

**Supplementary table 1. Sequences of primer, miR-221-3p inhibitor and its negative controls**

<b>Primers</b>	<b>Sequences (5'-3')</b>
<b>Primers for quantitative real-time PCR or RT-PCR</b>	
Hsa-miR-221-3p-Forward	GGGAGCTACATTGTCTGCTG
Hsa-miR-221-3p-Reverse	GAGAGGAGAGGAAGAGGGAA
Rno-miR-221-3p-Forward	GGGAGCTACATTGTCTGCTG
Rno-miR-221-3p-Reverse	GAGAGGAGAGGAAGAGGGAA
Cel-miR-39-3p Forward	GGGTCACCGGGTGTAATC
Cel-miR-39-3p Reverse	GAGAGGAGAGGAAGAGGGAA
Hsa-HIF-1 $\alpha$ Forward	GCAGCAACGACACAGAAA
Hsa-HIF-1 $\alpha$ Reverse	AGCGGTGGGTAATGGAG
GAPDH Forward	GAACGGGAAGCTCACTGG
GAPDH Reverse	GCCTGCTTCACCACCTTCT
<b>miR-221-3p inhibitor</b>	
miR-221-3p inhibitor	AGGAGACUCACAAGUCCUGC
miR-221-5p inhibitor negative control	CAGUACUUUUGUGUAGUACAAA

**Supplementary Table 2. Comparison of ecocardiographic parameters in each group**

<b>Parameters</b>	<b>PBS</b>	<b>NC-EVs</b>	<b>HIF-1<math>\alpha</math>-EVs</b>
Heart Rate (bpm)	392.18 $\pm$ 18.54	340.18 $\pm$ 24.03	370.02 $\pm$ 8.67
LVDs (mm)	8.12 $\pm$ 0.42	7.49 $\pm$ 0.29	6.83 $\pm$ 0.26*
LVDd (mm)	9.40 $\pm$ 0.37	9.05 $\pm$ 0.33	8.81 $\pm$ 0.32
LVEF (%)	28.01 $\pm$ 2.37	34.47 $\pm$ 1.09*	43.39 $\pm$ 0.54***##
FS (%)	13.81 $\pm$ 1.24	17.30 $\pm$ 0.61*	22.46 $\pm$ 0.31***##
LVPWs (mm)	2.51 $\pm$ 0.12	2.42 $\pm$ 0.33	3.13 $\pm$ 0.11#
LVPWd (mm)	1.98 $\pm$ 0.13	1.84 $\pm$ 0.25	2.10 $\pm$ 0.17

n=4 for each group. All data are mean  $\pm$  SEM. Statistical analysis was performed with one-way ANOVA followed by the Tukey's test. \*P<0.05, \*\*\*P<0.0001 compared with PBS group, #P<0.05, ##P<0.001 compared with NC-EVs group. bpm: beat per minute; LVDs: left ventricular end systolic diameter; LVDd: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; FS: fractional shortening; LVPWs: left ventricular posterior wall thickness at end-systole; LVPWd: Left ventricular posterior wall thickness at end diastolic.

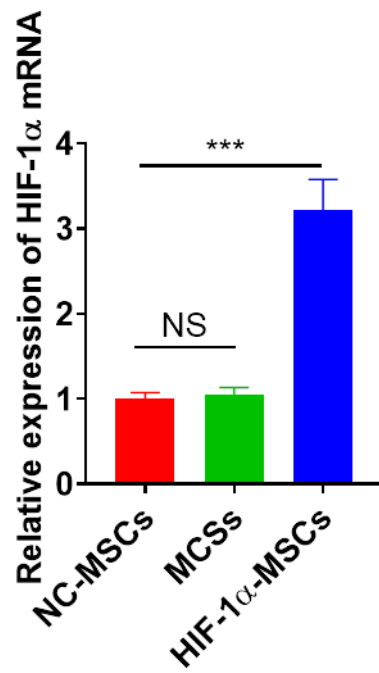
**Supplementary Table 3. Comparison of ecocardiographic parameters between HIF-1 $\alpha$ -EVs and HIF-1 $\alpha$ -EVs RGD-Biotin group**

<b>Parameters</b>	<b>HIF-1<math>\alpha</math>-EVs</b>	<b>HIF-1<math>\alpha</math>-EVs RGD-Biotin</b>
Heart Rate (bpm)	410.67 $\pm$ 23.77	364.10 $\pm$ 19.89
LVDs (mm)	6.50 $\pm$ 0.19	5.95 $\pm$ 0.32
LVDd (mm)	8.22 $\pm$ 0.22	8.38 $\pm$ 0.26
LVEF (%)	41.10 $\pm$ 0.97	53.82 $\pm$ 2.90**
FS (%)	20.99 $\pm$ 0.56	29.18 $\pm$ 1.99*
LVPWs (mm)	2.88 $\pm$ 0.09	2.93 $\pm$ 0.09
LVPWd (mm)	2.09 $\pm$ 0.15	1.79 $\pm$ 0.09

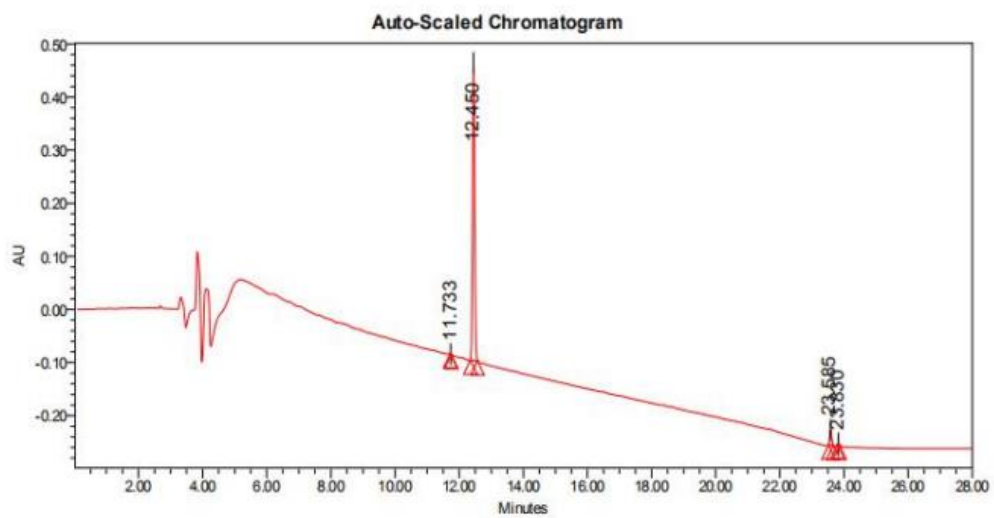
n=4-6 for each group. All data are mean  $\pm$ SEM. Statistical analysis was performed with t test.

\*P<0.05, \*\*P<0.001. bpm: beat per minute; LVDs: left ventricular end systolic diameter; LVDd: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; FS: fractional shortening; LVPWs: left ventricular posterior wall thickness at end-systole; LVPWd: Left ventricular posterior wall thickness at end diastolic.

**Supplementary Figure 1. qRT-PCR analysis of relative expression of HIF-1 $\alpha$  mRNA in MSCs, NC-MSCs and HIF-1 $\alpha$ -MSCs.** Continuous variables were described by means  $\pm$  SEM. n=3 for each group. \*\*\*P< 0.001, NS: not significant.

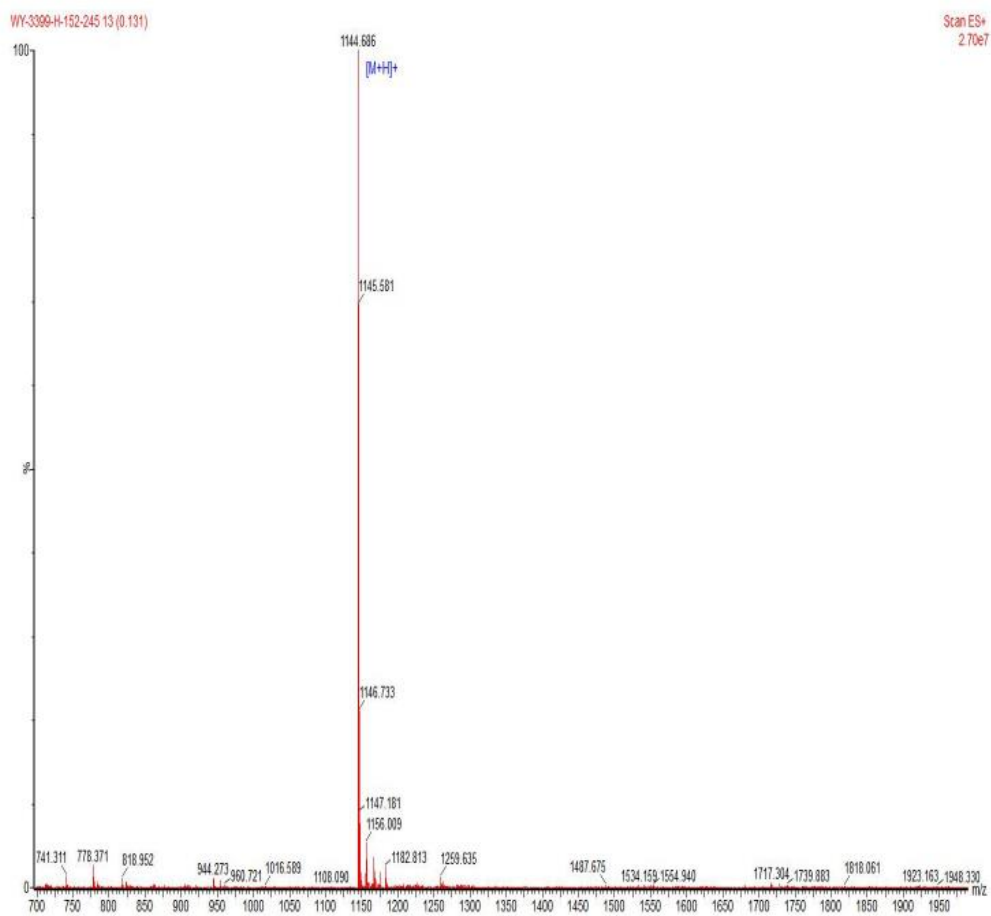


**Supplementary Figure 2. High performance liquid chromatography (HPLC) analysis of RGD-Biotin peptide.** HPLC analysis showed that the purity was 95.09%.

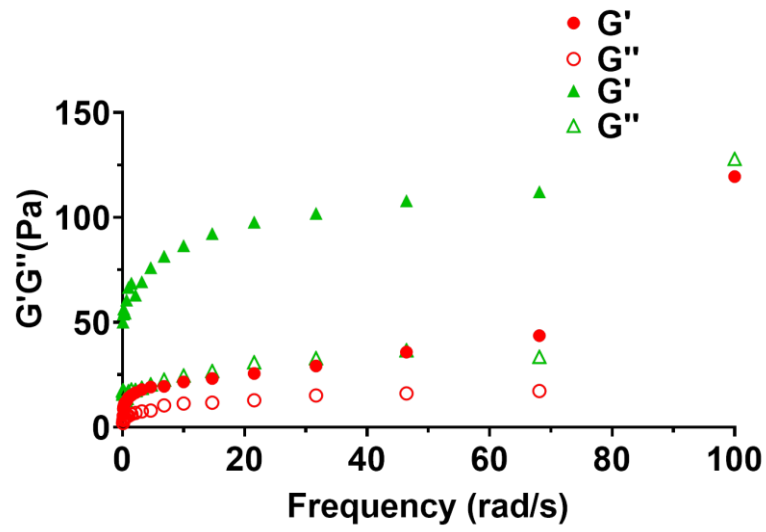


Peak Results				
	RT	Area	Height	% Area
1	11.733	178	178	0.01
2	12.450	2524262	549588	95.09
3	23.585	122945	28181	4.63
4	23.830	7126	2847	0.27

**Supplementary Figure 3.** Mass Spectrometry (MS) spectrum of RGD-Biotin molecule. Expected MS= 1144.29, observed (M+H)<sup>+</sup> = 1144.686.



**Supplementary Figure 4.** Dynamic frequency sweep of EV/RGD hydrogel encapsulating EVs at a mass ratio of 1:1 (green) and 2:1 (red), respectively at 37 °C.  $G'$ : storage moduli,  $G''$ : loss moduli.



**Supplementary Figure 5. qRT-PCR and westernblot analysis of relative expression of HIF-1 $\alpha$  mRNA and protein in EVs derived from NC-MSCs and HIF-1 $\alpha$ -MSCs. A) qRT-PCR analysis of relative expression of HIF-1 $\alpha$  mRNA in EVs derived from NC-MSCs and HIF-1 $\alpha$ -MSCs. B) westernblot and quantitative analysis of relative expression of HIF-1 $\alpha$  protein in EVs derived from NC-MSCs and HIF-1 $\alpha$ -MSCs. Continuous variables were described by means  $\pm$  SEM. n=3 for each group. NS: not significant.**

