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A single intra-placenta injection of a Tahnsionone IIA prodrug improves the pregnancy outcomes in a preeclampsia-prone mouse model

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Preeclampsia (PE) is a serious pregnancy disorder associated with approximately 70,000 maternal deaths and 500,000 fetal and infant deaths annually. It can lead to the fetal growth restriction (FGR), abruptio placentae, preterm rupture of the membranes, and premature delivery. Defective remodeling of the uterine spiral arteries and uteroplacental malperfusion were considered as the major contributing factors to PE. Pro-angiogenic agents were reported as a promising treatment option for PE. Their ubiquitous biodistribution, however, is known to be associated with significant safety risks. Thus, the improvement of safety of proangiogenic therapy for PE management became an intriguing research topic. Tanshinone IIA (TAN), a major lipophilic active compound isolated from the roots of Salvia miltiorrhiza, was reported to be vasodilatory, anti-infl ammatory, and angiogenic. Its poor water-solubility and lack of tissuespecifi city to placenta, however, have impeded its becoming a viable PE therapy candidate. To overcome these limitations, we propose to use a thermoresponsive water-soluble macromolecular prodrug (ProGel-TAN) of TAN as a local therapy for PE. We synthesized the ProGel-TAN and dissolved it saline. The formulation is a free-fl owing, low viscosity solution at room temperature, but transitions into a hydrogel at ≥27°C. Near-infrared IRDye 800CW-labeled ProGel-TAN was injected into the placenta/decidua tissue at embryonic day (E) 9.5 with ultrasonic guidance. The pregnant mice and the fetuses were monitored using the ultrasound at pre-designed time points. The mice were euthanized on predesigned time with the major organs, placentae/deciduae and fetuses collected. The optical imaging was performed to track the distribution of ProGel-TAN. The placental perfusion function and fetus resorption rate were evaluated in the PE prone mice model. The optical imaging study showed that the single intra-placenta dose of the ProGel-TAN was retained locally at the placenta/decidua tissue for 9 days. No detectable signal was found in the fetuses during the study. The ProGel-TAN treatment eff ectively prevented fetus resorption, resulting in a live fetus rate in the PE mice (79.76%) similar to the healthy control mice (83.33%), but signifi cantly higher than the rate of the Saline control group (35.12%). Using the ultrasound imaging, it was found that the ProGel-TAN treatment reduced the uterine artery resistance index (UARI) and umbilical cord resistance index (UCRI) when compared to those of the Saline control group, suggesting improving the placenta perfusion. The

intra-placenta/decidua administration of ProGel-TAN in the PE-prone mice improve placenta perfusion and pregnancy outcomes.