January 2, 2018

Re: 2016 Vision Grant Award Final Report

Dear Ms. Tsigas and Vision Grant Committee,

I am writing to inform you of my progress on the project entitled, “Metformin in a catechol-O-methyltransferase deficiency model of preeclampsia.” The goal of this project is to understand the potential role of metformin in preeclampsia prevention by investigating its effects on placental metabolism. We have utilized both a human cell culture system and an established mouse model of preeclampsia (catechol-O-methyltransferase (COMT) knockout) to investigate the effects of metformin on placental trophoblast function and to study the association between preeclampsia and metabolism.

In the latter half of 2017, we continued our in vitro studies using HTR-8/SVneo extravillous cytotrophoblast cells (derived from first trimester human tissue; ATCC) to study the mechanism of metformin action on placental trophoblasts. Early in pregnancy, normal placentation requires trophoblast proliferation and invasion, which are regulated by oxygen (O₂) tension. Defects in this process are central to the pathophysiology of preeclampsia. Therefore, we have tested the effects of metformin and combination metformin/aspirin (given the current use of aspirin for preeclampsia prevention in high-risk women), on trophoblast proliferation and ATP production (proxy for mitochondrial function). Our results suggest that metformin alone, or in combination with aspirin, promotes trophoblast proliferation under hypoxic conditions mimicking the first trimester uterine environment. Cellular ATP levels also differ in metformin-treated compared with untreated control cells. These results demonstrate the impact of treatment on trophoblast function, and suggest a possible mechanism by which metformin might mitigate the process of poor placental invasion in women predisposed to severe preeclampsia. An abstract of these results will be presented in poster format at the Society for Maternal-Fetal Medicine Annual Meeting in Dallas, Texas on February 1, 2018.

With regards to our mouse studies, we have performed further characterization of the COMT knockout preeclampsia model to investigate how placental metabolism is affected in these mice. Since we hypothesize that metformin functions in vivo by modulating placental metabolism, it was critical to characterize the metabolic defect in COMT knockout mice, as this is suspected to contribute to the pathophysiology of the disease. Placental histology revealed significantly altered levels of glycogen, an important energy/glucose source for the fetus, in knockout compared with wild type control placentas. We have previously shown that treatment of COMT knockout mice with 2-methoxyestradiol (2-ME), a product of COMT enzyme activity, ameliorates the preeclampsia-like phenotype in these mice. Consistent with this, 2-ME also rescued the placental glycogen phenotype. Placental glycogen has been shown to be increased in the context of preeclampsia. These findings provide additional evidence for the relationship between preeclampsia and metabolic syndromes, such as diabetes and obesity which are
known risk factors for preeclampsia, and further support the biologic plausibility of a metabolism modifying agent, such as metformin, as a prevention strategy. These mouse data were incorporated into a broader story investigating the role of placental growth factor (PIGF) in preeclampsia and placental metabolism, and resulted in the submission of a manuscript in December that is currently under review.