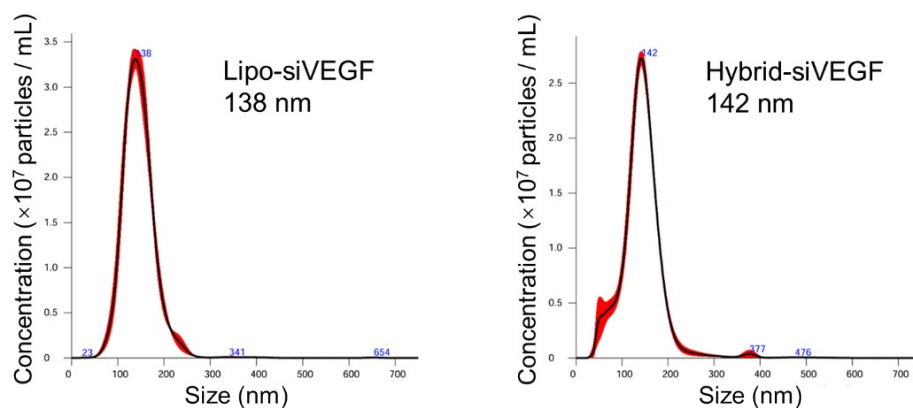
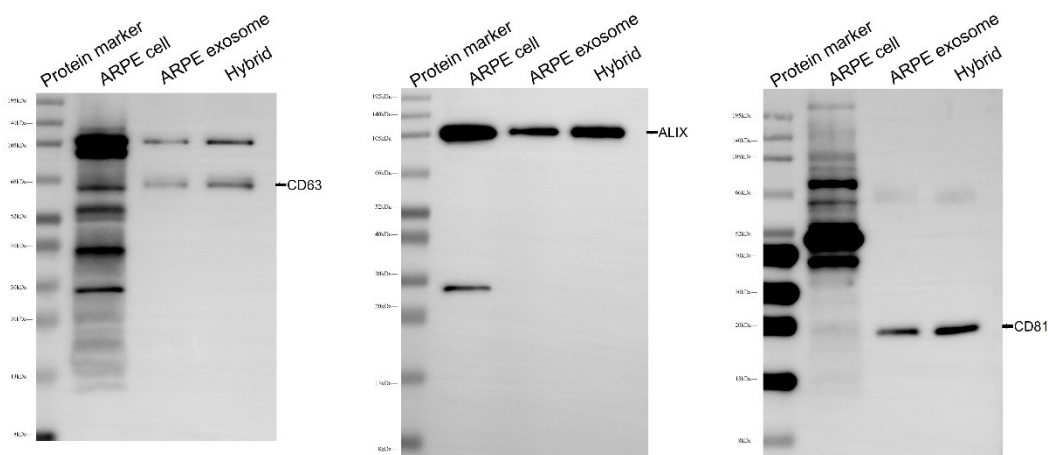


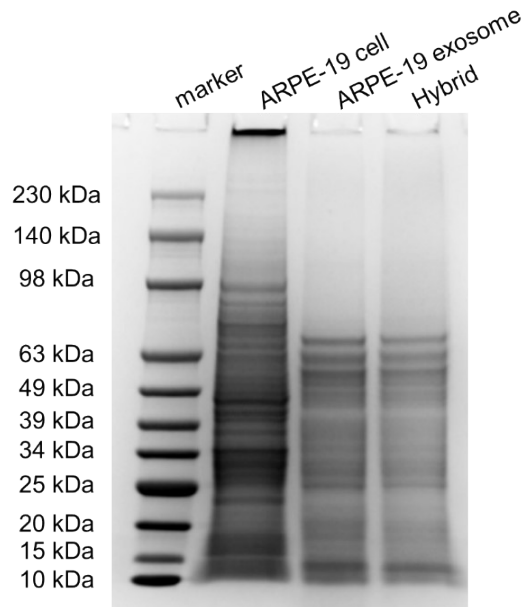
## Retina-targeted siRNA delivery via exosome-liposome hybrid vesicles for AMD treatment



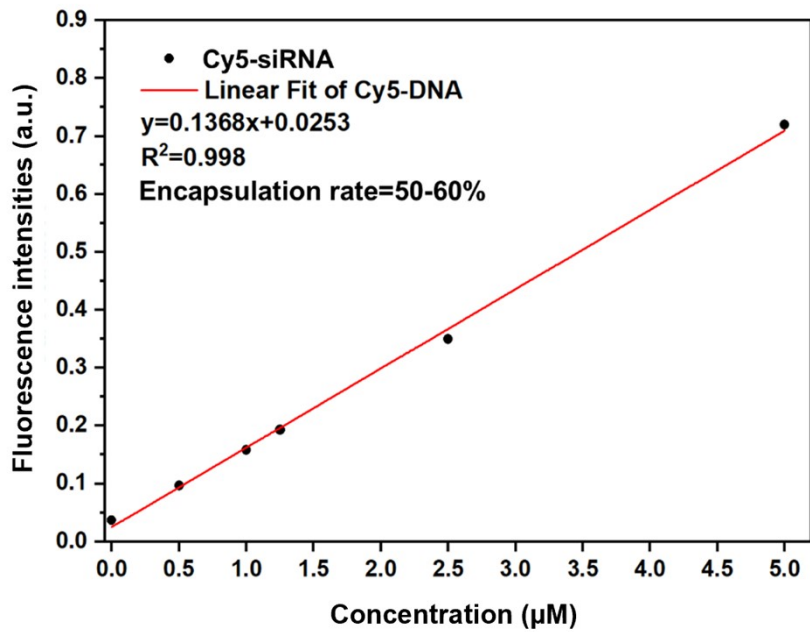
**Fig. S1** NTA analyses of Lipo-siVEGF and Hybrid-siVEGF vesicles.



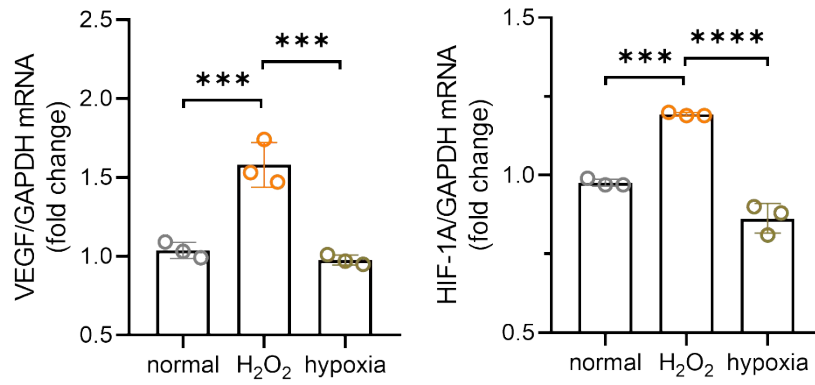
**Fig. S2** Uncropped western blot gel images used in Figure 1E where western blot analysis confirmed the presence of exosomal markers (ALIX, CD63, and CD81) in ARPE-19-derived exosomes



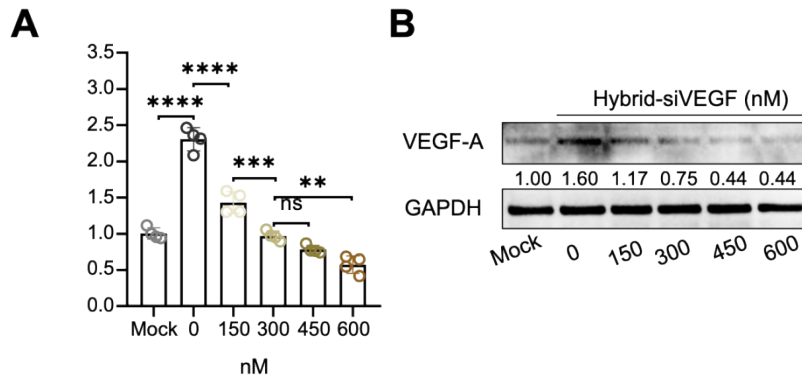
**Fig. S3** The results of Coomassie brilliant blue staining of ARPE-19 cell, ARPE-19 exosomes, and Hybrid samples.



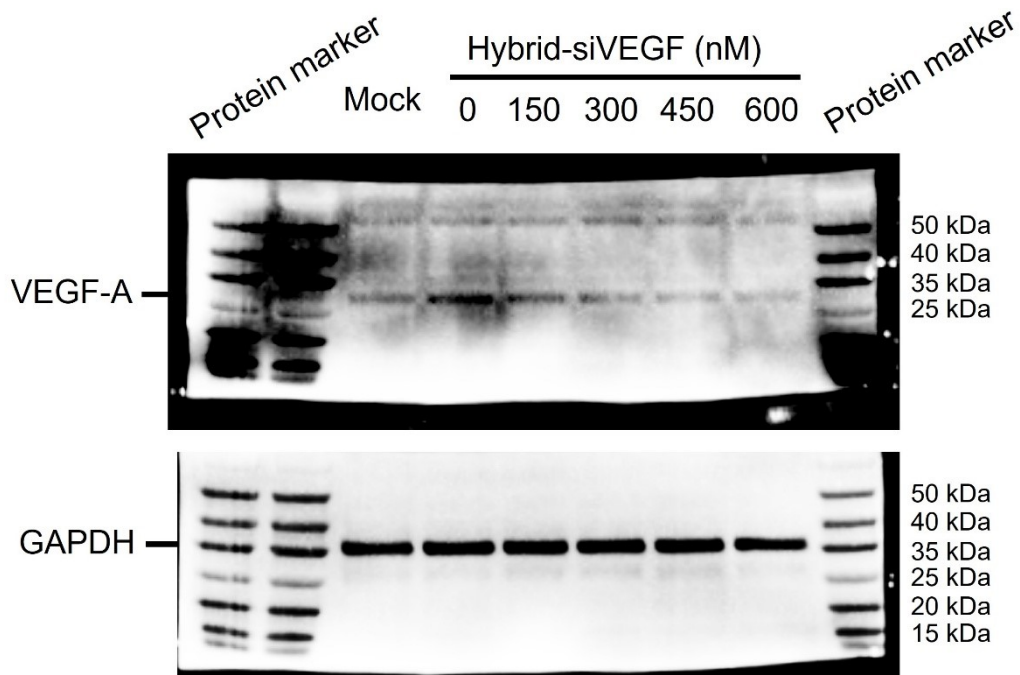
**Fig. S4** Standard curve of Cy5-modified siRNA and encapsulation rate of the Hybrid vesicles.



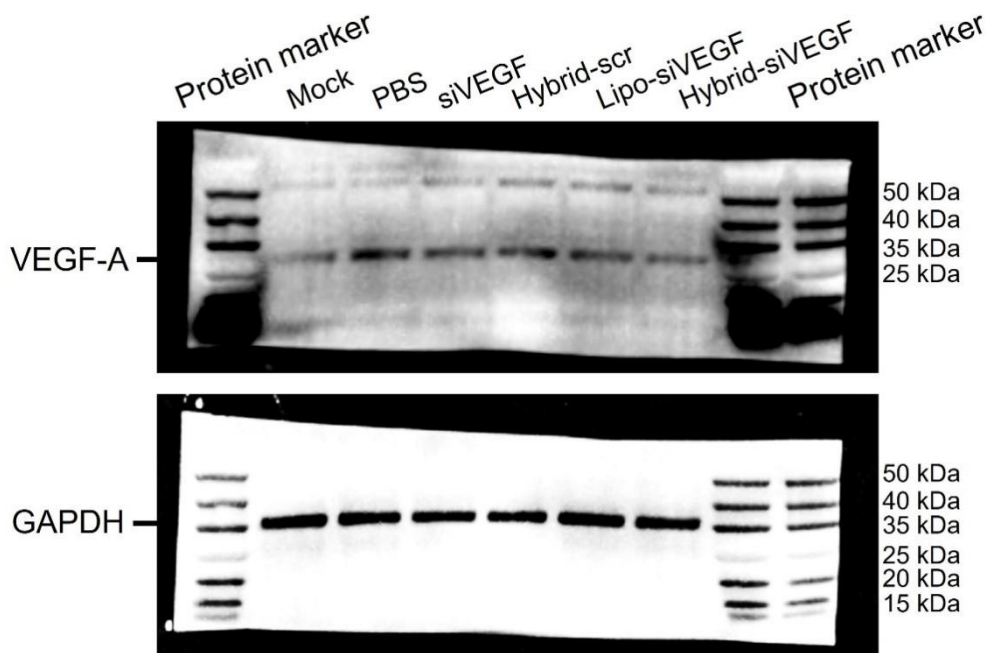
**Fig. S5** The qRT-PCR results of VEGF and HIF-1A mRNA expression in ARPE-19 cells stimulated with 200  $\mu$ M H<sub>2</sub>O<sub>2</sub> or under hypoxia condition for 6 h (n=3).



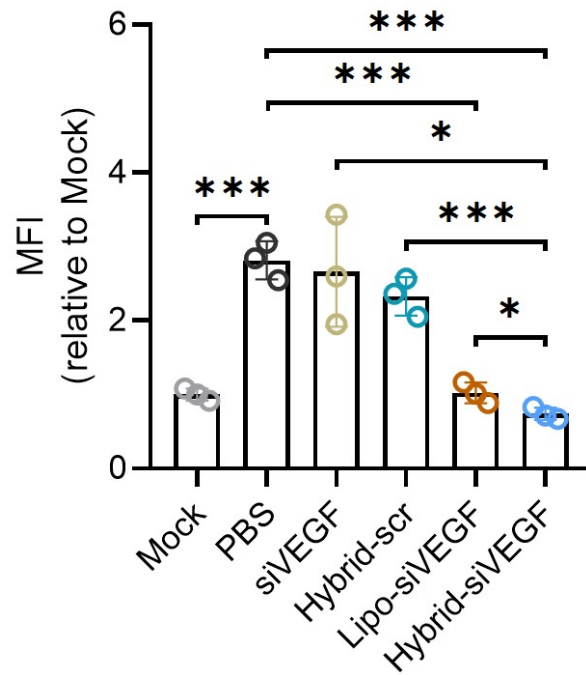
**Fig. S6** (A) qRT-PCR and (B) WB analysis of VEGF-A expression in ARPE-19 cells treated with different concentrations of Hybrid-siVEGF (n = 4).



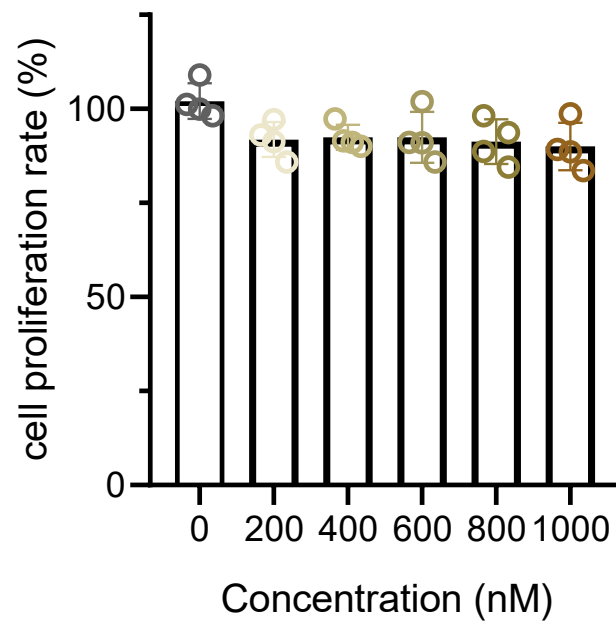
**Fig. S7** Uncropped western blot gel images used in Figure 3B, in which the increase of Hybrid-siVEGF concentrations progressively downregulates the VEGF-A expression.



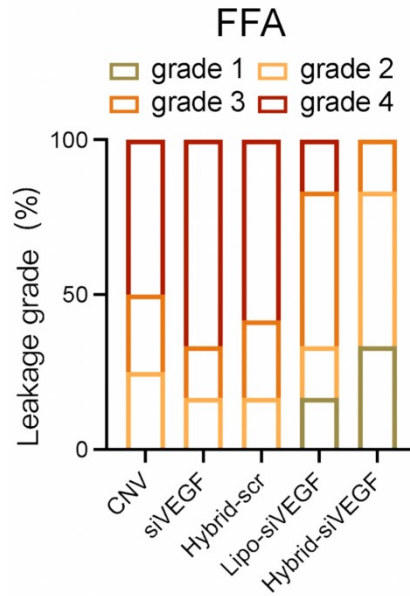
**Fig. S8** Uncropped western blot gel images used in Figure 3D, in which the Hybrid-siVEGF with 300 nM siRNA significantly silences the VEGF-A expression compare to those of control samples.



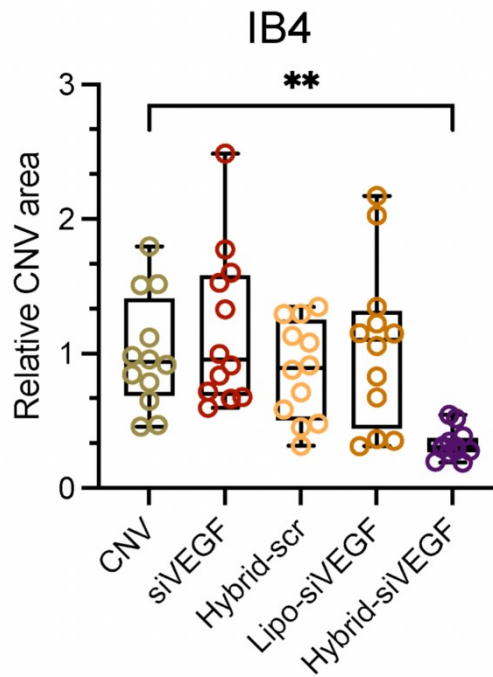
**Fig. S9** Semi-quantitative fluorescence intensity analysis using ImageJ, presented as mean  $\pm$  standard deviation (SD) from three independent images (n = 3).



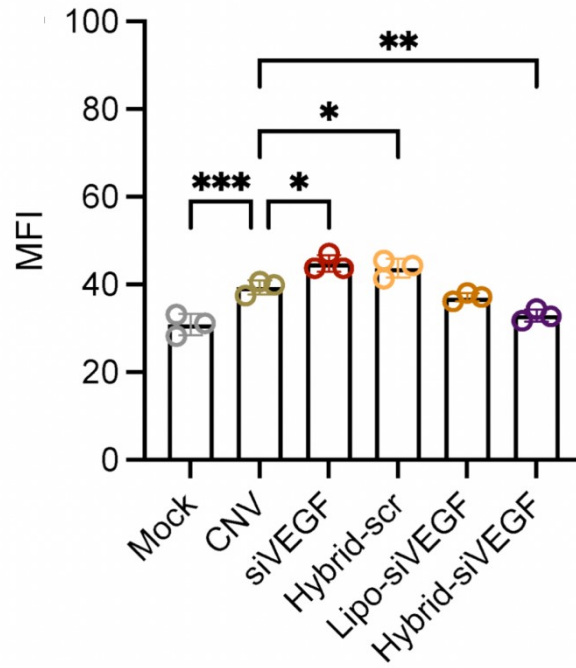
**Fig. S10** CCK-8 results of HCEC after incubated with different concentrations of Hybrid-siVEGF for 24 h (n=4).



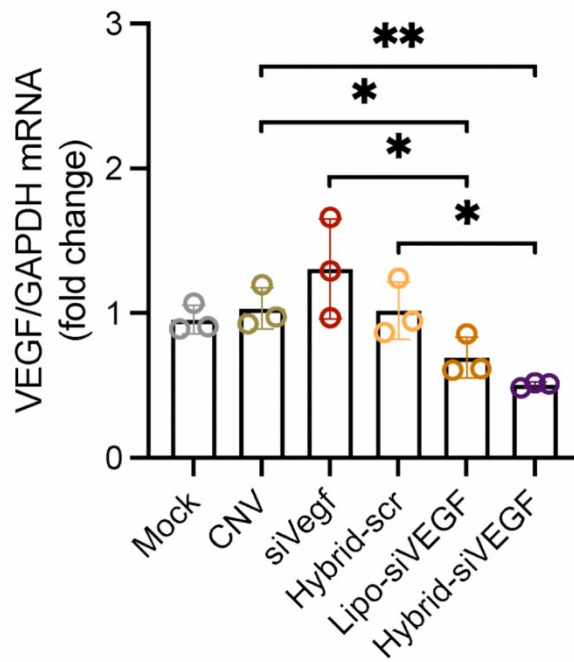
**Fig. S11** Quantification of leakage scores of FFA images at day 7 post-laser induction (n=12).



**Fig. S12** Corresponding quantitative analysis of neovascular area of IB4 staining of RPE-choroid flat mounts (n=12).



**Fig. S13** Quantitative analysis of VEGF-A fluorescence intensity, presented as mean  $\pm$  standard deviation (SD) (n=3).



**Fig. S14** Relative retinal VEGF-A mRNA expression detected by qRT-PCR, confirming the silencing efficiency of Hybrid-siVEGF (n=3).

**Table S1** Sequence information of siRNA and DNA primers used in this work.

RNA/DNA name	Sequences from 5' to 3'
h-VEGF-sen	mG*mG*mAmGfUmAfCfCfCmUmGmAmUmGmAmGmAmUmC*m U*mU
VEGF-scr-sen	mA*mC*mGmCfGmUfAfAfCmGmCmGmGmGmAmAmUmUmU*m U*mU
h-VEGF-anti	mG*fA*mUmCmUfCmAfUfCmAmGmGmGfUmAfCmUmCmC*mU* mU
VEGF-scr-anti	mA*fA*mAmUmUfCmCfCfGmCmGmUmUfAmCfGmCmGmU*mU* mU
m-VEGF-sense	mA*mU*mGmUfGmAfAfUfGmCmAmGmAmCmCmAmAmAmGmA mA*mU*mU
m-VEGF-anti	mU*fU*mCmUmUfUmGfGfUmCmUmGmCfAmUfUmCmAmCmAm U*mU*mU
hVEGF-Forward	AGGAGGGCAGAATCATCAG
hVEGF-Reverse	CAAGGCCACAGGGATTTTCT
hGAPDH- Forward	CAGGAGGCATTGCTGATGAT
hGAPDH- Reverse	CAAGGCCACAGGGATTTTCT
hHIF1A- Forward	ATCCATGTGACCATGAGGAAATG
hHIF1A- Reverse	TCGGCTAGTTAGGGTACACTTC
mVEGF-Forward	GCAGCTTGAGTTAAACGAACG
mVEGF-Reverse	GGTTCCCGA AACCTGAG
mGAPDH- Forward	GGTTGTCTCCTGCGACTTCA
mGAPDH- Reverse	TGGTCCAGGGTTTCTTACTCC

<sup>1</sup> m in the sequences indicates 2'-O-methylation (2'-OMe) modification, f indicates 2'-fluoro-deoxyribonucleotide (2'-F) modification and \* indicates phosphorothioate (PS) backbone modification.

<sup>2</sup> h in the name indicates human and m represents mouse.