M, Crenshaw B, Reyes L. Genital mycoplasmosis in rats: a model for intrauterine infection. Am J Reprod Immunol. 2001 Sep;46(3):232-41. PubMed PMID: 11554697.

3. We expanded the models to address potential mechanisms for the observed adverse outcomes. In placentas, infection resulted in increased TNF-alpha and IL-6 mRNA as well as metallomatrix proteinase MMP9. Because of the association with neurological morbidity as a sequeala of intrauterine infection, we examined infection and selected gene responses in fetal and perinatal brains. We observed in utero

infection of fetal brain and lung, with the microbe isolated from these sites. Interestingly, elevated mRNA from inflammatory cytokines was found in tissues if the microbe was present but not in litter mates without infection at the site. We also identified upregulation of microglial (CD11b) and astrocyte (GFAP) activation markers. *Our data supports direct interaction with the fetal compartment immune system rather than a maternally-induced inflammation as well as the ability of our model to address infection-induced damage to the developing fetal brain.*

a. Burton A, Kizhner O, Brown MB, Peltier MR. Effect of experimental genital mycoplasmosis on gene expression in the fetal brain. J Reprod Immunol. 2012 Jan;93(1):9-16. PubMed PMID: 22244476.
b. Peltier MR, Barney BM, Brown MB. Effect of experimental genital mycoplasmosis on production of matrix metalloproteinases in membranes and amniotic fluid of Sprague-Dawley rats. Am J Reprod Immunol. 2007 Feb;57(2):116-21. PubMed PMID: 17217365.
c. Peltier MR, Brown MB. Experimental genital mycoplasmosis causes increased levels of mRNA for IL-6 and TNF-alpha in the placenta. Am J Reprod Immunol. 2005 Apr;53(4):189-98. PubMed PMID: 15760380.

4. More recently, we have used our expertise with the naturally-occurring rodent genital model to facilitate development of models for human pathogens, including Porphyromonas gingivalis and Ureaplasma parvum. We demonstrated that the ability to cause pregnancy complications is dependent on the strain of P. gingivalis. This has contributed to our understanding of how a periodontal pathogen can cause systemic disease. With respect to U. parvum, we adapted our approach to a mouse model and, as we observed in the natural model with M. pulmonis, demonstrated that the maternal genetic background was critical in the adverse pregnancy outcome. Finally, we have combined the natural infection with prenatal nicotine exposure, showing that prenatal exposure to nicotine increases the risk for intrauterine infection, lowers the infectious dose required to breach the placental barrier and infect the amniotic fluid and fetus, and alters the pathology and inflammatory profile associated with maternal and fetal sites. *This suggests a paradigm shift in that ta modifiable risk factor (nicotine exposure) can directly impact what has been considered an immutable risk factor (infection) for perinatal complication*, leading to the development of this R15 proposal.

a. von Chamier M, Reyes L, Hayward LF, Brown MB. Impact of gestational nicotine exposure on intrauterine and fetal infection in a rodent model. Biol Reprod. 2017 May 1;96(5):1071-1084. PubMed PMID: 28419180.
b. Allam AB, von Chamier M, Brown MB, Reyes L. Immune profiling of BALB/C and C57BL/6 mice reveals a correlation between Ureaplasma parvum-Induced fetal inflammatory response syndrome-like pathology and increased placental expression of TLR2 and CD14. Am J Reprod Immunol. 2014 Mar;71(3):241-51. PubMed PMID: 24372928; PubMed Central PMCID: PMC3927638.
c. von Chamier M, Allam A, Brown MB, Reinhard MK, Reyes L. Host genetic background impacts disease outcome during intrauterine infection with Ureaplasma parvum. PLoS One. 2012;7(8):e44047. PubMed PMID: 22952869; PubMed Central PMCID: PMC3430619.
d. Bélanger M, Reyes L, von Deneen K, Reinhard MK, Progulske-Fox A, Brown MB. Colonization of maternal and fetal tissues by Porphyromonas gingivalis is strain-dependent in a rodent animal model. Am J Obstet Gynecol. 2008 Jul;199(1):86.e1-7. PubMed PMID: 18355778.
e. Reyes L, Philips P, Wolfe B, Walkenhorst M, Progulske-Fox A, Brown MB. 2017. *Porphyromonas gingivalis* and adverse pregnancy outcome J Oral Microbiol. 10.1080/20002297.2017.1374153. http://dx.doi.org/10.1080/20002297.2017.1374153.

D. Additional Information: Research Support and/or Scholastic Performance

Completed Research Support (past 3 years)

R15 HD081439-01 Brown, Mary B (PI) 08/01/14-07/31/17
Porphyromonas gingivalis strain specific effects on the deep placental bed

4KB11 FL Department of H James and Esther King Research Program. Hayward, L (PI) and Brown, MB (co-PI) 11/2013 to 10/2015
Impact of nicotine exposure on prenatal infection and a lifelong predisposition for cardiovascular disease.

Subcontract from Fred Hutchinson Cancer Research Center. PI (Brown, MB) 04/30/2016 to 5/2017
Mycoplasma hyorhinis investigation for HVTN096 Clinical Trial