

2016 Queenan Fellowships for Global Health Investigator-Initiated Research Project Award

“Vertical Transmission of Zika Virus: Placental Histopathology and Fetal Outcomes”

I am pleased to report on our studies on the placental pathology of Zika virus infection.

In December 2016, shortly prior to the start of my Queenan Fellowship funding period, Dr. Karin Nielsen (UCLA) and I traveled to Rio de Janeiro, Brazil to meet with Dr. Patricia Brasil and her research team at Fiocruz Institute. This trip not only solidified our research relationship, but also developed new relationships with the larger Rio de Janeiro research group. Prior to this trip, we had only met with Dr. Brasil, who had traveled to Los Angeles in February 2016, in the middle of the 2015-16 Zika outbreak in Rio de Janeiro.

The primary goal of the December 2016 meeting was relationship building and study planning, as our final report on the outcomes of the first 125 women had just been published in the *New England Journal of Medicine* (Brasil *et al.*, 2016). During the course of the year, most of our cohort study of 187 pregnant women with confirmed Zika infection had delivered at Instituto Fernandes Figueira. This maternity and pediatric hospital has become the primary referral center for perinatal Zika infection in the Rio de Janeiro state. We also met other team members that cared for these patients and their infants on the front lines, including Dr. José Paulo Pereira, Jr. (perinatologist), Dr. Elisabeth Moreira (neonatologist), Dr. Andrea Zin (pediatric ophthalmologist), Dr. Beth Portari (pathologist), and Dr. Zilton Vasconcelos (research laboratory director).



Figure 1. Instituto Fernandes Figueira



Figure 2. Dr. Gaw, Dr. Brasil, Dr. Halai, and Dr. Nielsen at Fiocruz Institute

Since our initial meetings, our research has developed into a truly international, two-way collaboration. Dr. Portari (the lead research pathologist responsible for processing and evaluating all the placentas from Zika-infected pregnancies, as well as the fetal/neonatal autopsies) subsequently came to visit my laboratory at UCSF in January 2017. She brought with her 140 placental biopsies, which have undergone preliminary histopathologic analysis.

We have performed systematic histopathologic analysis on these Zika-infected placentas and selected a subset of placentas with diverse clinical outcomes to undergo a more in-depth analysis. In 40 samples, we have performed in situ hybridization experiments to determine the placental cell populations that are infected with Zika virus. We have found that Zika virus is capable of infecting nearly all cell types of the maternal-fetal interface. These results are currently being prepared for publication.

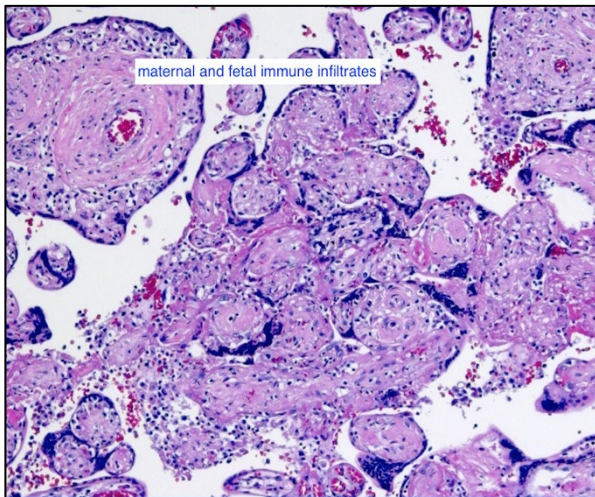


Figure 3. Chronic and discrete villitis in a Zika-infected placenta.



Figure 4. Dr. Portari, Dr. Gaw, and Dr. Pereira

The following works would not have been possible without the Queenan Fellowship and the Foundation for SMFM' support of our international collaboration. In addition, our group is planning to submit multiple R01 applications to continue this work in the next year.

Abstracts:

1. MM Maykin, E Avaad-Portari, M Esquivel, JP Pereira, Jr, SJ Fisher, ME Moreira, K Nielsen-Saines, P Brasil, and **SL Gaw**. "Placental Histopathologic Findings in Zika-infected Pregnancies" (Poster at SMFM 38th Annual Meeting, Dallas, TX; February 2018)
2. M Esquivel, E Avaad-Portari, ZC Vasconcelos, ME Moreira, and **SL Gaw**. "Vertical transmission and placental pathology of twin pregnancies from Zika virus infected mothers." (Poster at SMFM 38th Annual Meeting, Dallas, TX; February 2018)
3. MM Maykin, JP Pereira Jr., Z Vasconcelos, HD Gama, BR Torres Dutra, HA Valle, RF Cardozo, K Nielsen-Saines, ME Moreira, and **SL Gaw**. "The Role of Amniocentesis in the Diagnosis of Congenital Zika Syndrome" (Poster at Infectious Diseases Society for Obstetrics and Gynecology Annual Meeting, Philadelphia, PA; August 2018)

Publications:

1. Zin AA, Tsui I, Rossetto J, Vasconcelos Z, Adachi K, **Valderramos S**, Halai U-A, Pone M, Pone S, Silveira Filho JC, Aibe MS, Costa ACC, Zin OA, Belfort Jr. R, Brasil P, Nielsen-Saines K, Moreira ME. Screening criteria for ophthalmic manifestations of congenital Zika virus infection. *JAMA Pediatr.* 2017 Sep 1;171(9):847-854. doi: 10.1001/jamapediatrics.2017.1474. PMID: 28715527; PMCID: PMC5710409.
2. Tsui I, Moreira MEL, Rossetto JD, Vasconcelos Z, **Gaw SL**, Neves LM, Zin OA, Haefeli L, Filho JC, Gomes Jr. SC, Adachi K, Pone M, Pone S, Pereira Jr. JP, Belfort Jr. R, Arumugaswami V, Brasil P, Nielsen-Saines K, and AA Zin. Eye Findings in Infants with Suspected or Confirmed Antenatal Zika Virus Exposure. *Pediatrics.* 2018; 142(4) doi: 10.1542/peds.2018-1104. PMID: 30213843; PMCID: PMC6317824

3. Zin AA*, Tsui I*, Rossetto JD, **Gaw SL**, Neves LM, Zin OA, Haefeli L, Filho JC, Adachi K, Pone M, Pone S, Moller N, Pereira Jr JP, Belfort R, Arumugaswami J, Vasconcelos Z, Brasil P, Nielsen-Saines K, and ME Moreira. Visual Function in Infants with Antenatal Zika Virus Exposure. *J AAPOS*. 2018; 22(6):452-456.e1. doi: 10.1016/j.jaapos.2018.07.352. Epub 2018 Oct 22. PMID: 30359768 PMCID: PMC6289819.
4. Lopes Moreira ME, Nielsen-Saines K, Brasil P, Kerin T, Damasceno L, Pone M, Carvalho LMA, Pone SM, Vasconcelos Z, Ribeiro IP, Zin AA, Tsui I, Adachi K, **Gaw SL**, Halai UA, Salles TS, da Cunha DC, Bonaldo MC, Raja Gabaglia C, Guida L, Malacarne J, Costa RP, Gomes SC, Reis AB, Soares FVM, Hasue RH, Aizawa CYP, Genovesi FF, Aibe M, Einspieler C, Marschik PB, Pereira JP, Portari EA, Janzen C, Cherry JD. Neurodevelopment in Infants Exposed to Zika Virus In Utero. *N Engl J Med*. 2018 Dec 13; 379(24):2377-2379. PMID: 30575464; PMCID: PMC6478167.
5. Pereira Jr JP, Nielsen-Saines K, Sperling J, Maykin MM, Damasceno L, Cardozo RF, Valle HA, Dutra BR, Gama HD, Adachi K, Zin AA, Tsui I, Vasconcelos Z, Brasil P, Moreira ME, **Gaw SL**. Association of Prenatal Ultrasonographic Findings With Adverse Neonatal Outcomes Among Pregnant Women With Zika Virus Infection in Brazil. *JAMA Netw Open*. 2018;1(8):e186529. doi:10.1001/jamanetworkopen.2018.6529. PMID: 30646333; PMCID: PMC6324324
6. Pereira Jr. JP*, Maykin MM*, Vasconcelos Z, Avvad-Portari E, Zin AA, Tsui I, Brasil P, Nielsen-Saines K, Moreira ME, **Gaw SL**. The Role of Amniocentesis in the Diagnosis of Congenital Zika Syndrome. *Clin Infect Dis*. 2019 Jan 8. doi: 10.1093/cid/ciz013. [Epub ahead of print] PMID: 30624579; PMCID: PMC6669287. (*Co-First author)
7. Nielsen-Saines K, Brasil P, Kerin T, Vasconcelos Z, Gabaglia CR, Damasceno L, Pone M, Abreu de Carvalho LM, Pone SM, Zin AA, Tsui I, Salles TRS, da Cunha DC, Costa RP, Malacarne J, Reis AB, Hasue RH, Aizawa CYP, Genovesi FF, Einspieler C, Marschik PB, Pereira JP, **Gaw SL**, Adachi K, Cherry JD, Xu Z, Cheng G, Moreira ME. Delayed childhood neurodevelopment and neurosensory alterations in the second year of life in a prospective cohort of ZIKV-exposed children. *Nat Med*. 2019 Aug;25(8):1213-1217. doi: 10.1038/s41591-019-0496-1. Epub 2019 Jul 8. PMID: 31285631; PMCID: PMC6689256.
8. Pool K-L, Adachi K, Karnezis S, Salamon N, Romero T, Nielsen-Saines K, Pone S, Boechat M, Aibe M, Gomes da Silva T, Trevisan C, Boechat I, Brasil P, Zin A, Tsui I, **Gaw SL**, Daltro P, Guedes Ribeiro B, Fazecas T, Hygino C, Nogueira R, Vasconcelos Z, Pereira Jr. JP, Saad Salles T, Neves Barbosa C, Chen W, Foo S, Jung J, Pone M, Moreira ME. Association Between Neonatal Neuroimaging and Clinical Outcomes in Zika-Exposed Infants From Rio de Janeiro, Brazil. *JAMA Netw Open*. 2019 Jul 3;2(7):e198124. doi: 10.1001/jamanetworkopen.2019.8124. PMID: 31365112; PMCID: PMC6669783.
9. Adachi K, Romero T, Nielsen-Saines K, Pone S, Aibe M, Barroso de Aguiar E, Sim M, Brasil P, Zin A, Tsui I, **Gaw SL**, Halai U-A, Vasconcelos Z, Pereira, Jr JP, Saad Salles T, Neves Barbosa C, Portari E, Cherry JD, Pone M, Moreira ME. Early clinical infancy outcomes for microcephaly and/or SGA Zika-exposed infants. *Clin Infect Dis*. 2019 Jul 26. PMID: 31346616.
10. Tsui I, Neves LM, Adachi K, **Gaw SL**, Pereira Jr JP, Brasil P, Nielsen-Saines K, Moreira ME, Zin AA. Overlapping Spectrum of Retinochoroidal Scarring in Congenital Zika Virus and Toxoplasmosis Infections (*Ophthalmic Surg Lasers Imaging Retina*, in press)
11. Sobhani NC, Avvad-Portari E, Nascimento ACM, Machado HN, Lobato DSS, Pereira, Jr JP, Esquivel MS, Vasconcelos ZC, Zin AA, Tsui I, Adachi K, Brickley EB, Fisher SJ, Nielsen-Saines K, Brasil P, Moreira ME, **Gaw SL**. Discordant Zika virus findings in twin pregnancies complicated by antenatal Zika virus exposure: a prospective cohort (In revision)