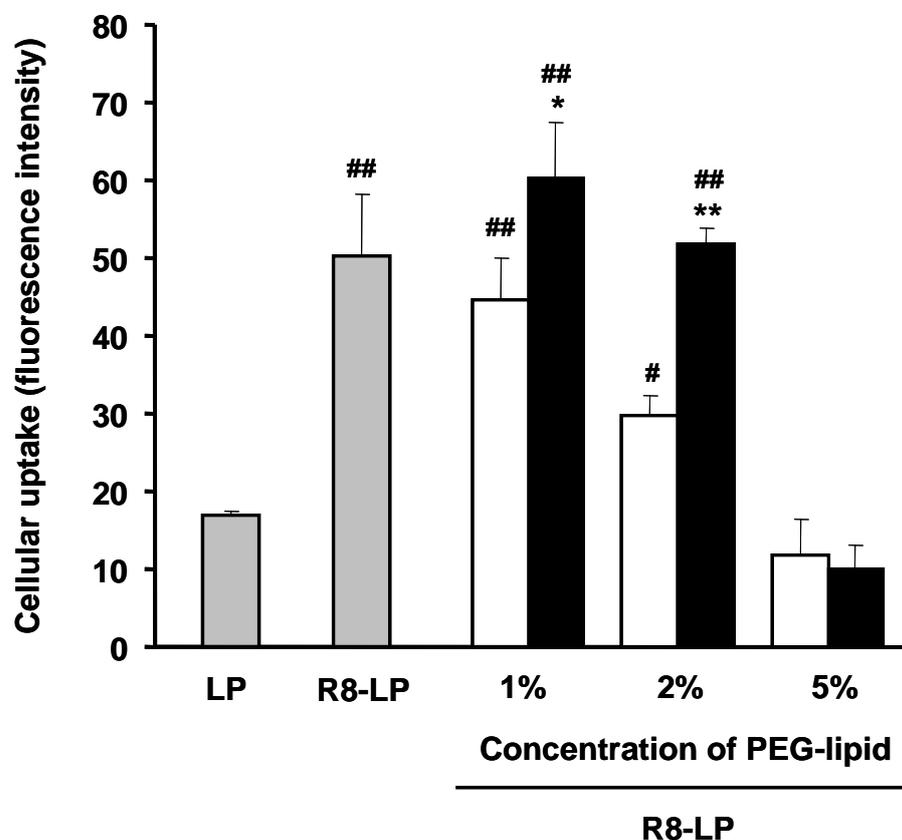




Title	Design of a dual-ligand system using a specific ligand and cell penetrating peptide, resulting in a synergistic effect on selectivity and cellular uptake
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Supplementary information



Supplementary Fig. 1 Cellular uptake of dual-ligand liposomes mediated by NGR and STR-R8.

Different formulations of liposomes were incubated with SM-EC cells for 3 hr and the amount of cellular uptake was determined as described in material and methods. Cellular uptake is expressed as the mean \pm SD ($n=3$). Statistical differences v.s. LP were determined by one-way ANOVA followed by Dunnett test. # $P<0.05$, ## $P<0.01$. Comparisons between PEG and NGR-PEG were determined by the Student's t -test. * $P<0.05$, ** $P<0.01$.

The dual-ligand system containing STR-R8 instead of STR-R4 was evaluated using SM-EC cells. The size and zeta-potential of the dual-ligand formulations containing STR-R8 are shown in supplementary Table 1. The zeta-potential of the dual-ligand system with STR-R8 was higher than that for the STR-R4 version, and the size is comparable in both formulations. R8-LP showed a higher cellular uptake than LP and the amount decreased along with PEG-lipid concentration (open bars). However, uptake

for the dual-ligand system was maintained within 1 to 2 mol% of NGR-PEG-lipid. Considering the negligible cellular uptake obtained by NGR single modification as shown in Fig. 3, these results suggest that the synergistic effect was induced by the dual-ligand of NGR and STR-R8.

Supplementary Table 1 Physical properties of dual-ligand liposomes containing STR-R8

Conc. of PEG-lipid	LP		PEG/R8-LP		NGR-PEG/R8-LP	
	Size (nm)	zeta-potential (mV)	Size (nm)	zeta-potential (mV)	Size (nm)	zeta-potential (mV)
0%	98±1	-2.4±3.1	101±5	13.5±1.4	-	-
1%	-	-	98±5	11.3±3.1	103±2	8.3±2.5
2%	-	-	98±3	7.6±2.4	102±5	6.6±3.0
5%	-	-	97±2	3.4±3.1	99±3	6.16±2.9

The data are expressed as mean ± SD. (n=3)

The conc. of PEG-lipid 0% means PEG-unmodified formulation (LP or R8-LP).