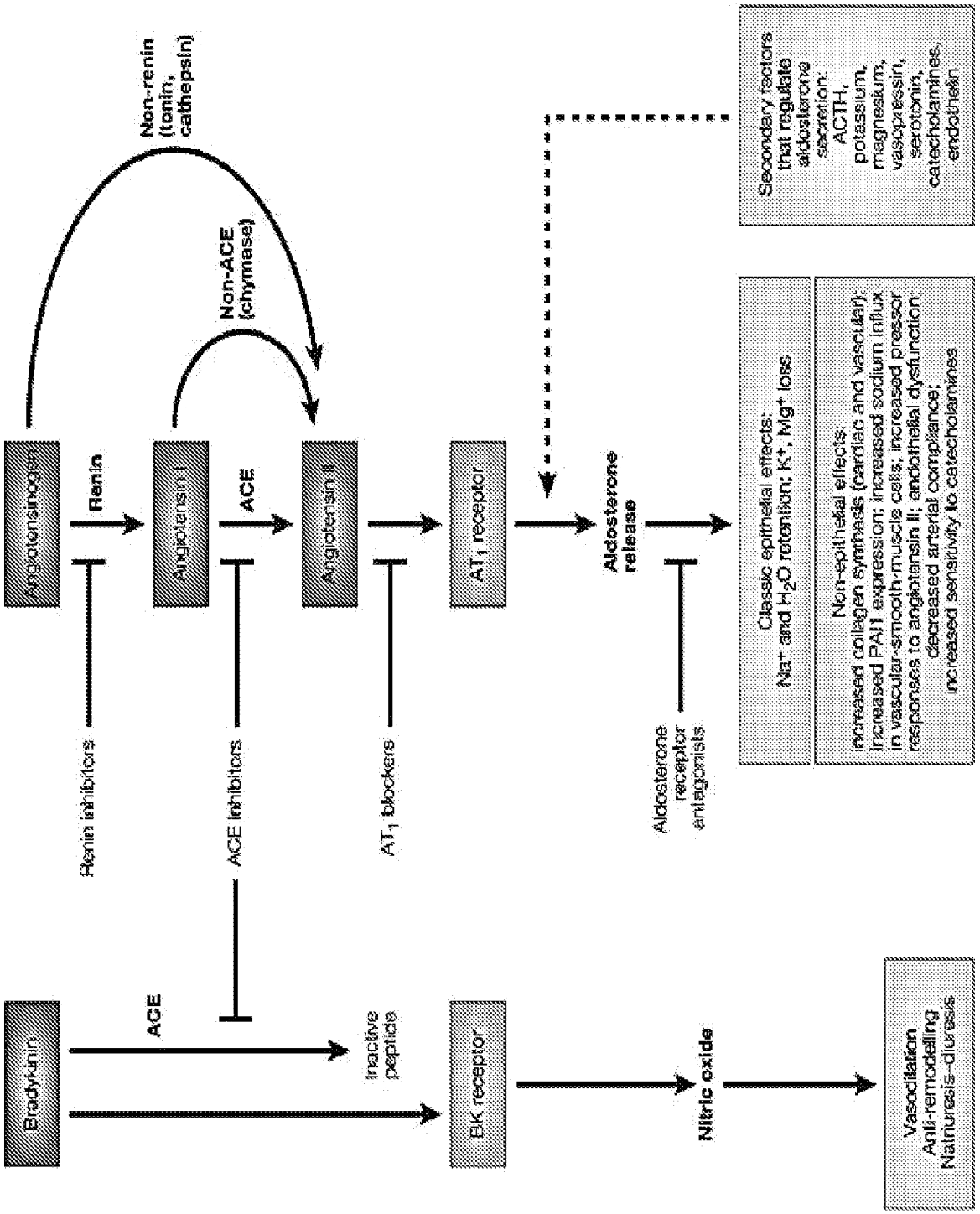

Angiotensinogen
Renin
Angiotensin I
ACE
Angiotensin II
AT1 receptor
Aldosterone release
Non-renin (tonin, cathepsin)
Non-ACE (chymase)
Secondary factors that regulate aldosterone secretion: ACTH, potassium, magnesium, vasopressin, serotonin, catecholamines, endothelin
Renin inhibitors
ACE inhibitors
AT1 blockers
Aldosterone receptor antagonists
Classic epithelial effects: Na+ and H2O retention; K+, Mg+ loss
Non-epithelial effects: increased collagen synthesis (cardiac and vascular); increased PAI1 expression; increased sodium influx in vascular-smooth-muscle cells; increased pressor responses to angiotensin II; endothelial dysfunction; decreased arterial compliance; increased sensitivity to catecholamines
Bradykinin
ACE
Inactive peptide
BK receptor
Nitric oxide
Vasodilation Anti-remodelling Natriuresis–diuresis

Figure 1

Reduction of blood pressure and albuminuria

Figure 2A

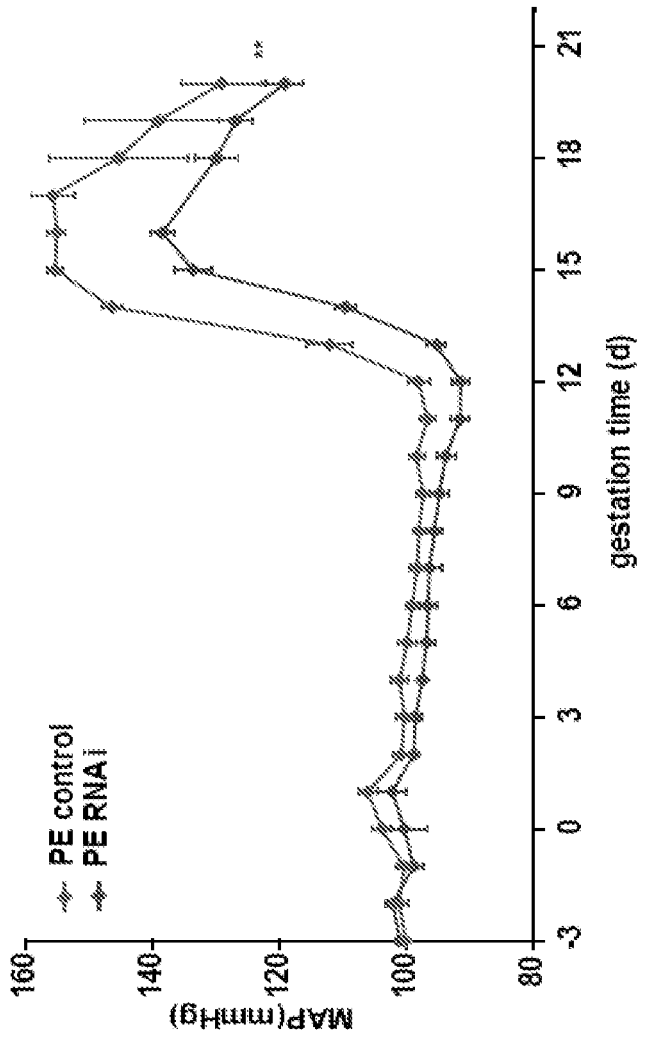
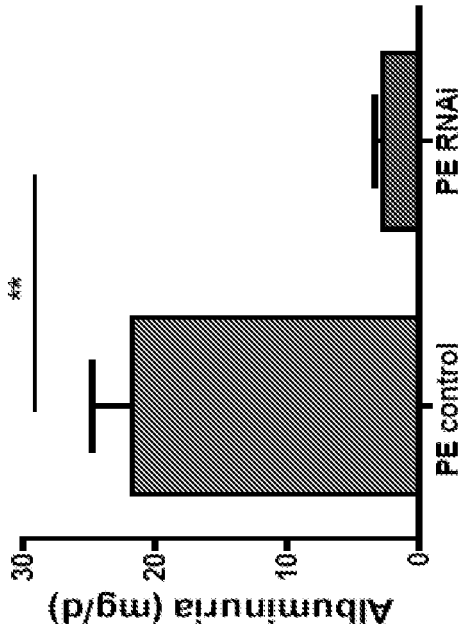


Figure 2B



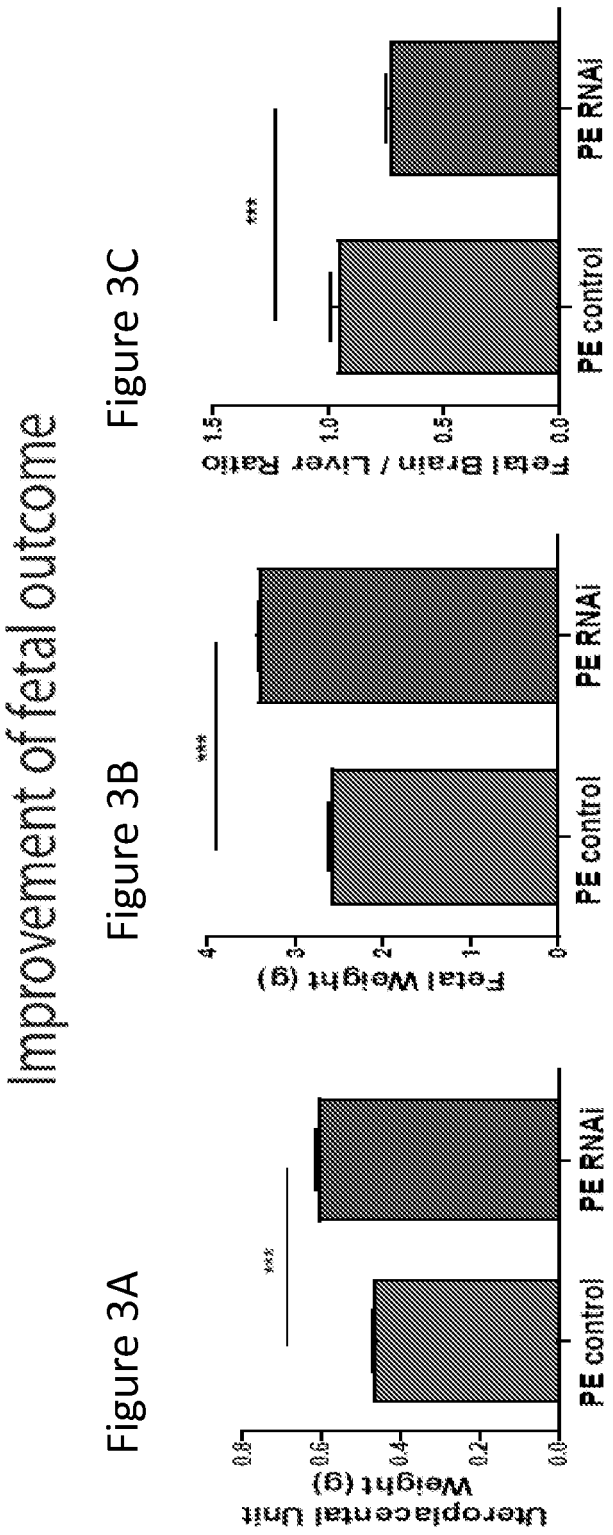

Improvement of fetal outcome
Figure 3A
Uteroplacental Unit Weight (g)
0.0
0.2
0.4
0.6
0.8
***
PE control
PE RNAi
Figure 3B
Fetal Weight (g)
0
1
2
3
4
***
PE control
PE RNAi
Figure 3C
Fetal Brain / Liver Ratio
0.0
0.5
1.0
1.5
***
PE control
PE RNAi

Figure 4A

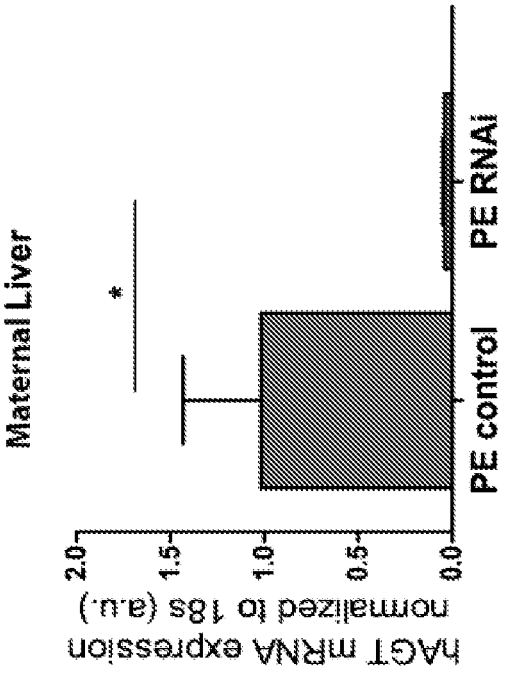
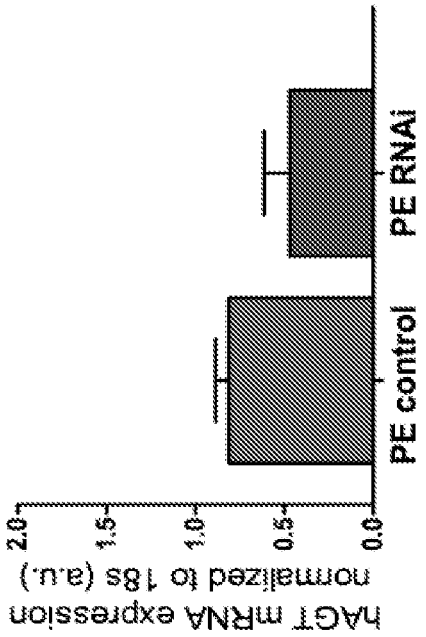


Figure 4B

siRNA does not enter placental barrier



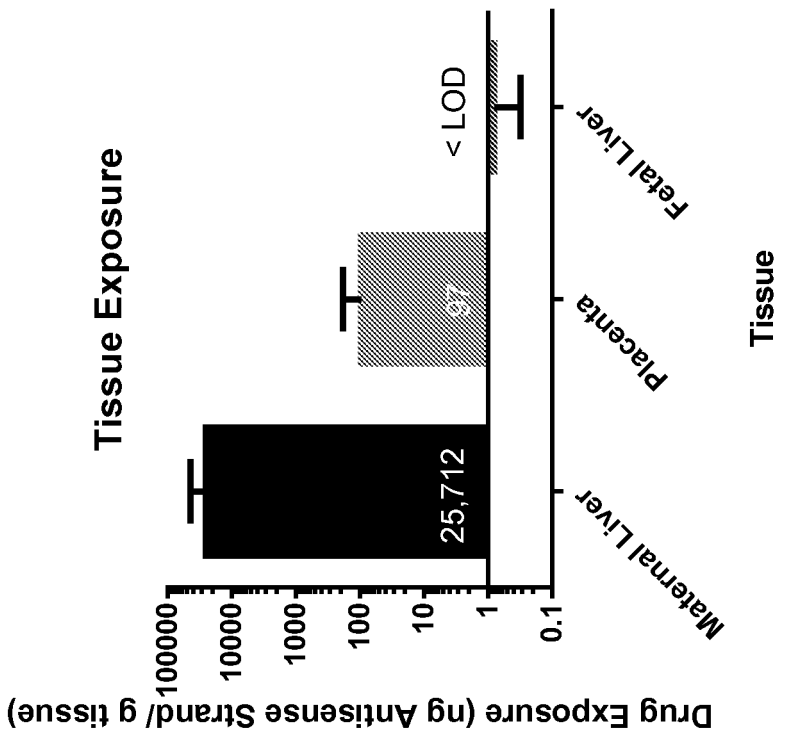

Tissue Exposure
Drug Exposure (ng Antisense Strand/ g tissue)
100000
10000
1000
100
10
1
0.1
25,712
97
< LOD
Maternal Liver
Placenta
Fetal Liver
Tissue

Figure 5

Figure 6A

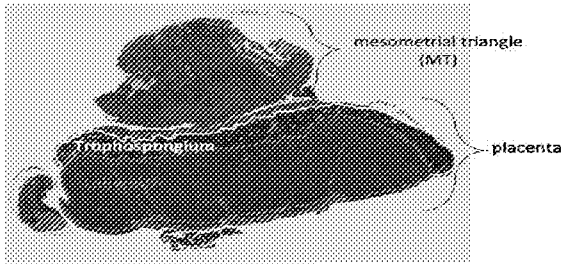


Figure 6B

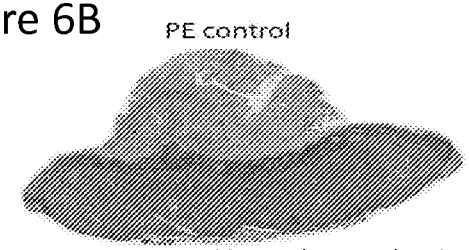
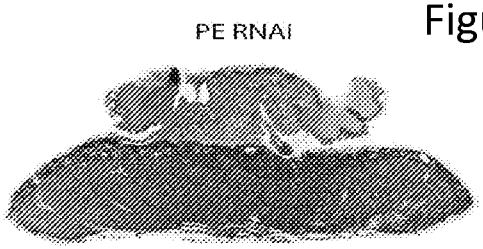


Figure 6C



Uteroplacental unit stained for cytokeratin

Figure 6D

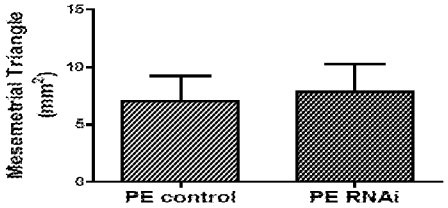


Figure 6E

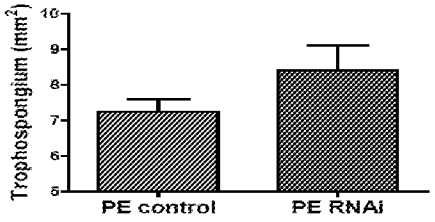


Figure 6F

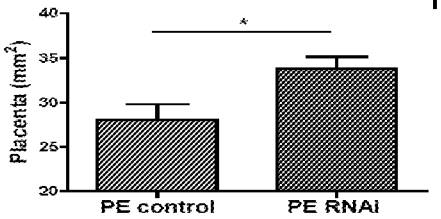
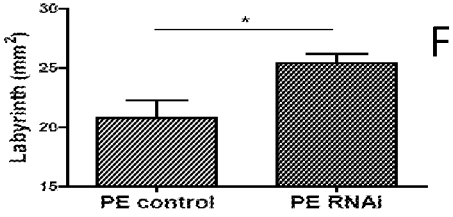


Figure 6G



Reduced sFLT1 and PLGF expression in maternal kidney

Figure 7A

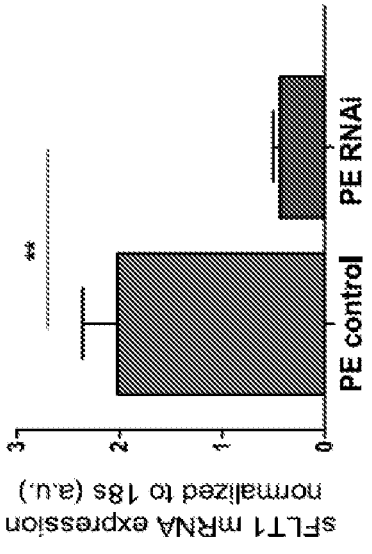


Figure 7B

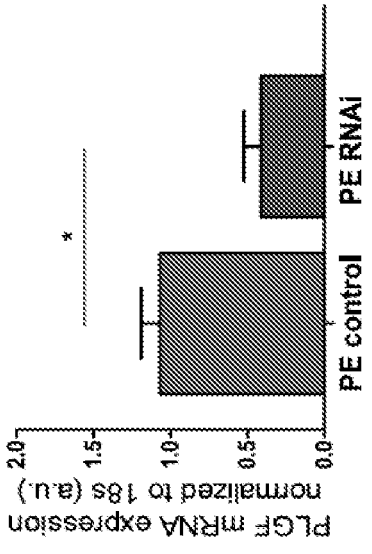


Figure 7C

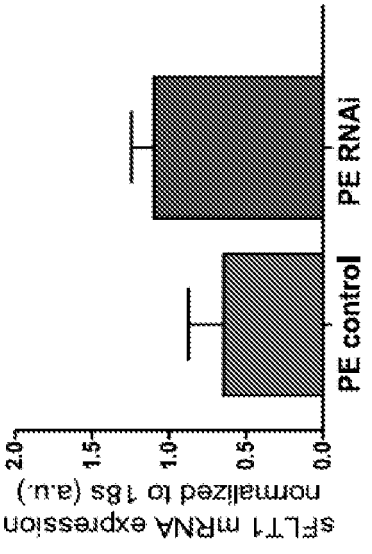
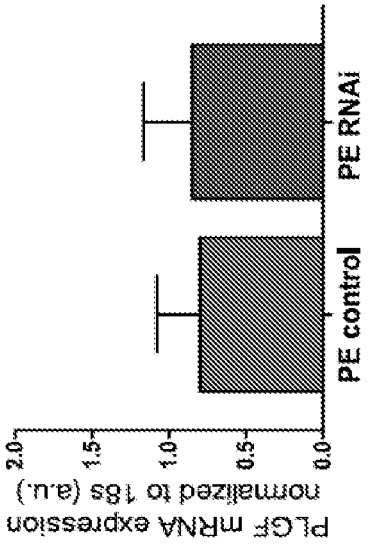


Figure 7D



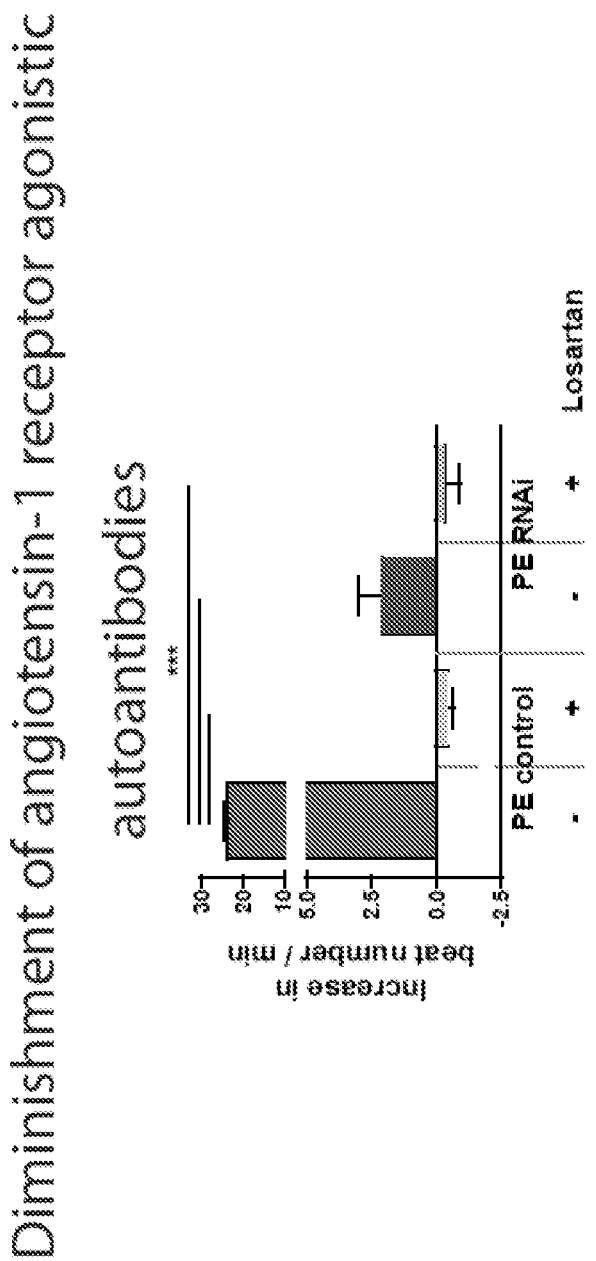

Diminishment of angiotensin-1 receptor agonistic autoantibodies
***
30
20
10
5.0
2.5
0.0
-2.5
increase in beat number / min
PE control
PE RNAi
Losartan
-
+
-
+

Figure 8

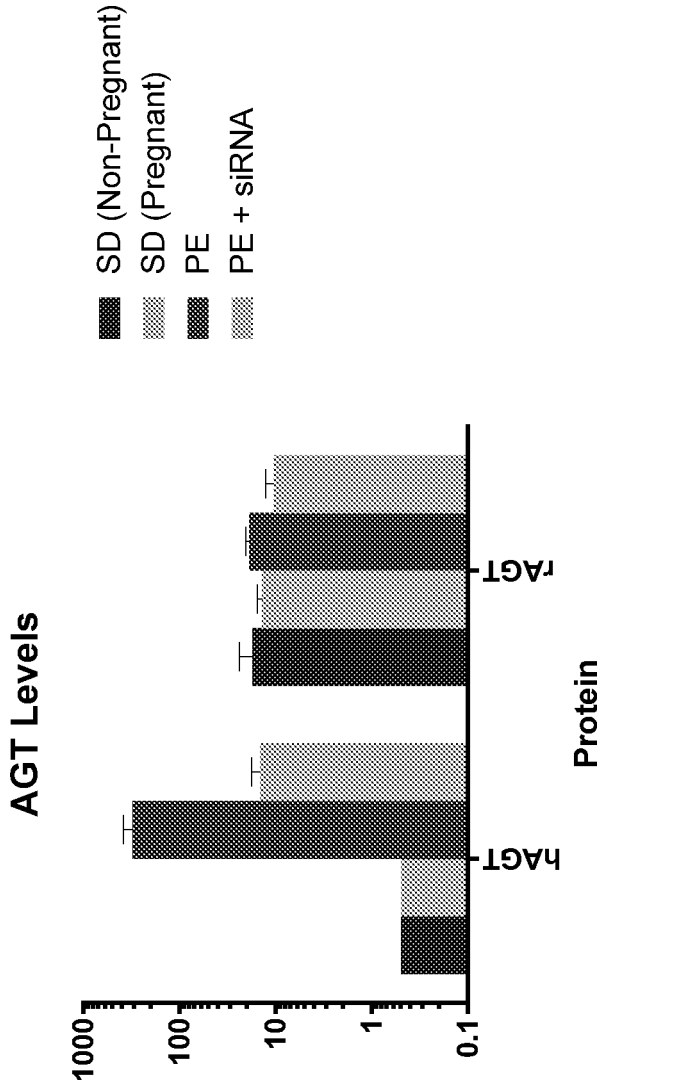


Figure 9B

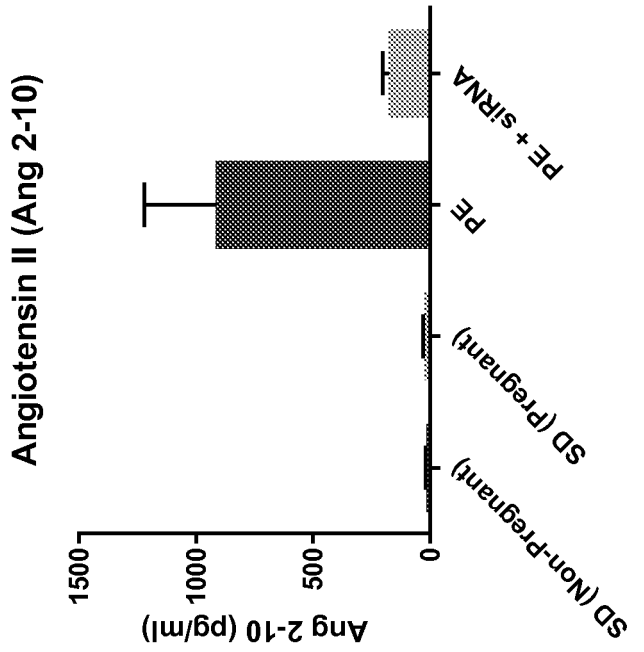


Figure 9A