Supporting Information

Programmed Delivery of Cyclopeptide RA-V and Antisense Oligonucleotide for Combination Therapy on Hypoxic Tumors and Therapeutic Self-Monitoring

Yongrong Yao,‡ Li Feng,‡ Zhe Wang, Huachao Chen,* Ninghua Tan*

State Key Laboratory of Natural Medicines, Jiangsu Key Laboratory of TCM Evaluation and Translational Research, School of Traditional Chinese Pharmacy, China Pharmaceutical University, Nanjing 211198, China.

*Corresponding author, Ninghua Tan, Email: nhtan@cpu.edu.cn; huachao.chen@163.com

‡These authors contributed equally
Additional Figures

1. **Fig. S1.** TEM micrographs of the RA/RX Liposome at pH 5.0, 6.0 and 7.4.

2. **Fig. S2.** Size distribution of the nanoparticle characterized by Malvern Instruments at 25 °C.

3. **Fig. S3.** Zeta distribution of the RA/RX Liposome (without anti-DR5 modification) compared with RA/RX Liposome (-29.83 ± 0.75 mV), characterized by Malvern Instruments at 25 °C.

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6. **Fig. S6.** In vitro release profiles of the caspase 8 probe from the RA/RX Liposome at pH 5.0, 6.0 and 7.4.

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18. **Fig. S18.** Fluorescence images of activities of caspase-8 in HCT116 tumor-bearing mice with i.v. injection of caspase 8 probe Liposome, RX-0047 Liposome, RA-V Liposome and RA/RX Liposome recorded at 12 h.
**Fig. S1.** TEM micrographs of the RA/RX Liposome at pH 5.0, 6.0 and 7.4. Scale bar: 200 nm.

**Fig. S2.** Size distribution of the nanoparticle characterized by Malvern Instruments at 25 °C. (pH = 6.0: 151 ± 2.21 nm; pH = 5.0: 111.07 ± 2.35 nm)
**Fig. S3.** Zeta distribution of the RA/RX Liposome (without anti-DR5 modification) were -44.2 ± 0.1 mV, compared with the RA/RX Liposome (-29.83 ± 0.75 mV), characterized by Malvern Instruments at 25°C.

**Fig. S4.** Zeta distribution of the RA/RX Liposome were -29.83 ± 0.75 mV, compared with the RA/RX Liposome (without anti-DR5 modification) (-44.2 ± 0.1 mV), characterized by Malvern Instruments at 25°C.
Fig. S5. In vitro release profiles of RX-0047 from the RA/RX Liposome at pH 5.0, 6.0 and 7.4. Data are given as mean ± SD (n = 3).

Fig. S6. In vitro release profiles of the caspase 8 probe from the RA/RX Liposome at pH 5.0, 6.0 and 7.4. Data are given as mean ± SD (n = 3).
Fig. S7. Quantitative fluorescent intensities data of HCT116 cells fluorescence images in Fig. 3a. Data are given as mean ± SD (n = 3).

Fig. S8. Colocalization images of the RX-0047 Liposome in HCT116 cells. Cells were incubated with the RX-0047 Liposome for 3 h and then incubated with 100 nM Hoechst 33342, MitoTracker Red, or LysoTracker Red for 10 minutes. Scale bars: 10 μm.
**Fig. S9.** Colocalization images of the RA/RX Liposome (non-DR5) in HCT116 cells. Cells were incubated with the RA/RX Liposome (non-DR5) for 3 h and then incubated with 100 nM Hoechst 33342, MitoTracker Red, or LysoTracker Red for 10 minutes. Scale bars: 10 μm.
Fig. S10. Confocal fluorescence images of apoptosis by the JC-1 assay in HCT116 and HT29 cells treated with the RA/RX Liposome for 0 h or 12 h. Scale bars: 10 μm.
**Fig. S11.** The blots in Fig. 5d were analyzed by optical densitometry using Image J. Data are expressed as mean ± SD. *P < 0.05, **P < 0.01, ***P < 0.001, compared with control group.

**Fig. S12.** The levels of HIF-1α protein in cells upon treatments with different concentrations of the RX-0047 Liposome were also investigated, which were tested in the total cell lysates from HCT 116 cells.
**Fig. S13.** Confocal fluorescence images showing increased intracellular O$_2$ level after treated with the RA/RX Liposome. HCT116 cells were incubated with 5 μM [Ru(dpp)$_3$]Cl$_2$ for 4 h, followed by incubation with the RA/RX Liposome for 0 h, 3 h, 6 h, 12 h. Scale bars: 10 μm.
**Fig. S14.** Tumor weights of different groups of HCT116 cells tumor-bearing nude mice after various administrations. *P < 0.05, **P < 0.01, #P < 0.05.

**Fig. S15.** Changes of relative tumor volume upon treatments with different concentrations of the RA/RX Liposome on HCT116 cells tumor-bearing nude mice.
**Fig. S16.** H&E stained images of major organs for in vivo toxicity assay. Histological observation of the organs collected from HCT116 cells tumor-bearing nude mice after different treatments. No obvious organ damages were observed in major organs. Scale bars: 100 μm.
**Fig. S17.** The evaluation of levels of serum ALT, AST, creatinine and BUN in different groups after various administrations.

**Fig. S18.** Fluorescence images of activities of caspase-8 in HCT116 tumor-bearing nude mice with i.v. injection of caspase 8 probe Liposome, RX-0047 Liposome, RA-V Liposome and RA/RX Liposome recorded at 12 h.