Supplementary materials for

Universal Cell Membranes Camouflaged Nano-Prodrug with Right-Side-Out Orientation Adapting for the Positive Pathological Vascular Remodeling in Atherosclerosis

Xian Qin<sup>1,2,3,&</sup>, Li Zhu<sup>1,&</sup>, Yuan Zhong<sup>1</sup>, Yi Wang<sup>5</sup>, Xiaoshan Luo<sup>6</sup>, Jiawei Li<sup>2,3</sup>, Fei Yan<sup>2</sup>, Guicheng Wu<sup>2</sup>, Juhui Qiu<sup>1</sup>, Guixue Wang<sup>1,4</sup>, Kai Qu<sup>1,2,3,\*</sup> Kun Zhang<sup>1,2,3,\*</sup> Wei Wu<sup>1,4,\*</sup>

<sup>1</sup>Key Laboratory for Biorheological Science and Technology of Ministry of Education, State and Local Joint Engineering Laboratory for Vascular Implants, Bioengineering College of Chongqing University, Chongqing, 400030, China.

<sup>2</sup>Chongqing University Three Gorges Hospital, Chongqing Municipality Clinical Research Center for Endocrinology and Metabolic Diseases, Chongqing, 404000, China.

<sup>3</sup>School of Medicine, Chongqing University, Chongqing, 404010, China.

<sup>4</sup>JinFeng Laboratory, Chongqing, 401329, China.

<sup>5</sup>College of Basic Medical Sciences, Chongqing Medical University, Chongqing, 400016, China.

<sup>6</sup>College of Information Engineering, Guizhou Engineering Science University, Bijie, 551700, China



Supplementary Figure. 1 The synthesis of ETBNPs.



Supplementary Figure. 2 <sup>1</sup>H NMR spectrum of **a**, Mal-PEG<sub>2K</sub>-ETB-PEG<sub>2K</sub>-Mal, and **b**, PS-Mal-PEG<sub>2K</sub>-ETB-PEG<sub>2K</sub>-Mal-PS. **c**, <sup>13</sup>C NMR spectrum of PS-Mal-PEG<sub>2K</sub>-ETB-PEG<sub>2K</sub>-Mal-PS.



Supplementary Figure. 3 GPC traces of PS-Mal-PEG<sub>2K</sub>-ETB-PEG<sub>2K</sub>-Mal-PS.



**Supplementary Figure. 4** Proteins in OEC, OEM, and OEM-ETBNPs were characterized by SDS-PAGE.



Supplementary Figure. 5 DLS raw data of a, ETBNPs, b, EM-ETBNPs, and c, OEM-ETBNPs (n = 3).



Supplementary Figure. 6 a, Hydrodynamic diameter of ETBPD, EM-ETBPD, and OEM-ETBPD. b, Zeta potentials of ETBPD, EM-ETBPD, and OEM-ETBPD (n = 3).



**Supplementary Figure. 7 a**, Polydispersity index of ETBNPs, EM-ETBNPs, and OEM-ETBNPs. **b**, Polydispersity index of ETBPD, EM-ETBPD, and OEM-ETBPD (n = 3).



**Supplementary Figure. 8** The stability of free ETB, EM-ETBPD, OEM-ETBPD, EM-ETBNPs, and OEM-ETBNPs in **a**, PBS and **b**, 10% serum (n = 3).



Supplementary Figure. 9 Emission spectra of a, probe-OEM-ETBNPs and probe-OEM-ETBPD, c, probe-EM-ETBNPs and probe-EM-ETBPD, e, probe-RBC-ETBNPs and probe-RBC-ETBPD, probe-MC-ETBNPs and probe-MC-ETBPD, i, g, probe-LC-ETBNPs and probe-LC-ETBPD, k, probe-SMC-ETBNPs and probe-SMC-ETBPD in PBS before and after adding ssDNA quencher under excitation at 480 nm, and b, d, f, h, j, l quantifying the membrane right-side-out orientation of a, c, e, g, i, k with FRET. Data shown as mean  $\pm$  SD. Statistical analysis: Student's *t*-test, n = 8. \*\*\*P < 0.0001.



**Supplementary Figure. 10** <sup>1</sup>H NMR spectrum of PS-Mal-PEG<sub>2K</sub>-ETB-PEG<sub>2K</sub>-Mal-PS with or without  $H_2O_2$ , the drug release before and after  $H_2O_2$  treatment was marked with a red dotted box. The blue line represented PS-Mal-PEG<sub>2K</sub>-ETB-PEG<sub>2K</sub>-Mal-PS with  $H_2O_2$ , The black line represented PS-Mal-PEG<sub>2K</sub>-ETB-PEG<sub>2K</sub>-Mal-PS without  $H_2O_2$ .



Supplementary Figure. 11 Cell viability of **a**, SMCs and **b**, MCs after incubation with formulations for 24 h. Data shown as mean  $\pm$  SD. Statistical analysis: one-way ANOVA with Tukey's post-hoc test, n = 3. For **a**, \*\*\*P < 0.0001, \*P = 0.0367. For **b**, \*\*\*P < 0.0001.



**Supplementary Figure. 12** Images of the hemolysis and quantification analysis measured at 545 nm (n = 3).



Supplementary Figure. 13 High density lipoprotein efflux treated by formulations. Data shown as mean  $\pm$  SD. Statistical analysis: one-way ANOVA with Tukey's post-hoc test, n = 5. \*\*\*P < 0.0001.

## DAPI/Lysosome



Supplementary Figure. 14 Lysosome staining was treated with blank, saline and OEM-ETBNPs (n = 5, scale bar: 50 µm).



Supplementary Figure. 15 a, Quantification analysis of the fluorescence intensity of Vimentin. b, Quantification analysis of the fluorescence intensity of SM22 $\alpha$ . c, Quantification analysis of the fluorescence intensity of iNOS. d, Quantification analysis of the fluorescence intensity of ARG1. Data shown as mean  $\pm$  SD. Statistical analysis: one-way ANOVA with Tukey's post-hoc test, n = 5. For a, \*\*\*P < 0.0001. For b, \*\*\*P < 0.0001. For c, \*\*\*P < 0.0001.



Supplementary Figure. 16 Expression of TNF- $\alpha$ , IL-6, and IL-1 $\beta$  in MFCs after treatment with formulations. Data shown as mean  $\pm$  SD. Statistical analysis: one-way ANOVA with Tukey's post-hoc test, n=5. For **a**, \*\*\*P< 0.0001, \*\*P=0.0012. For **b**, \*\*\*P< 0.0001. \*P=0.039. For **c**, \*\*\*P< 0.0001. \*\*P=0.0024.



**Supplementary Figure. 17** GO analysis of all genes differentially expressed with or without OEM-ETBNPs treatment in **a**, SFCs and **b**, MFCs.



**Supplementary Figure. 18 a-b**, GSEA to analyze the signaling pathway between the model group and the OEM-ETBNPs group in SFCs. **c-d**, GSEA to analyze the signaling pathway between the model group and the OEM-ETBNPs group in MFCs.



Supplementary Figure. 19 a, Quantification analysis of whole blood in Figure 8b. b, Quantification analysis of aorta in Figure 8c. c, *Ex vivo* images of heart, lung, spleen, liver, and kidneys treated with free Cy5, Cy5-labled EM-ETBNPs, and OEM-ETBNPs in 12 h and 24 h. d-e, Quantification analysis of 12 h and 24 h in c. Data shown as mean  $\pm$  SD. Statistical analysis: (a-b, d-e) one-way ANOVA with Tukey's post-hoc test, n = 5. For a, \*\*\**P* < 0.0001. \**P* = 0.0291. For b, \*\*\**P* < 0.0001. For d, \*\*\**P* < 0.0001. For e, \*\*\**P* < 0.0001.



Supplementary Figure. 20 a, The body weight. b-d, WBC, RBC, ALP, ALT, BUN, and CK analysis of blood or serum from mice after various treatments for 1 month (n = 5).



**Supplementary Figure. 21** H&E stained sections of the major organs resected from mice subjected to treatment with formulations for 1 month (n = 5, scale bar: 500 µm).

Position	Chemical shift (δ, ppm)	Ingredient		
1				
2				
3	3.08~3.12			
4	4.86			
5				
6,6'	7.21~7.22			
7,7'	6.68			
8				
9		Ezetimibe		
10				
11,11'	7.23~7.26			
12,12'	7.01~7.14			
13				
14	1.05, 1.04			
15	1.03~1.94			
16	4.54			
17				
18,18'	7.21~7.23			
19,19'	7.01~7.14			
20				
21				
22	3.6~3.64	PEG		
-NH <sub>2</sub>				
+N <i>H</i> 3-	6.89~6.99	PS		
Ar				
CH <sub>3</sub> -	1.24~1.34	_		
-CH2-	0.85			

## Supplementary Table. 1 <sup>1</sup>H NMR chemical shift of PS-Mal-PEG<sub>2K</sub>-ETB-PEG<sub>2K</sub>-Mal-PS

Position	Chemical shift (δ, ppm)	Ingredient		
1				
2	166.85			
3	62.64			
4	64.29			
5	128.96~130.42			
6,6'	128.96~130.42			
7,7'	129.22			
8	129.1			
9	127.97			
10	128.2	Ezetimibe		
11,11'	128.96~130.42			
12,12'	118.91~120.39			
13	164.10~164.66			
14	27.64			
15	37.01			
16	72.39			
17	135.44			
18,18'	117.63~117.92			
19,19'	32.87			
20	164.10~164.66			
21				
22	72.39~73.05	PEG		
	128.96~130.42	PS		
Ar	117.63~117.92			
- <i>C</i> H <sub>2</sub> -NH-	41.84			
- <i>C</i> H <sub>2</sub> -NH <sub>2</sub> <sup>+</sup> -	48.06			
- <i>C</i> H <sub>2</sub> -	11.15	_		
$\equiv CH$	32.31			

Supplementary Table. 2 <sup>13</sup> C NMI	R chemical shift of PS-Mal-PEG <sub>2K</sub> -ETB-PEG <sub>2K</sub> -Mal-PS
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Raw data of SDS-PAGE



## Raw data of western blot







	TBPD. ETBPD BNPS E	TBNPS	
Blank Saline ETB EM-E	OEM-EM-E OEM-E	Vimentin	
		SM22α	
		β-actin	