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**Supplemental Information**

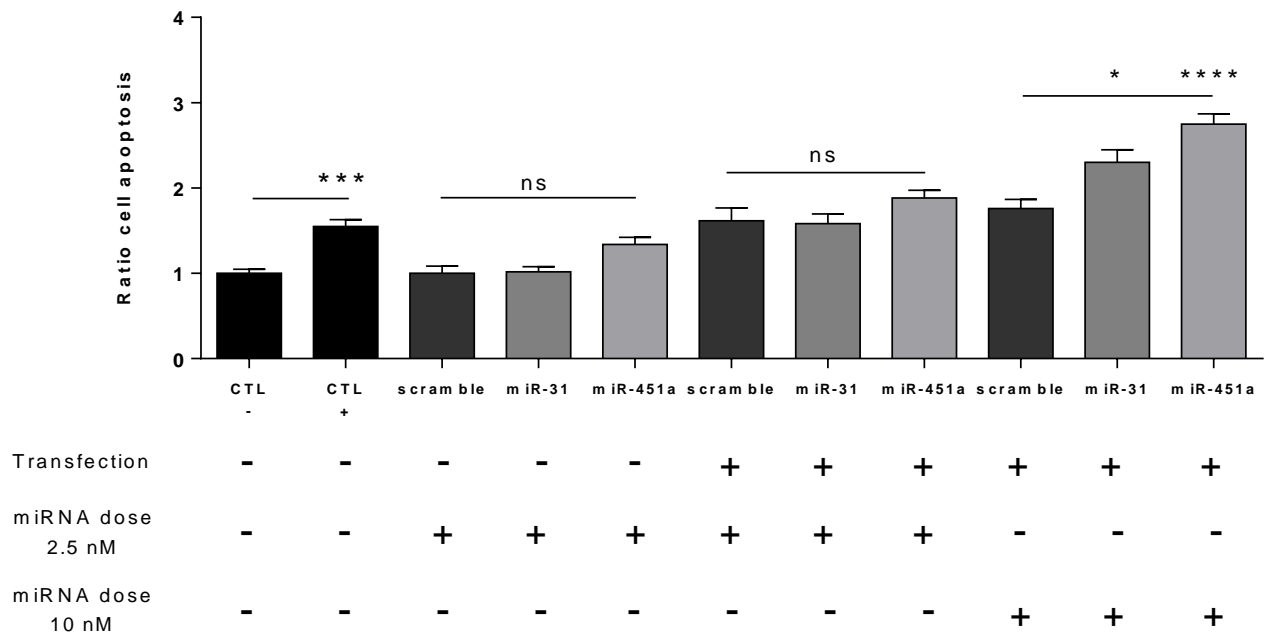
**Improved Loading of Plasma-Derived**

**Extracellular Vesicles**

**to Encapsulate Antitumor miRNAs**

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## Supplementary material



**Supplementary Figure S1. miRNAs pro-apoptotic effect on cancer cells.** HepG2 cells were stimulated with two antitumor miRNAs, miR-31 and miR-451a, and control miRNA scramble to verify their effect without EV engineering. Cells were treated with free-miRNAs or transfected with miRNAs using a dose comparable to the dose transferred by engineered EVs (2,5 nM) or an effective dose of 10 nM. miRNA dose comparable to engineered EV treatment did not promote cell apoptosis, whereas the cell transfection with a higher miRNA dose (10 nM) was able to significantly promote cancer cell apoptosis in comparison to scramble treatment. Cells were stimulated for 24 hours and total cell apoptosis was detected by Muse™ Annexin V kit and showed as ratio in comparison to untreated cells (CTL-) (n=6). ANOVA with Turkey's multiple comparisons test. The activity of each miRNA treatment was compared to cells treated with control miRNA scramble using the same protocol. CTL-: cells cultured in DMEM 10% FCS; CTL+: cells stimulated with doxorubicin as positive apoptosis control (150 ng/ml). Data are expressed as means  $\pm$ SEM. \*  $p < 0.05$ , \*\*\*\*  $p < 0.001$ .