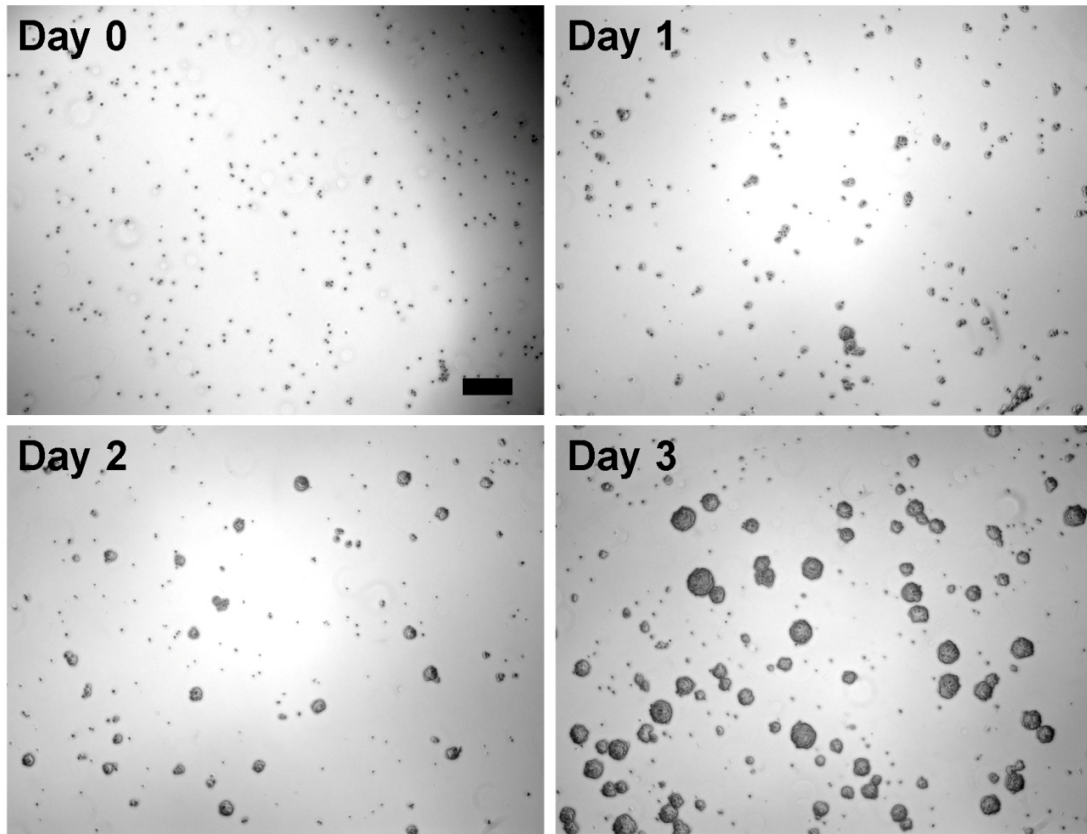
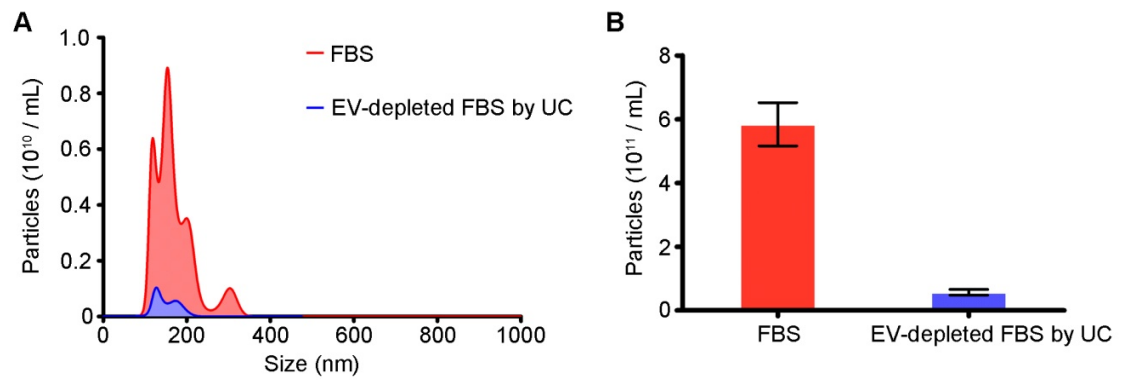


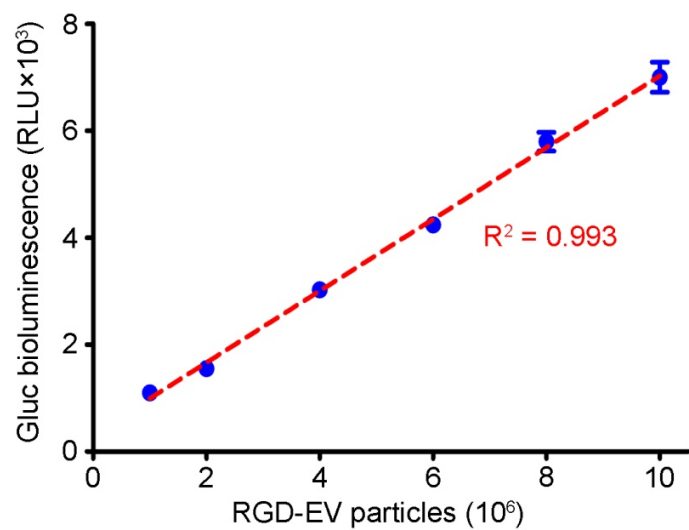
**Supplementary Materials**



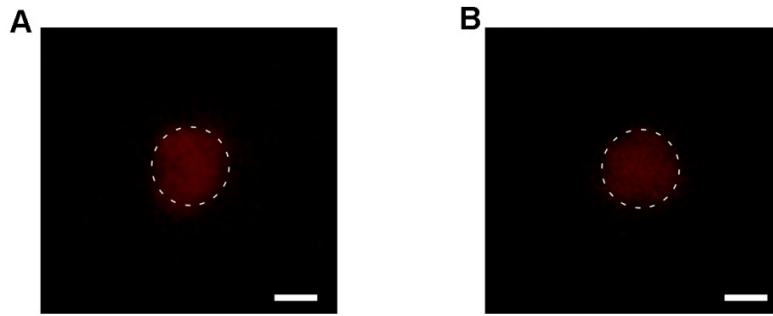
**Figure S1.** Bright field images of ReN cells cultured for 3 days. Scale bar, 200  $\mu\text{m}$ .



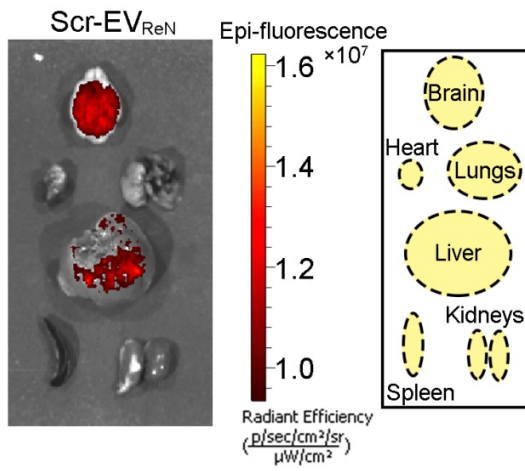
**Figure S2.** Size distributions (A) and particle concentrations (B) of FBS and EV-depleted FBS based on NTA measurements. UC: ultracentrifugation.



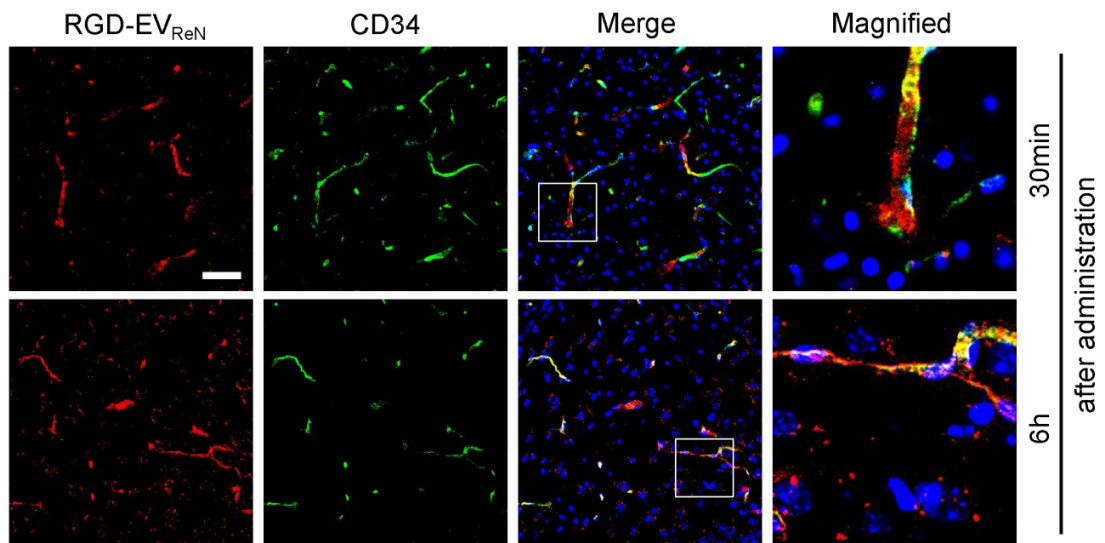
**Figure S3.** The linear relationship between Gluc activity in Gluc-labeled RGD-EV<sub>ReN</sub> and the EV number. Blue dots indicate the average luminescence intensities of 1-10 × 10<sup>6</sup> Gluc-labeled RGD-EV<sub>ReN</sub>. Red dash line is a linear fitting curve.



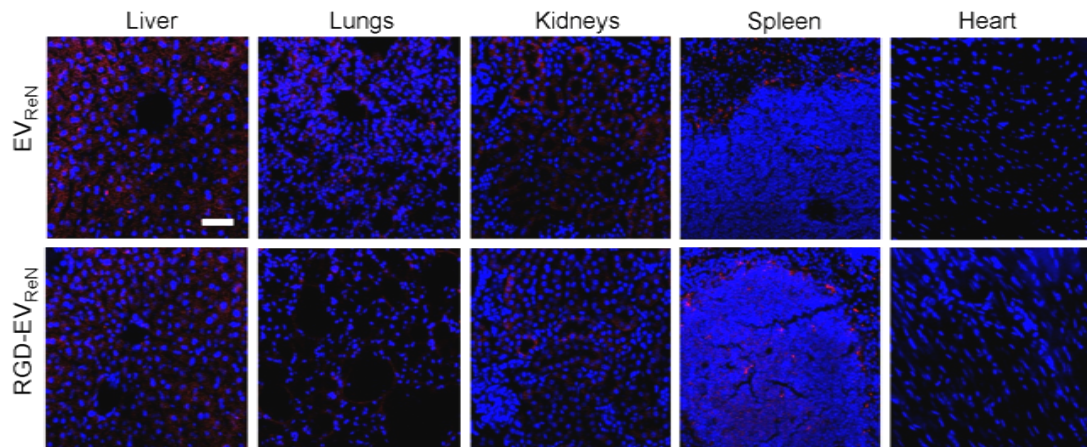
**Figure S4.** tdTomato-labeled  $EV_{ReN}$  were incubated with RGD-C1C2 following by a pull-down assay using anti-HA beads, and the fluorescence on the beads were detected by microscopy. Preincubation of the  $EV_{ReN}$  with lactadherin (A) or preincubation of the beads with the HA peptide (B) prevented the association of  $EV_{ReN}$  on the beads. The beads are around by dashed line. Scale bars, 1  $\mu\text{m}$ .



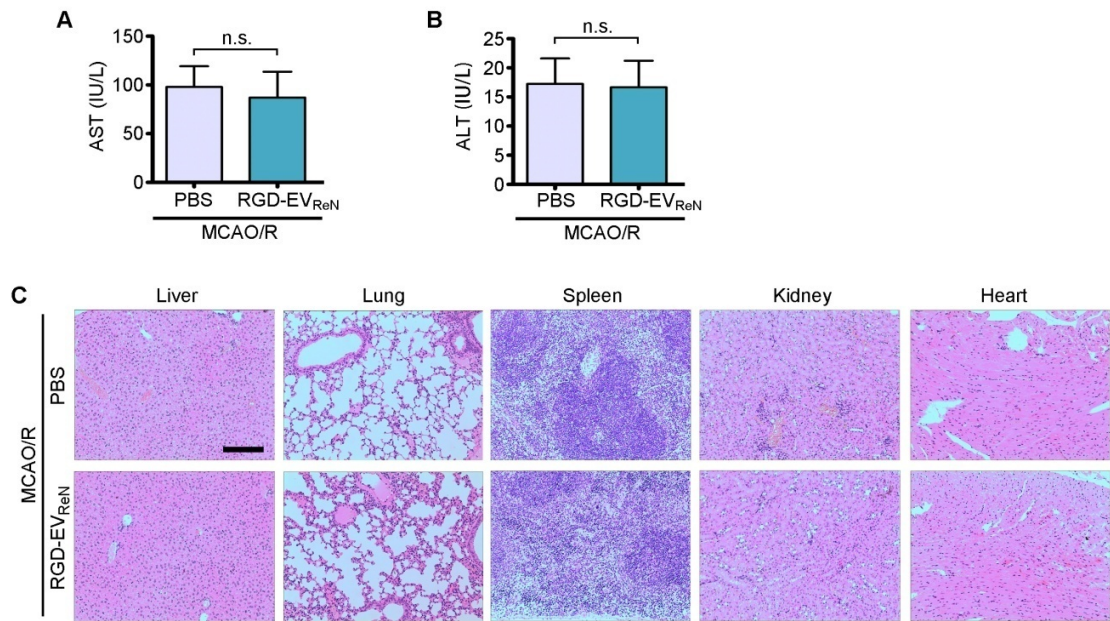
**Figure S5.** NIRF images of organs dissected from mice which received MCAO/R along with the administration of Cy5.5-labeled Scr-EV<sub>ReN</sub>.



**Figure S6.** Co-labeled fluorescence images of CD34 (green) with RGD-EV<sub>ReN</sub> (red) in the lesion region 30 min after intravenous administration (12.5 h after reperfusion). Blue indicates nuclei. Scale bars, 50  $\mu$ m. The images of 6 h after intravenous administration were borrowed from Figure 4D.



**Figure S7.** tdTomato-labeled EV<sub>ReN</sub> or RGD-EV<sub>ReN</sub> were administered intravenously on mice receiving 1 h of MCAO and 12 h of reperfusion. Fluorescence images of EVs (red) in the organs 24 h after administration (36 h after reperfusion). Blue indicates nuclei. Scale bar, 50  $\mu$ m.



**Figure S8.** Safety evaluation for RGD-EV<sub>ReN</sub> treatment. (A) The activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the mice serum. (B) Hematoxylin and eosin (H&E) staining images for the organs in the mice. The mice were intravenously injected with PBS or 300  $\mu$ g RGD-EV<sub>ReN</sub> every day for 3 times. On the fourth day, the serum and organs of the mice were collected for analyzing. Scale bar, 200  $\mu$ m.