The effect of the placental microenvironment on drug delivery for treatment of preeclampsia

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Preeclampsia (PE) occurs in 5-8% of pregnant people and accounts for about 12% of pregnancy-related mortality worldwide. PE is characterized by maternal hypertension occurring after 20 weeks of gestation with maternal organ dysfunction or fetal growth restriction. If managed poorly or left untreated, PE can lead to maternal eclampsia (seizures) and death for both the pregnant person and the fetus. Despite medical advances, the incidence of PE in the United States is growing, likely due to an increase in the prevalence of risk factors such as age, obesity, diabetes, and hypertension.

While the etiology of the disease is not well characterized, the initial stages of embryo implantation and placenta development are thought to occur incorrectly. In healthy placentation, the invasive placental cells, extravillous trophoblasts, remodel the uterine spiral arteries replacing the smooth muscle cells and increasing the diameter of the arteries. In PE, this remodeling event is incomplete or, in some cases, completely absent. Healthy remodeling successfully decreases the maternal blood velocity to the placenta, resulting in a higher blood residence time and contact time with the cells of the placental surface, syncytiotrophoblasts, where nutrients and oxygen are transported. With incomplete remodeling, seen in PE, the high blood velocity into the placenta causes physical damage to the tissue initiating a series of downstream events, like fibrosis, hypoxia, increased shear stress, and the resulting symptoms of the disease.

There is no established treatment for PE, and pregnant people with preeclampsia often deliver preterm, either naturally or induced to reduce the morbidity associated with PE. However, preterm birth is associated with its own set of morbidities; there is a delicate balance between induction and extending pregnancy. To this end, a therapeutic that can safely extend pregnancy for even one week would improve both maternal and fetal outcomes. This thesis explores multiple methods and mechanisms that can be used to develop an efficient therapeutic for PE.

We used well-established nanoparticle technologies, gold nanoparticles (AuNPs) and lipid nanoparticles (LNPs), to probe the biodistribution, safety, and efficacy of these nanoparticles during pregnancy in a mouse model. We found that gestational age altered placental and embryonic AuNP tissue content but not maternal organ biodistribution. We also found that LNP formulation altered the relative placental biodistribution and that LNPs could deliver a therapeutic mRNA, placental growth factor, increasing maternal serum and placental levels. Neither type of nanoparticle induced short-term toxicity to the dam or embryos, indicating that these delivery vehicles may be of use to treat PE.

We then wanted to understand how the microphysiological alterations seen in PE directly impacted the ability of trophoblasts to uptake and translate LNP-delivered mRNA. We cultured two types of trophoblast cell lines on substrates of different stiffnesses, ranging from healthy to

preeclamptic, with different extracellular matrix (ECM) proteins known to be dysregulated during PE. We found that both substrate stiffness and composition altered the uptake and translation of mRNA in BeWo b30 cells. In addition, the differentiation status of the cells to a healthy, fused state increased LNP transfection efficiency. However, there was no effect of substrate stiffness when HTR8 cells were transfected with LNPs. These data indicate that the physical alteration of a preeclamptic placenta must be considered when developing novel therapies to treat the disease, as the cells themselves may become dysregulated and respond to the therapeutic differently than cells in a healthy placenta.

Lastly, we created an easy-to-use, inexpensive, reproducible microphysiological model of the placental to enable screening of potential drug candidates for toxicity and transplacental transport. In addition, this model allows for the elucidation of the exact mechanisms behind transplacental drug transport. This model inherently includes fluid flow and shear stress; however, it also is designed to be able to incorporate different types of tissue stromal layers. We have shown that both thin membranes made from various ECM proteins and hydrated, cell-embedded ECM gels can be incorporated into the model to replicate physiologic conditions better.

These studies better understand how the placenta functions during preeclampsia and lay the foundation for understanding drug transport and drug delivery during pregnancy.