

Figure S1. Characterization of EXOs derived from HUVECs.

(A) Representative transmission electron microscopy image of HUVEC-derived EXOs.

Scale bar, 100 nm.

(B) Nanosight analysis of the size distribution of EXOs derived from HUVECs (black), particles isolated from equal volume of fresh culture medium (red) and PBS blank control (blue).

(C) Exosomes labeled with DiR were added to cultured HUVECs. Confocal images show the cellular uptake of exosomes into HUVECs after 24 h of incubation. Scale bar, 25 μ m.

(D) Western blot analysis for the expression of Alix, CD63, CD81 and Cytochrome C proteins in HUVEC-derived exosomes (EXO), supernatant and total cell lysate (HUVEC). 50 μ g total protein from cell lysate or EXOs was loaded. Cytochrome C was used as an organelle marker.

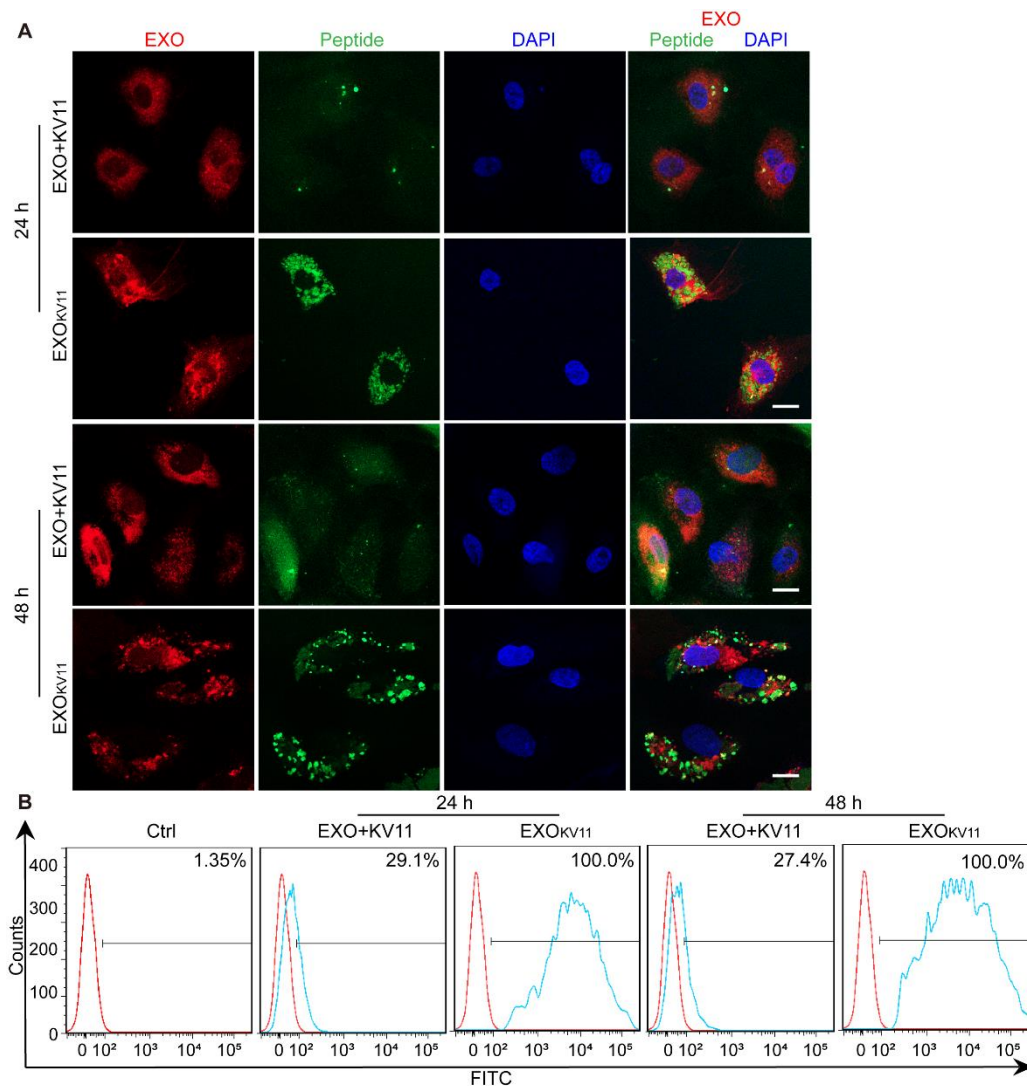


Figure S2. Cellular uptake of KV11 in HRMECs.

(A) DiR labeled EXOs were incubated with FITC- labeled KV11 (EXO+KV11) or FITC- labeled KV11-CP05 (EXO_{KV11}). After incubation, each mixture was added to HRMECs in culture. Representative confocal images from at least three different experiments show the cellular uptake in HRMECs at 24 and 48 h.

(B) EXO+KV11 and EXO_{KV11} obtained as in (A) were added to HRMECs in culture. After 24 or 48 h, cells were trypsinized for flow cytometry to analyze the cellular uptake efficiency. The red line represents the no-treatment control (Ctrl). The percentage of FITC-positive events out of total events is indicated in each histogram.

Scale bars, 20 μ m in (A)

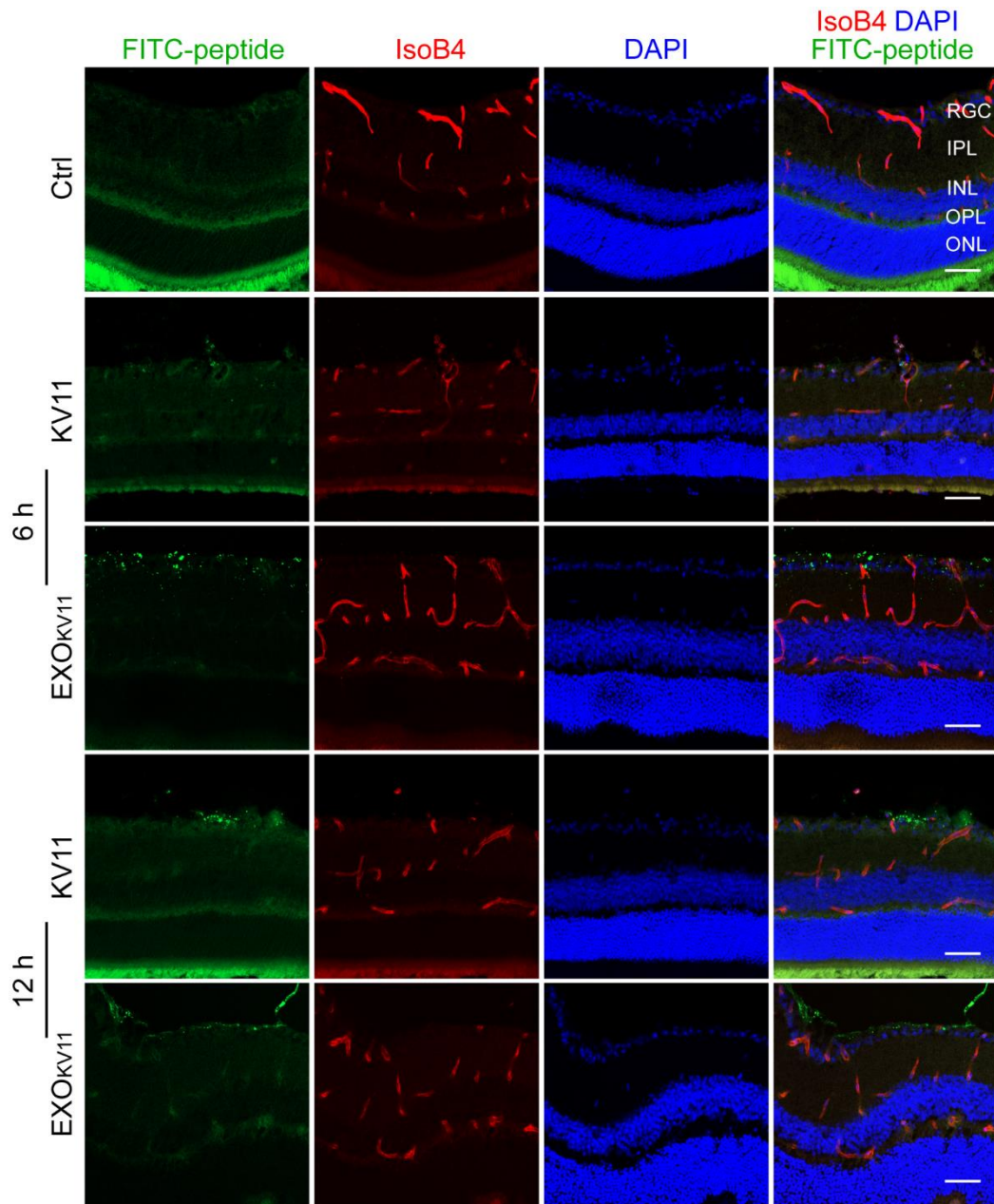


Figure S3. Ocular distribution of KV11 and EXO_{KV11} after intravitreal injection.

KV11 or EXO_{KV11} was injected intravitreally into CD-1 mice. Confocal images show the ocular distribution of KV11 and EXO_{KV11} in cryosections of retinas harvested at the indicated time points (6 h or 12 h). IsoB4 was used to label blood vessels. Ctrl represents the uninjected group. For checking *in vivo* distribution, FITC-labeled peptides were used. Images are representative of at least three mice per condition. Scale bars, 20 μ m.

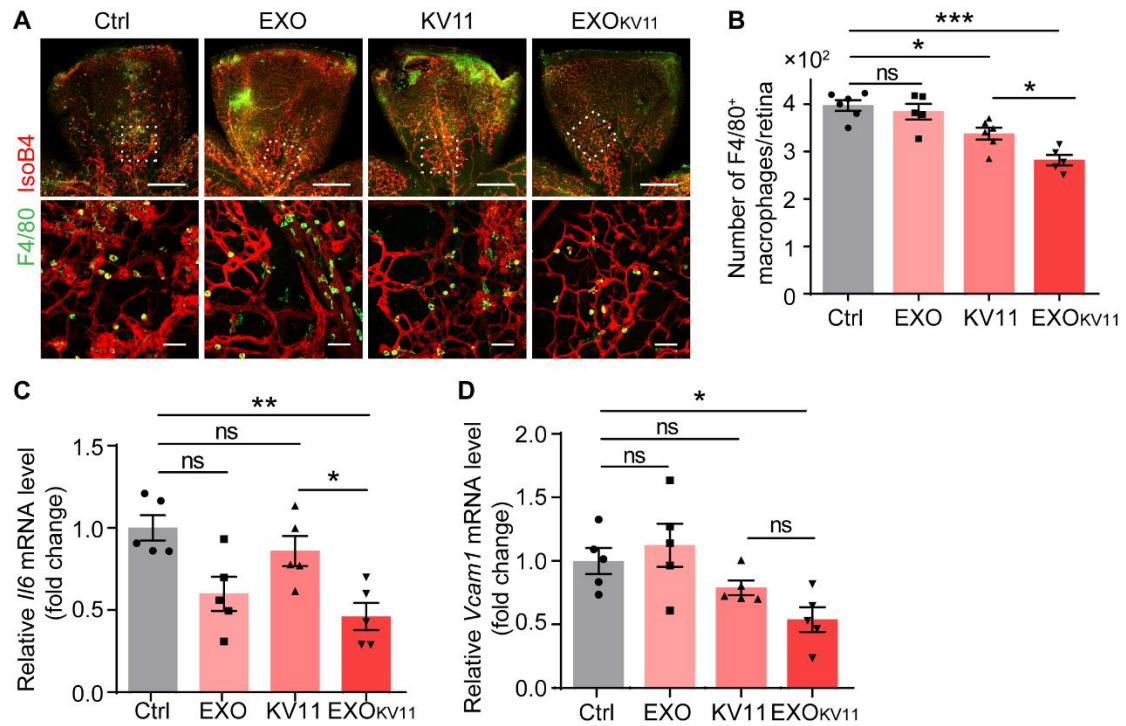


Figure S4. EXO_{KV11} inhibits inflammation in the OIR model

(A and B) Representative confocal images (A) of F4/80⁺ macrophage infiltration (green) and quantification (B) (n = 5 - 6 mice per condition).

(C and D) qPCR analysis of the expression of *I/6* and *Vcam1* in retinas of saline vehicle (Ctrl)-, EXO-, KV11-, and EXO_{KV11}-treated pups at P17 (n = 5 mice per condition).

The data represent as mean ± SEM, *p < 0.05, **p < 0.01, ***p < 0.001, one-way ANOVA followed by Tukey's multiple comparisons test in (C), (E), (H), (I), (J).

Scale bars, 1 mm in (A); 500 μm (lower magnification) and 50 μm (insets) in (B) and (G); 50 μm in (D and F).

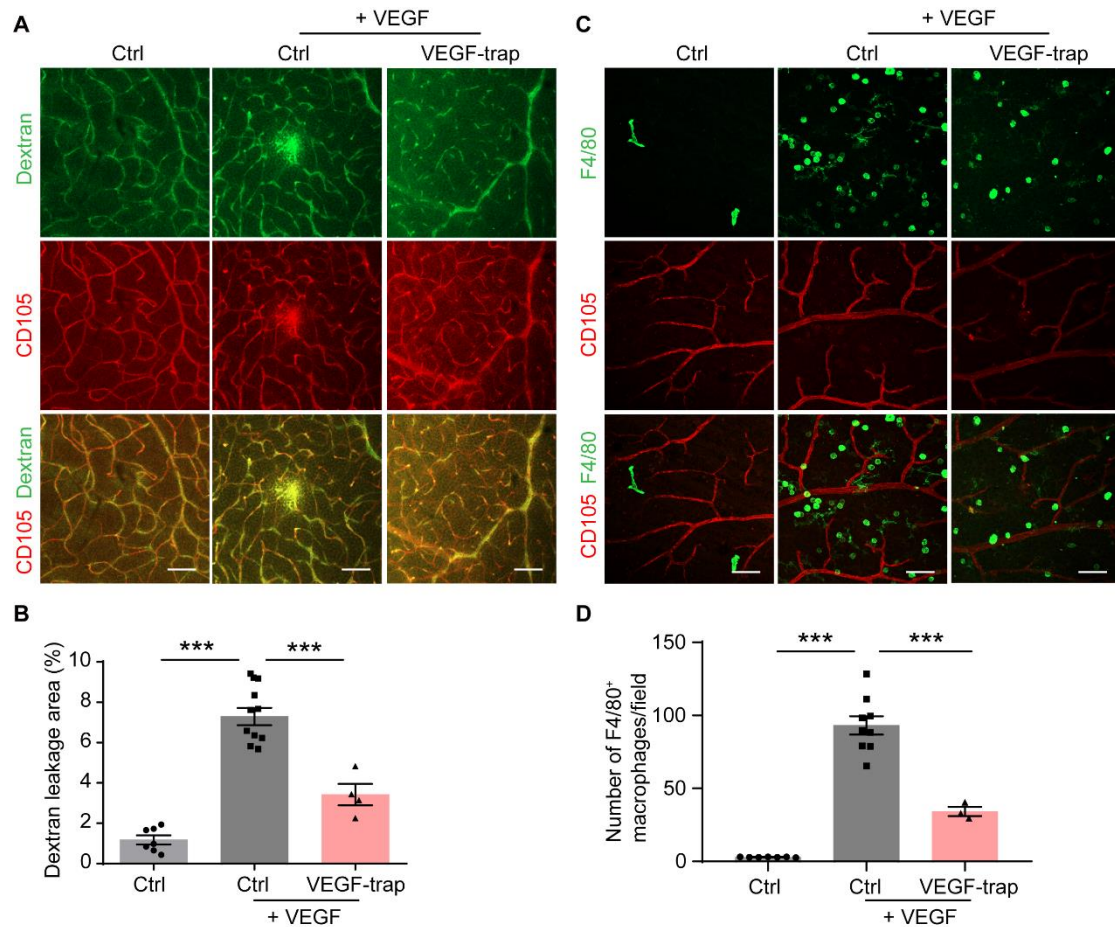


Figure S5. VEGF-trap suppresses VEGF-induced vascular leakage *in vivo*.

(A) VEGF-trap (15 μ g; 1.5 μ L of 10 mg/mL Conbercept) was intravitreally injected into adult mice. 100 ng VEGF was then intravitreally injected to induce vascular leakage in the retina as performed in Figure 5A. 24 h after VEGF administration, FITC-dextran was injected and the retinas were dissected. Representative images of flat-mounted retina showing extravasated FITC-dextran and CD105⁺ vessels.

(B) Quantification of dextran leakage of (A) (n= 4 - 10 mice per condition).

(C) Representative images of retinas treated as in (A) immunostained for macrophage (F4/80) and blood vessels (CD105).

(D) Quantification of macrophage infiltration of (C) (n= 3 - 9 mice per condition).

The data represent as mean \pm SEM. ***p < 0.001, one-way ANOVA followed by Tukey's multiple comparisons test in (B), (D).

Scale bars, 50 μ m.

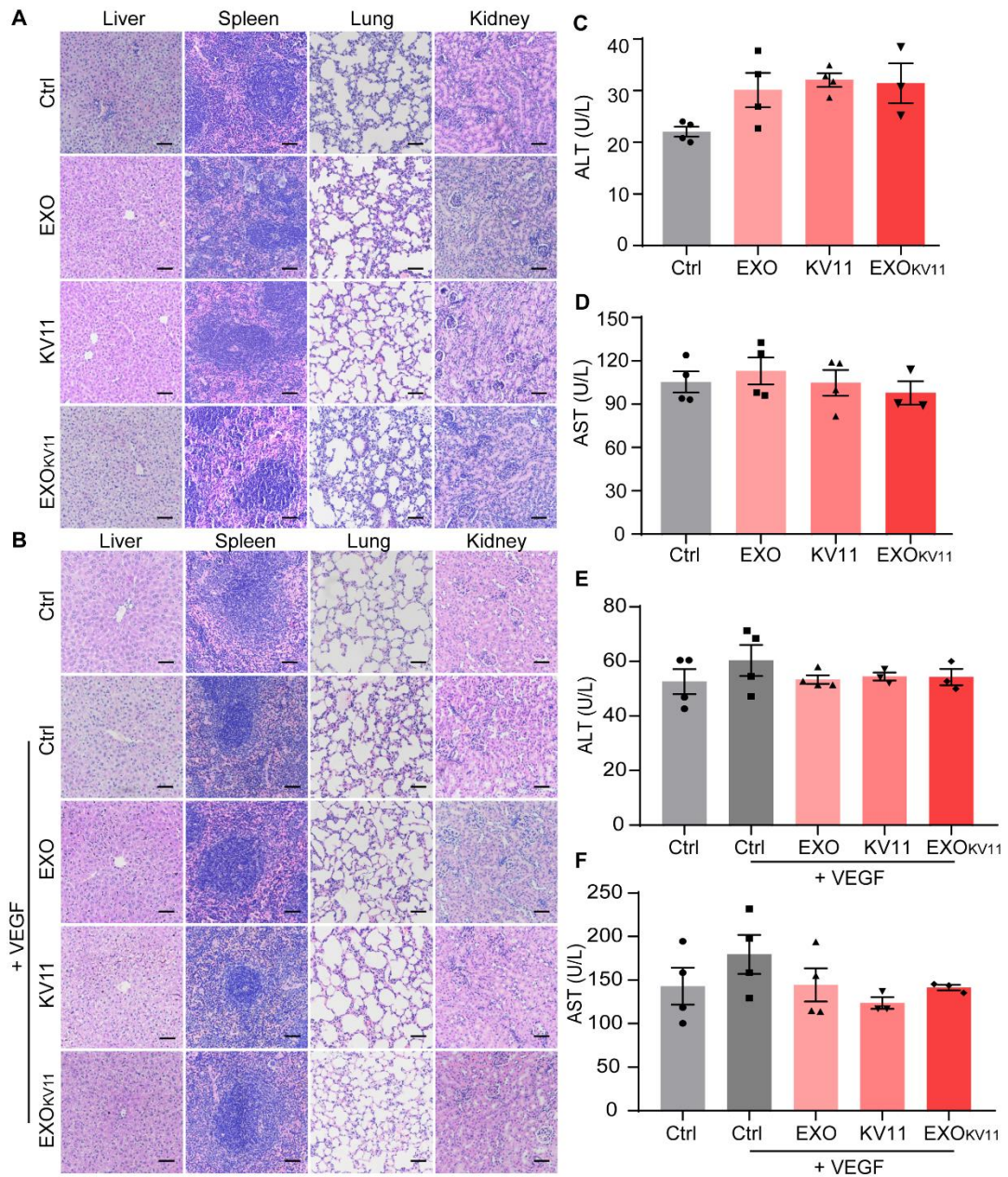


Figure S6. Assessment of organ toxicity in EXO_{KV11}-treated mice.

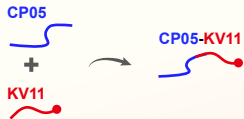
(A and B) Representative images of hematoxylin and eosin staining of tissue sections from saline-treated controls (Ctrl), EXO-, KV11-, or EXO_{KV11}-treated mice in the OIR at P17 (A) and pre-treated VEGF-induced vascular leakage model at indicated endpoint (B).

(C, D, E and F) Measurement of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity in mice treated as in (A and B)

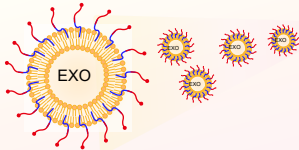
The data represent as mean \pm SEM, one-way ANOVA followed by Tukey's multiple comparisons test in (E), (F), (G), (H).

Scale bars, 50 μ m.

Conjugation



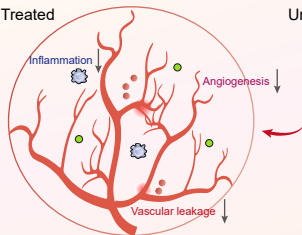
Incubation



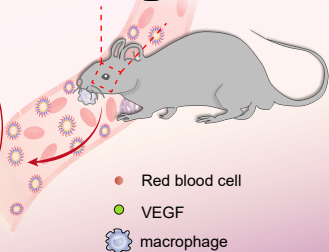
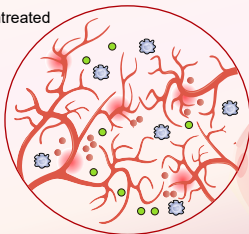
Retro-orbital injection



Treated



Untreated



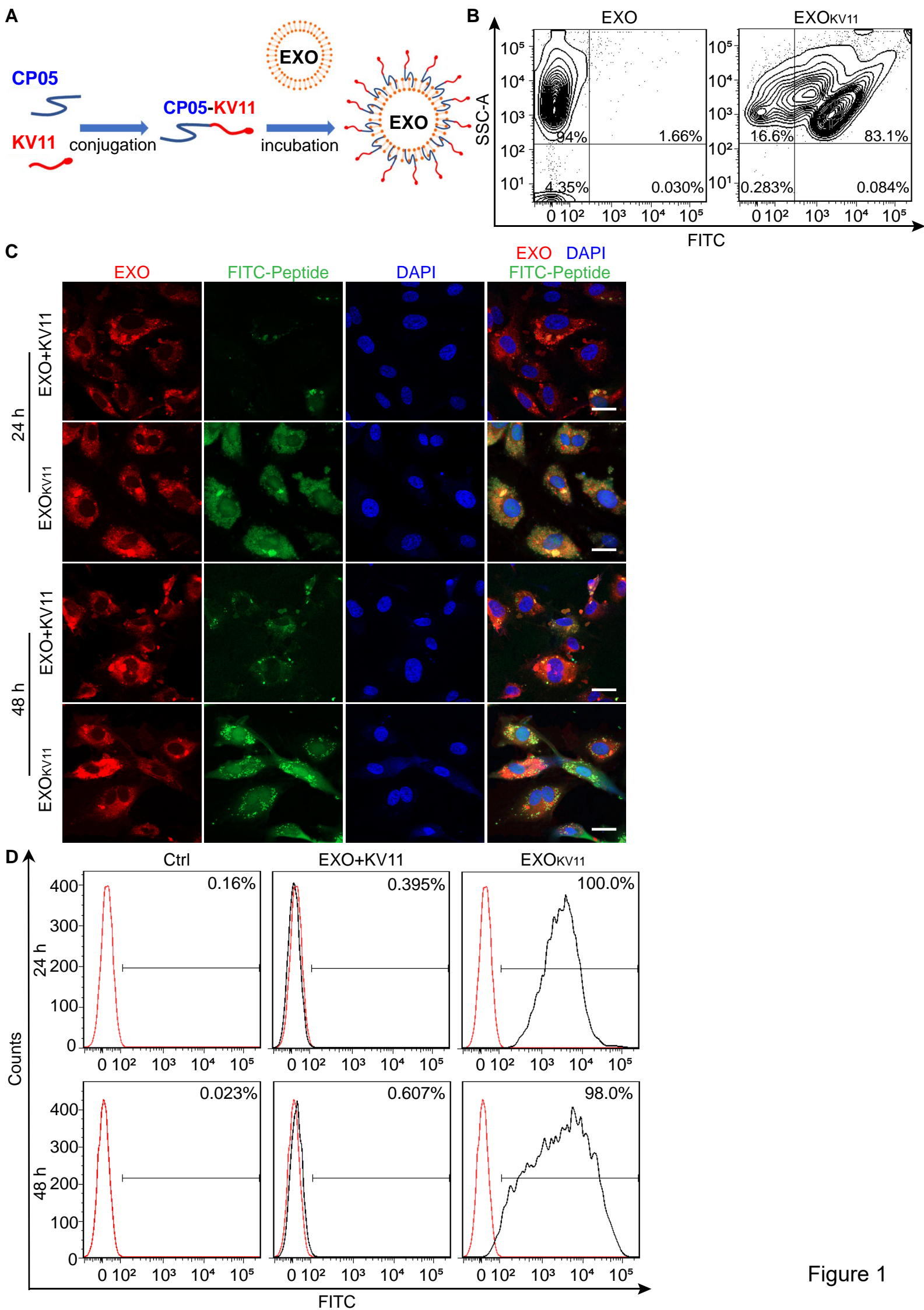


Figure 1

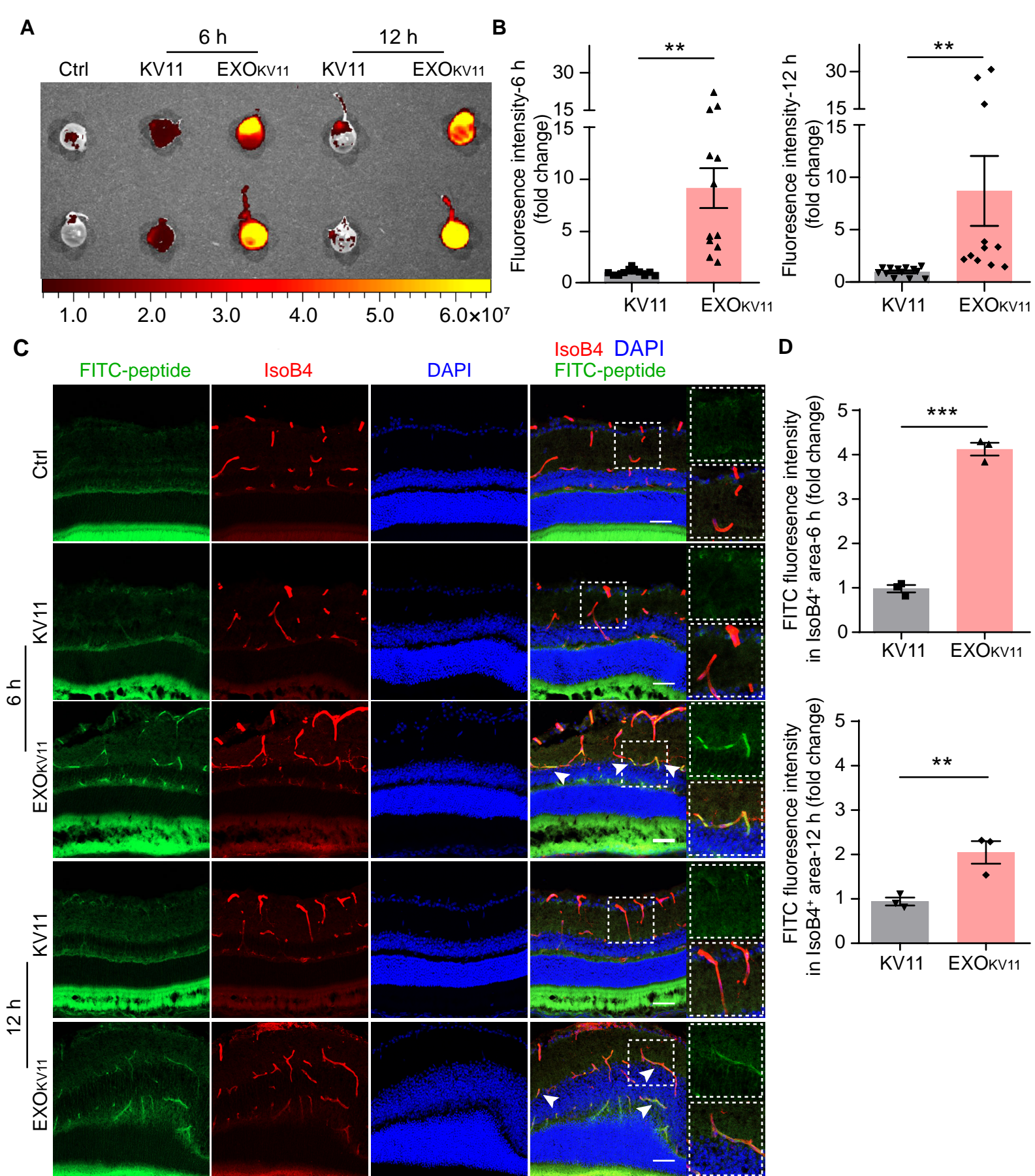


Figure 2

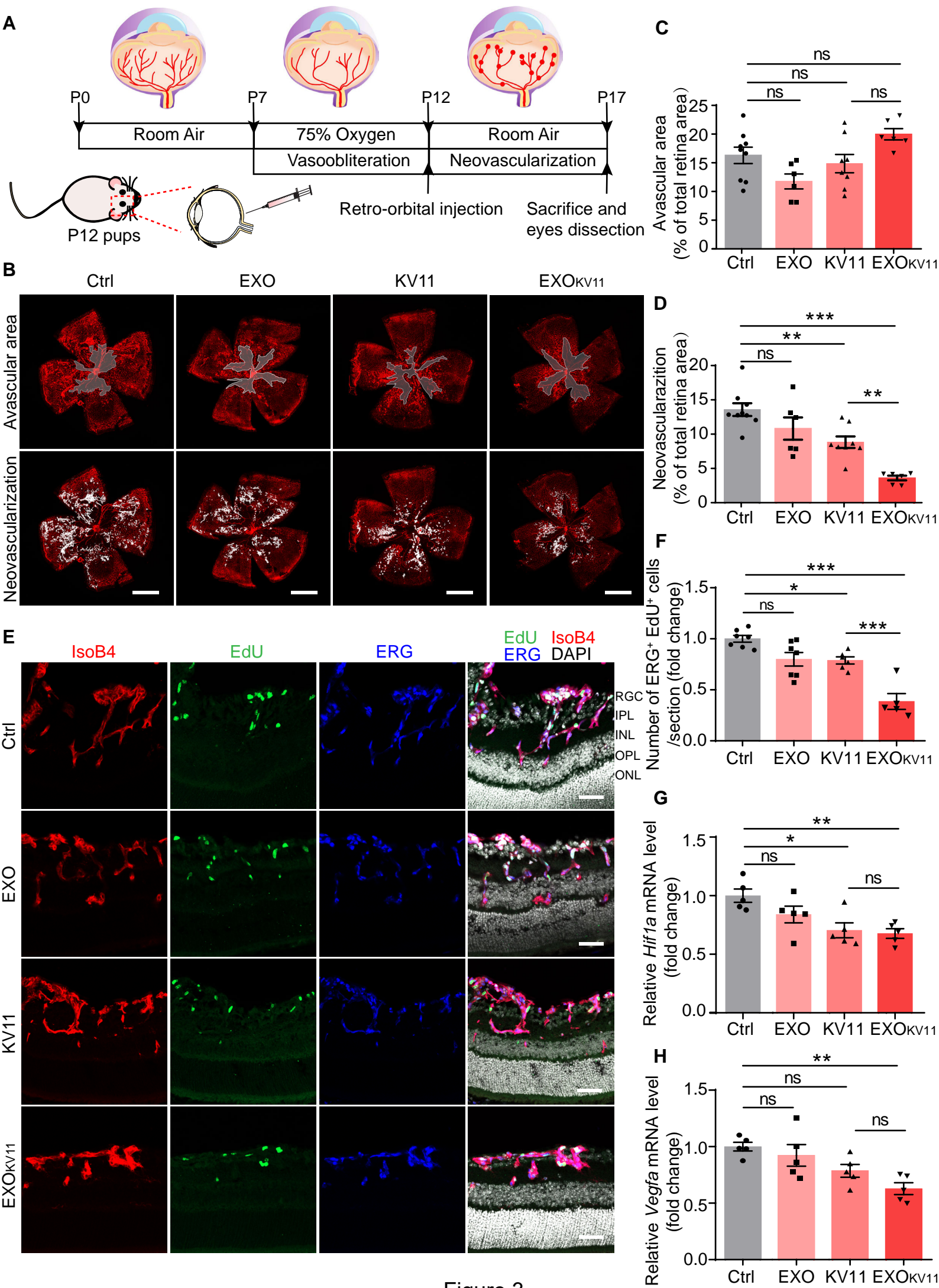


Figure 3

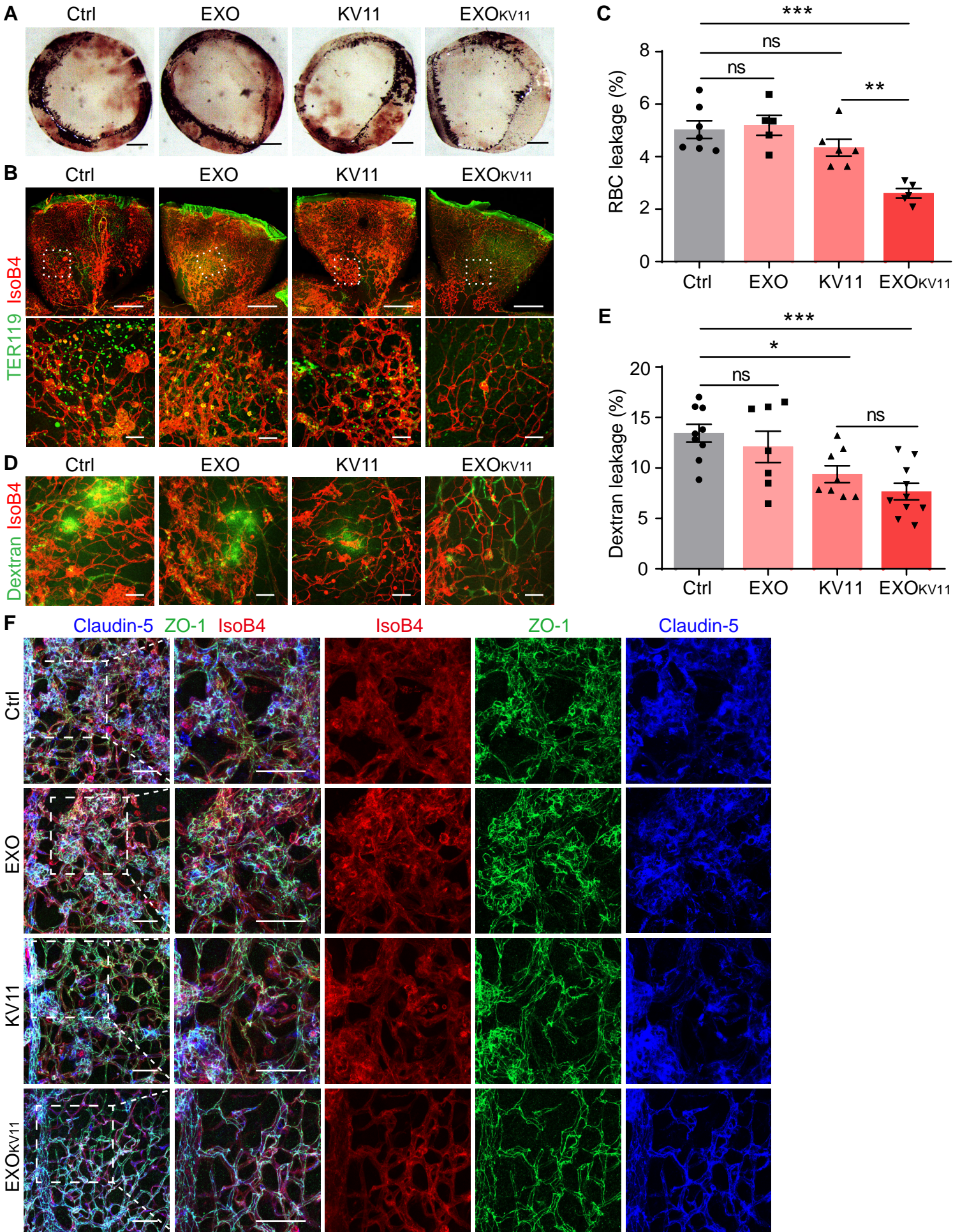


Figure 4

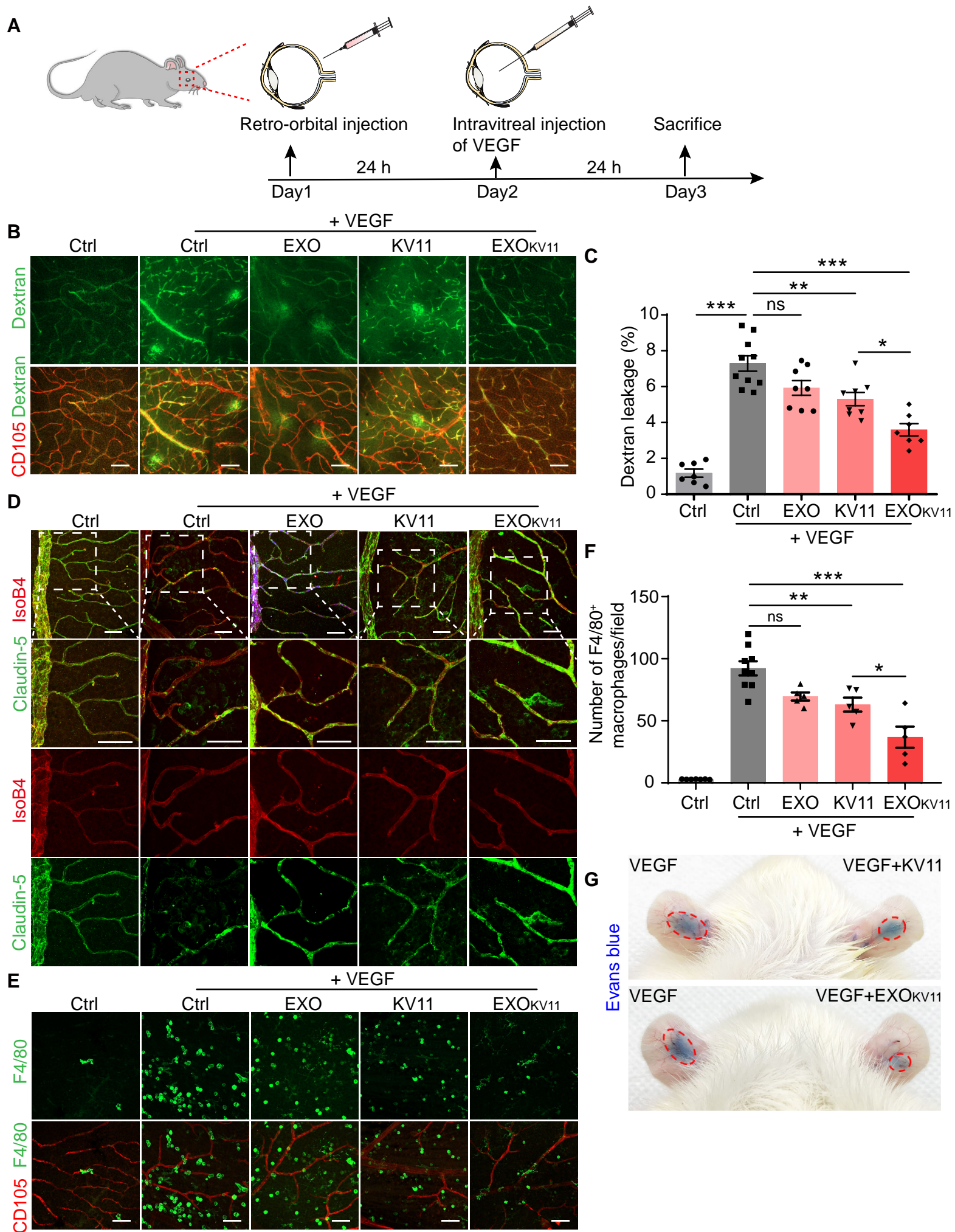


Figure 5

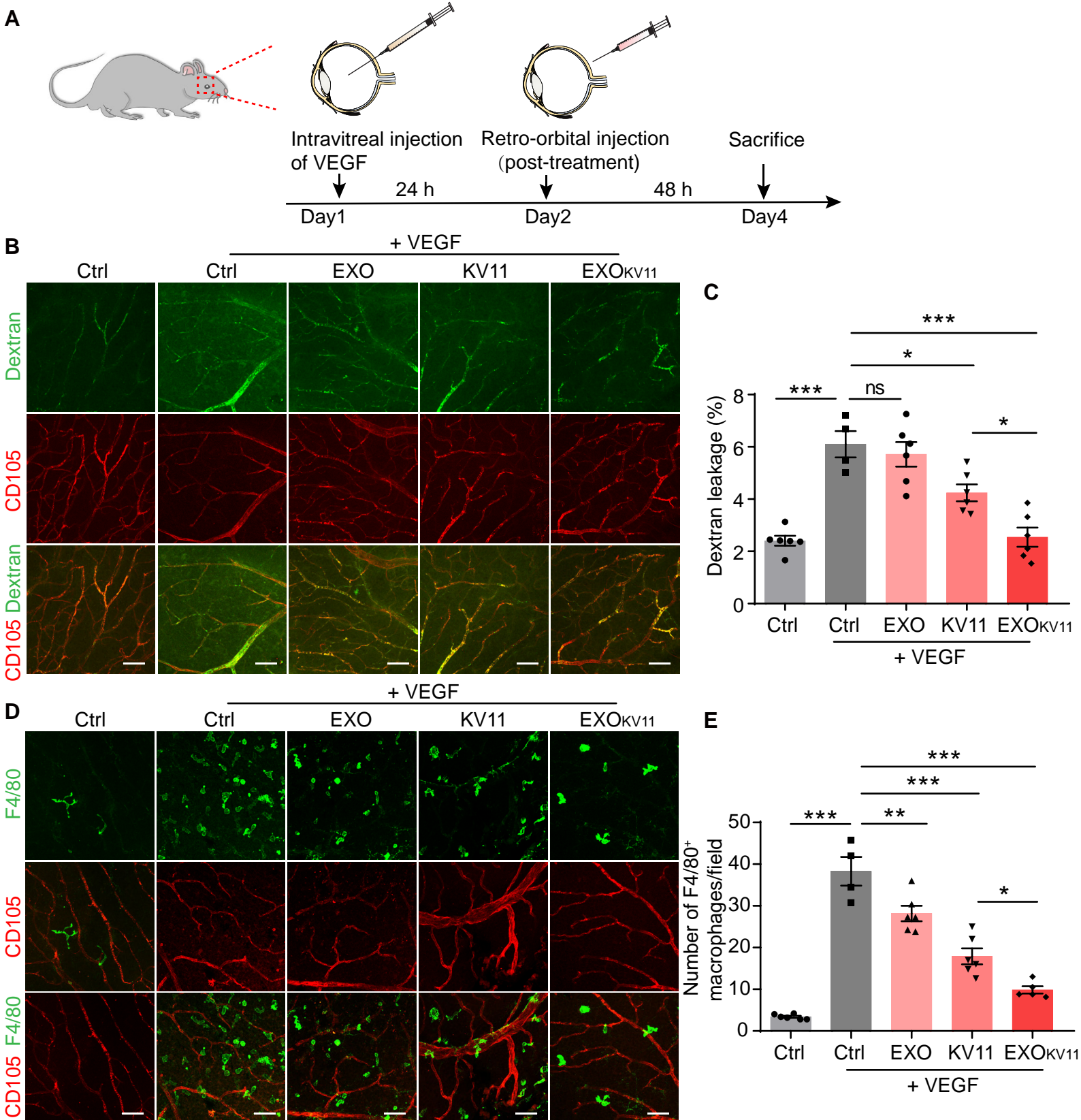


Figure 6

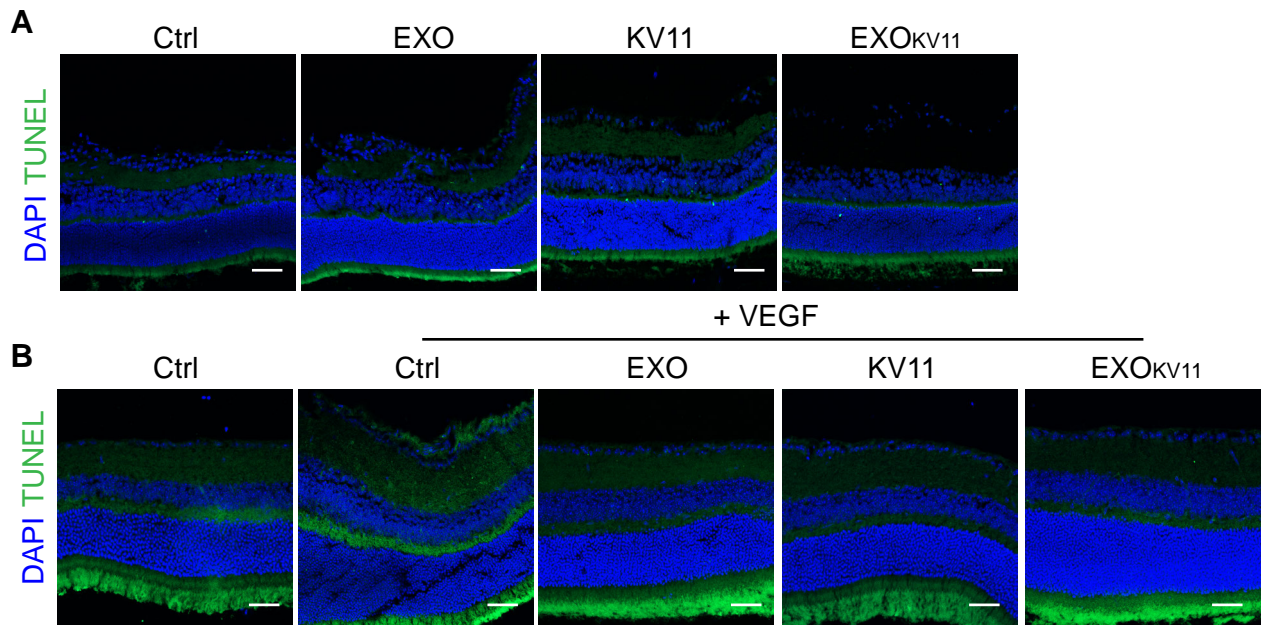


Figure 7

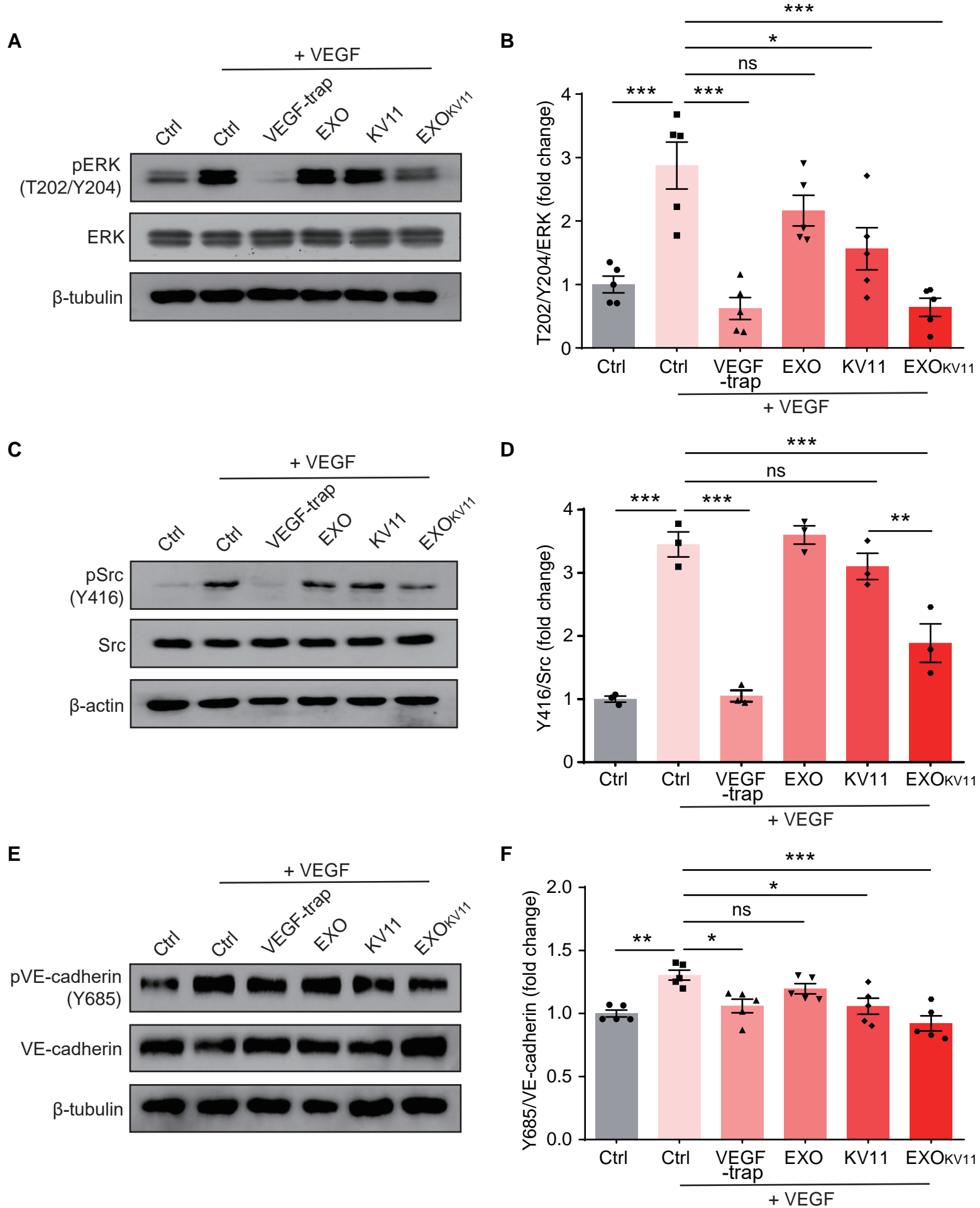


Figure 8

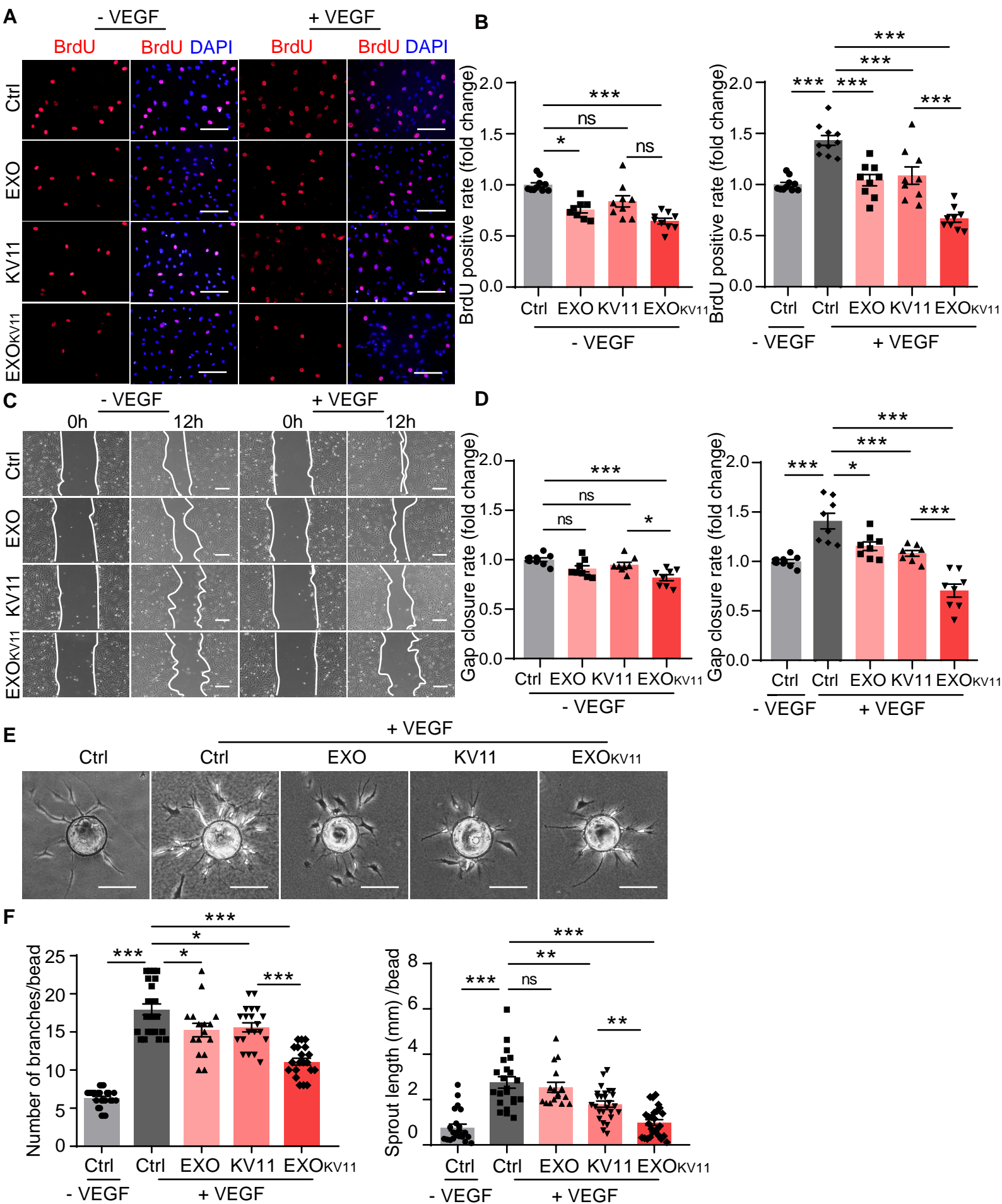


Figure 9

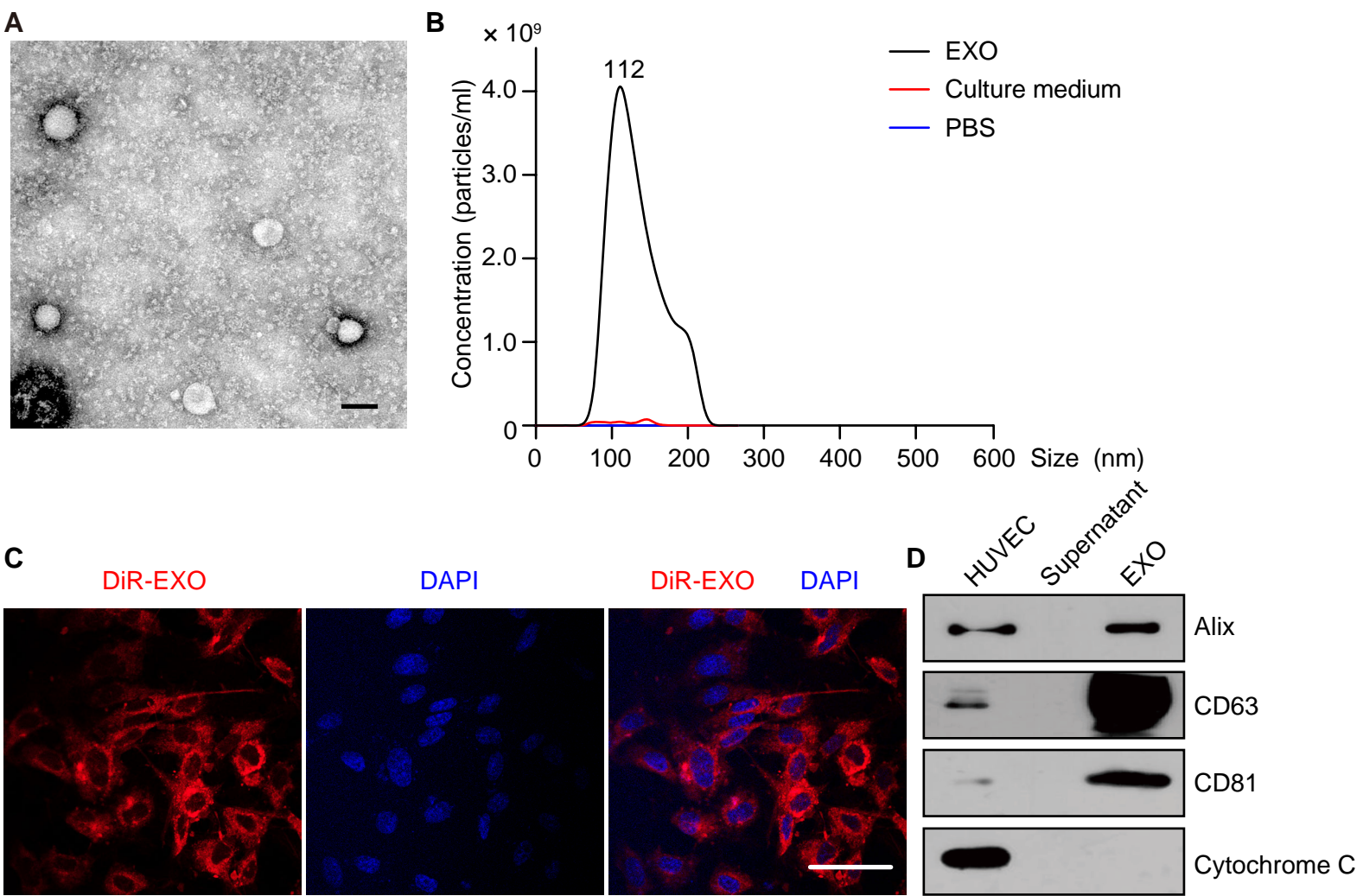


Figure S1

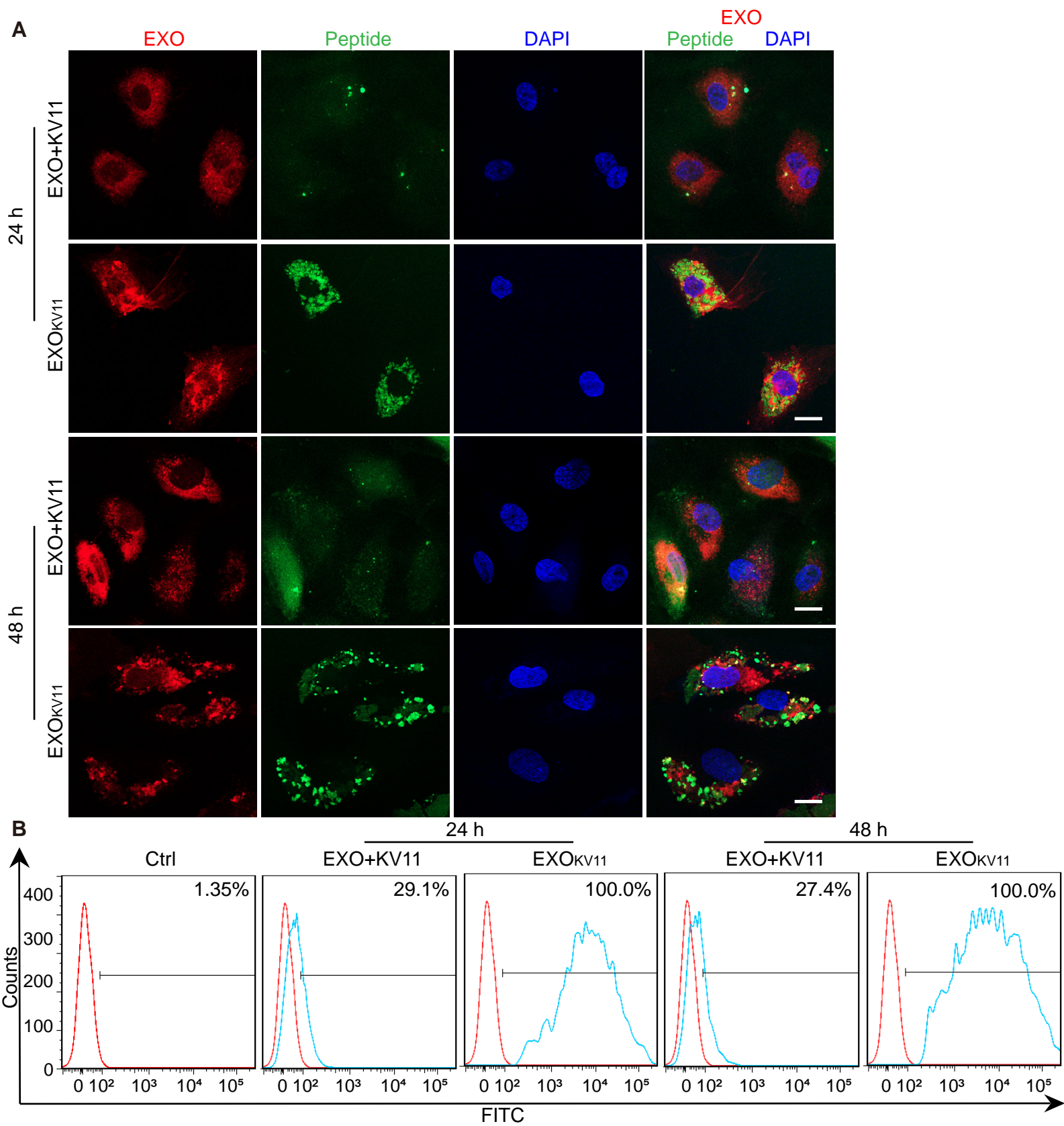


Figure S2

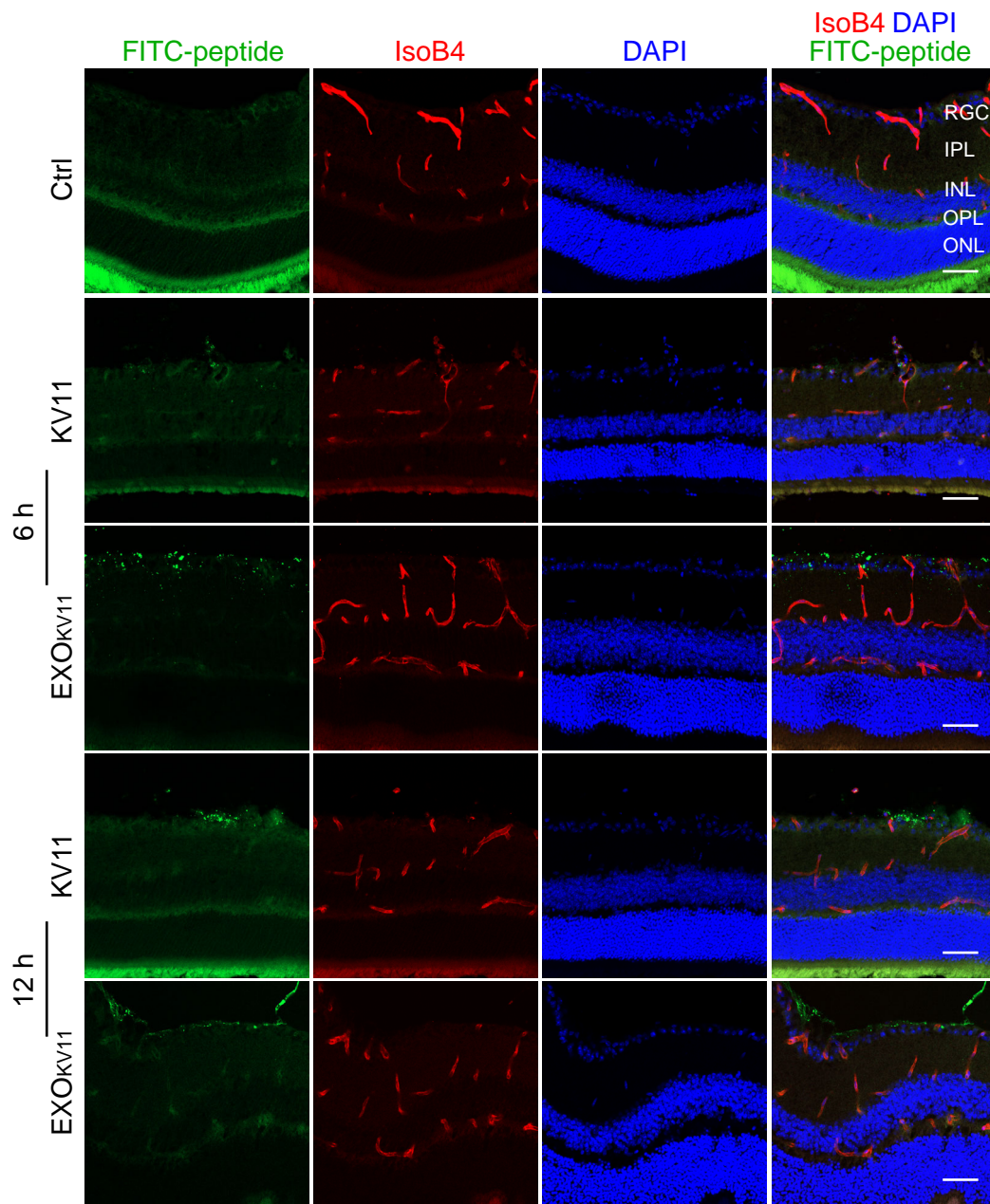


Figure S3

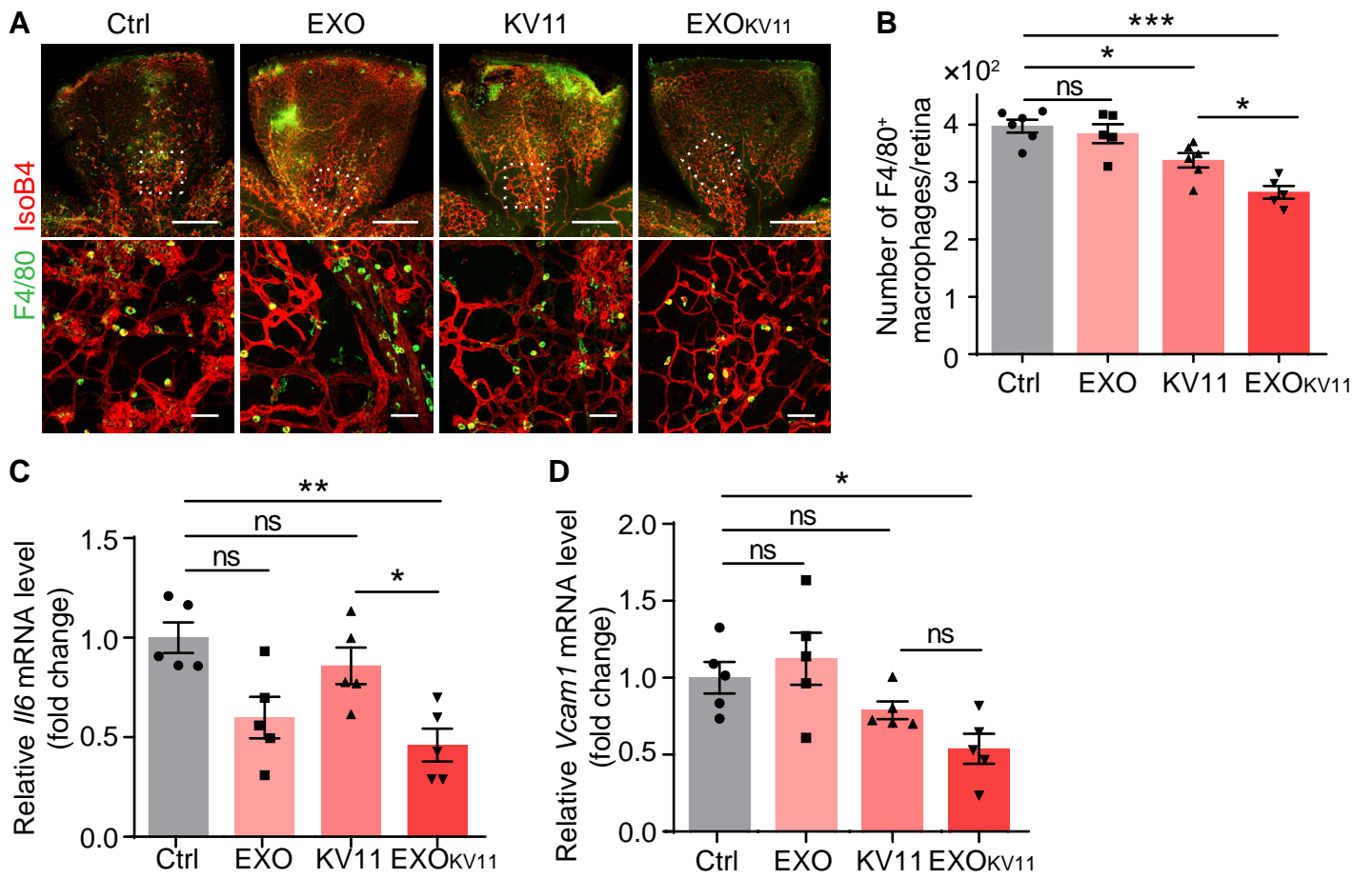


Figure S4

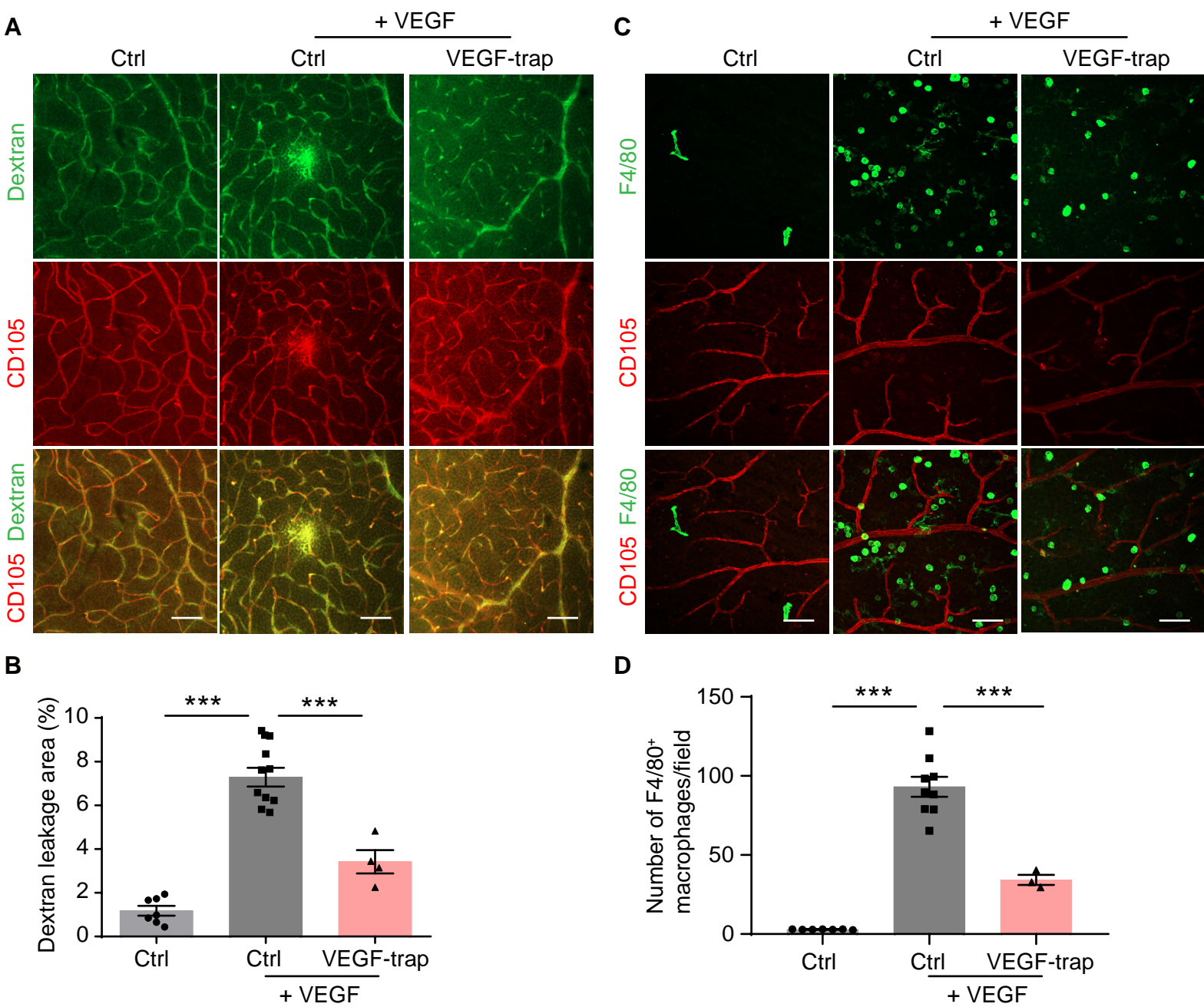


Figure S5

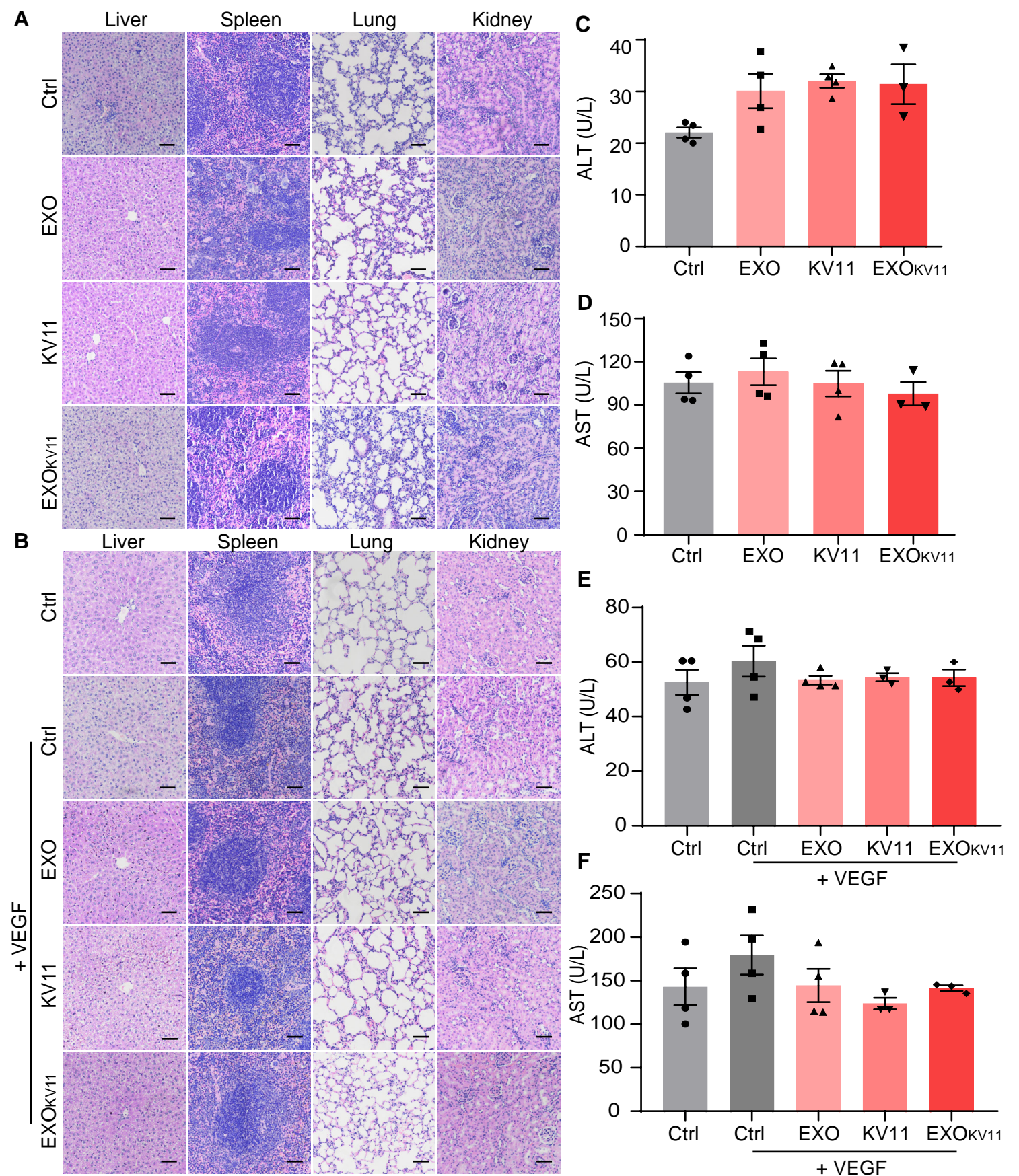


Figure S6