RNAi Therapeutics Targeting Human Angiotensinogen (hAGT) Ameliorate Preeclamptic Sequelae in an Established Transgenic Rodent Model for Preeclampsia

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Objective
Preeclampsia is a common complication of hypertension in pregnancy. We tested a human angiotensinogen (hAGT)-specific siRNA, conjugated to a triantennary GalNAc ligand for liver targeting, for the ability to ameliorate symptoms of preeclampsia in an established rat model. We also evaluated fetal drug exposure and the impact of treatment on fetal outcomes.

Background
Hypertension in pregnancy affects 6-8% of pregnancies in developed nations, but few prophylactic and management agents exist; treatment with ACE inhibitors or AT1 receptor blockers is contraindicated due to fetal toxicity. Much of the maternal and fetal mortality and morbidity associated with hypertension in pregnancy occurs in the context of preeclampsia, a disorder with the hallmark features of new-onset hypertension and proteinuria beginning after 20 weeks of gestation. Several studies have demonstrated that angiotensinogen is involved in the manifestation and progression of the disease, including studies linking an angiotensinogen variant with increased risk of preeclampsia. RNAi therapeutics are highly potent mediators of gene-specific silencing, their utility in an animal model of preeclampsia was investigated.

Methods
Preeclampsia is a common complication of hypertension in pregnancy. We tested a human angiotensinogen (hAGT)-specific siRNA, conjugated to a triantennary GalNAc ligand for liver targeting, for the ability to ameliorate symptoms of preeclampsia in an established rat model. We also evaluated fetal drug exposure and the impact of treatment on fetal outcomes. Beginning on day 3 of gestation, transgenic hAGT dams were dosed subcutaneously with 10 mg/kg siRNA every third day through gestation day 15.

Conclusion
These data demonstrate that an RNAi therapeutic targeting maternal hepatic hAGT ameliorates the clinical sequelae of preeclampsia in a transgenic rat model and improves the outcome of the fetus. This treatment strategy offers selective drug delivery to the pregnant mother with no detectable delivery to the fetus.