Supporting Information

of

Intelligent "Peptide-gathering Mechanical Arm" Tames Wild "*Trojan-Horse*" Peptides for the Controlled Delivery of Cancer Nanotherapeutics

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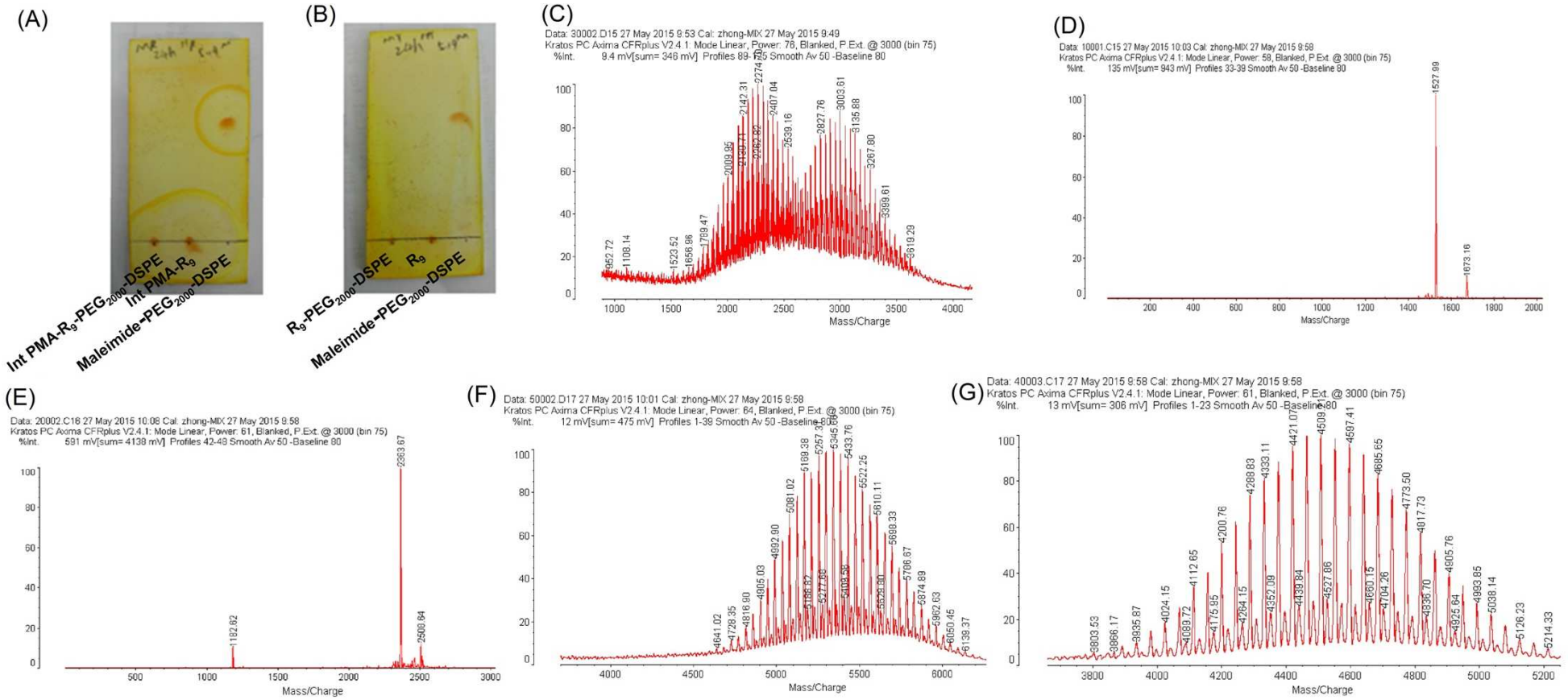

Figure S-1. Characterization of Int PMA-R_9-PEG_{2000}-DSPE and R_9-PEG_{2000}-DSPE using TLC and MALDI-TOF MS analysis. TLC chromatograms of Int PMA R_9-PEG_{2000}-DSPE (**A**) and R_9-PEG_{2000}-DSPE (**B**) were recorded. The developing solvent for TLC was chloroform/methanol (4/1, *v/v*). The PEG chains were visualized by Dragendorff's reagent. The peptides were visualized using ninhydrin staining. MALDI-TOF MS spectra of PEG_{2000}-DSPE (**C**), -C-R_9 (**D**), Int PMA-R_9 (**E**), Int PMA- R_9-PEG_{2000}-DSPE (**F**) and R_9-PEG_{2000}-DSPE (**G**) were measured.

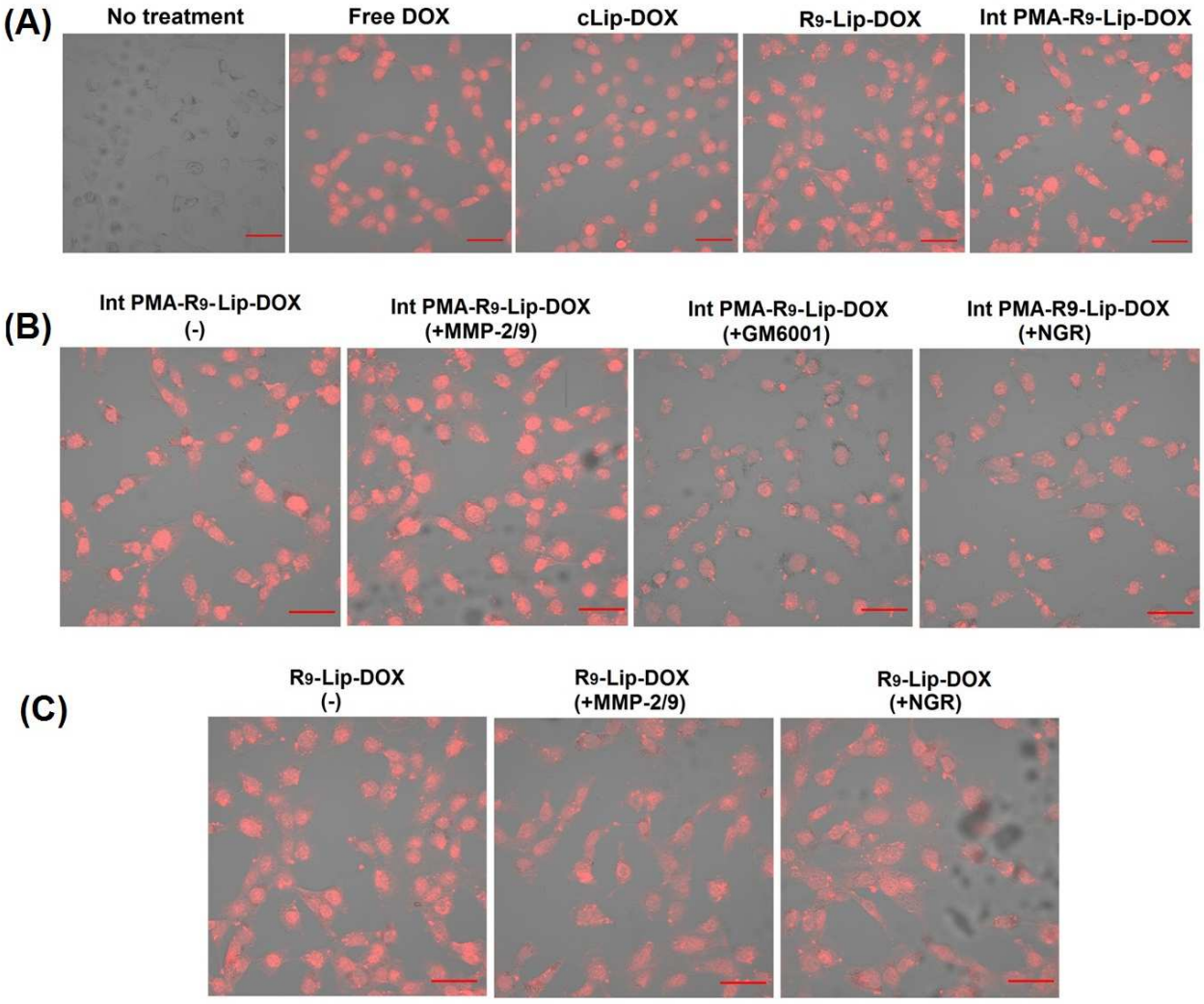

Figure S-2. Cell uptake visualized using confocal laser scanning microscopy (CLSM) under endogenous or exogenous triggers. (**A**) CLSM images of HT-1080 cells were recorded after incubation with free DOX, cLip-DOX, R_9-Lip-DOX and Int PMA-R_9-Lip-DOX (DOX 2.5 μg/mL) at 37 °C for 24 h. (**B**) CLSM images of HT-1080 cells was recorded after incubation with Int PMA-R_9-Lip-DOX (DOX 2.5 μg/mL) at 37 °C for 24 h after 4 h of pre-incubation of 0.1 mg/mL MMP-2/9, 250 ng/mL GM6001 or 0.1 mg/mL NGR. (**C**) CLSM images of HT-1080 cells were recorded after incubation with R_9-Lip-DOX (DOX 2.5 μg/mL). HT-1080 cells were pre-incubated with excess MMP-2/9 or NGR for 4h followed by co-incubation with R_9-Lip-DOX for another 24 h. Cells were fixed with 4% paraformaldehyde. DOX fluorescence (Red) was recorded. All images were taken under identical instrumental conditions and presented at the same intensity. Scale bar, 50 μm.

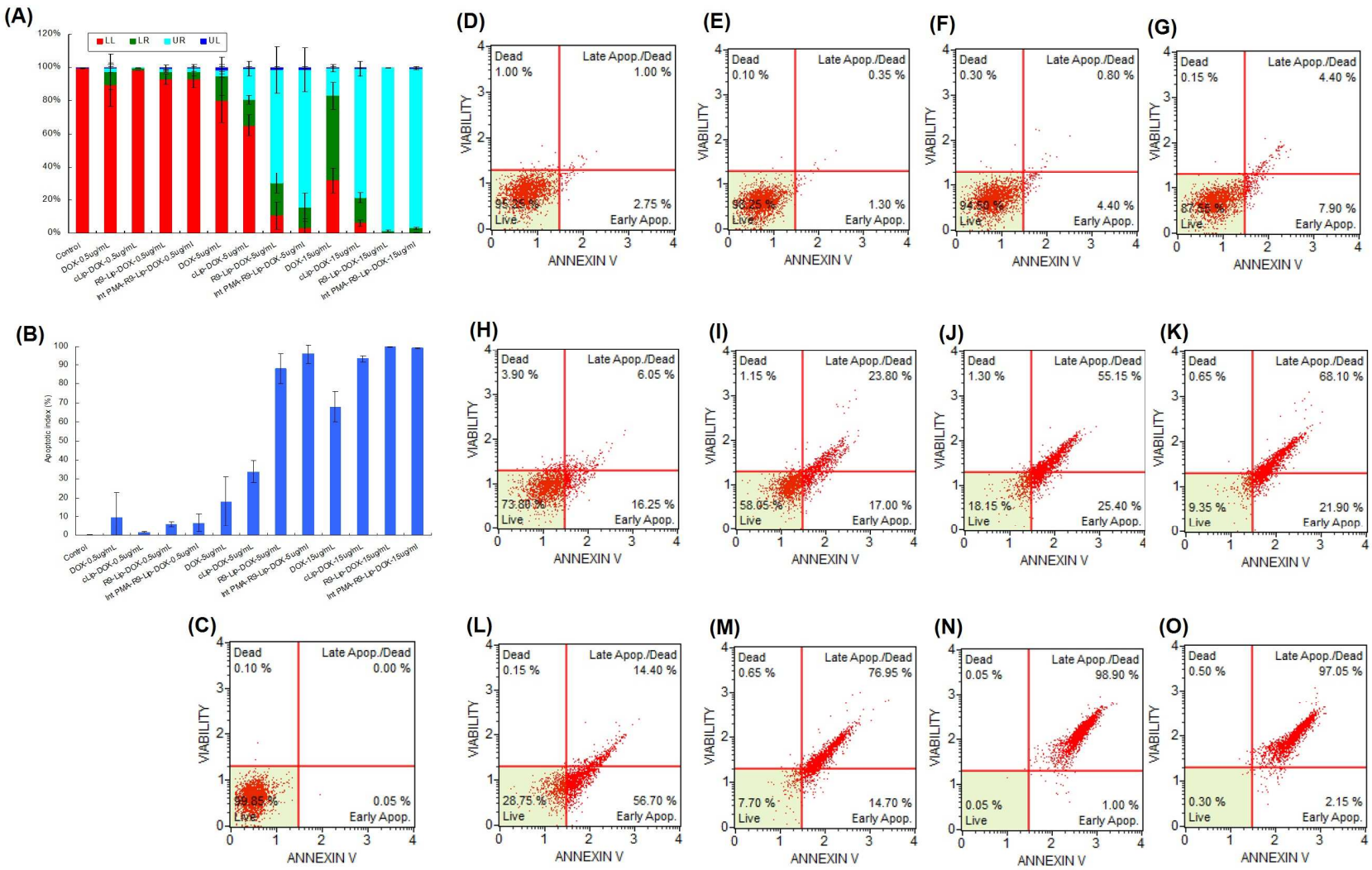

Figure S-3. (**A**) *In vitro* cell apoptosis was evaluated for various DOX formulations in HT-1080 cells. UL: live cells; UR: early apoptotic cells; LR: late apoptotic cells; LL: necrotic cells. (**B**) Apoptotic indexes were calculated in HT-1080 cells for each group. (**C-O**) Representative cell apoptotic diagrams were detected by flow cytometry. Cells were treated with DOX in solution or in DOX-loaded liposomes containing total DOX concentrations of 0.5, 5 and 15 µg/mL for 24 h. These representative diagrams included non-treatment group (control, **C**), 0.5 µg/mL of DOX (**D**), cLip-DOX (E) R_9-Lip-DOX (**F**) and Int PMA-R_9-Lip-DOX (G), 5 µg/mL of DOX (**H**), cLip-DOX (**I**), R_9-Lip-DOX (**J**) and Int PMA-R_9-Lip-DOX (**K**), and 15µg/mL of DOX (**L**), cLip-DOX (**M**), R_9-Lip-DOX (**N**) and Int PMA-R_9-Lip-DOX (**O**). Data are shown as the mean ± SD (n = 3).

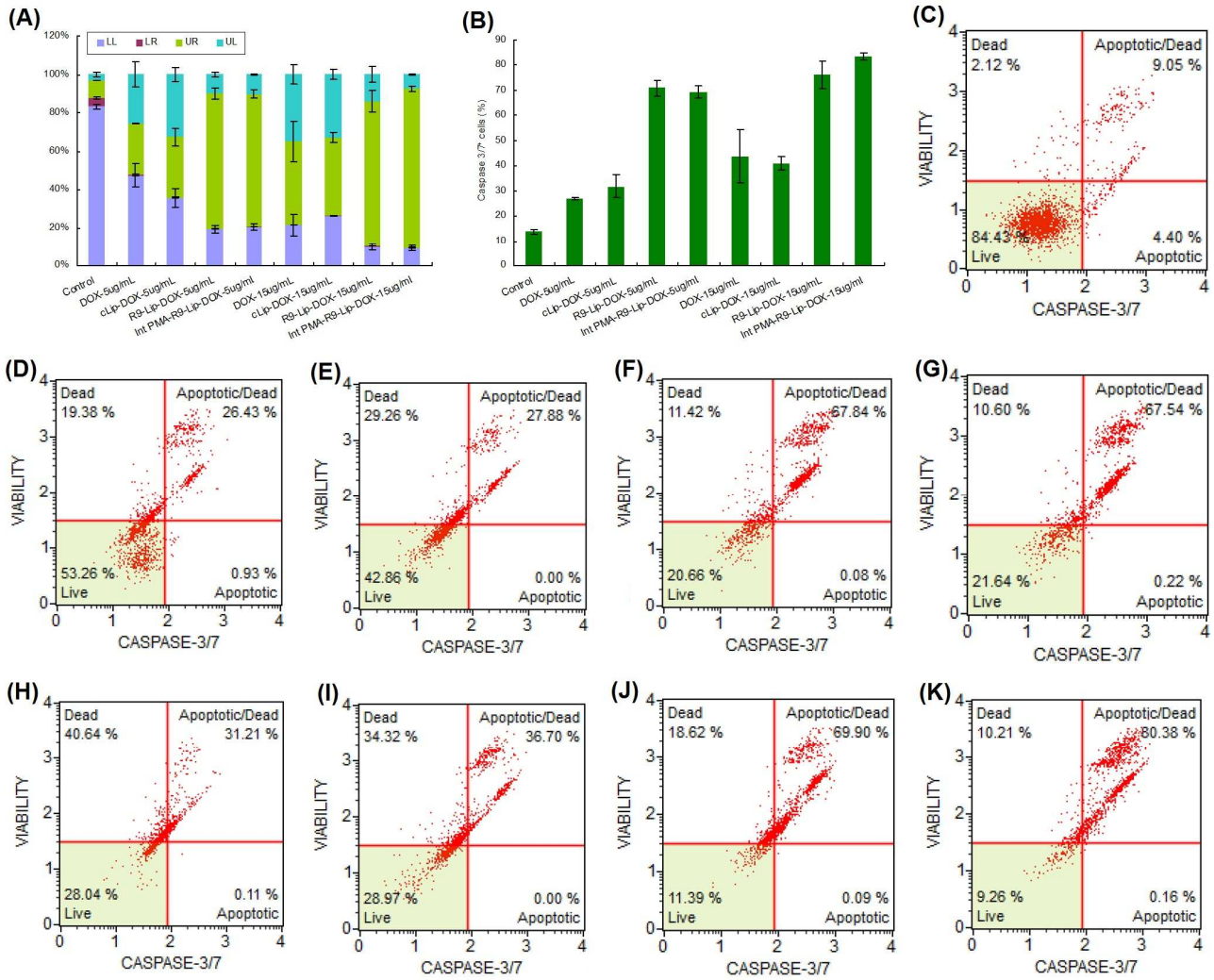

Figure S-4. (**A**) Caspase 3/7-induced cell apoptosis was evaluated for various DOX formulations in HT-1080 cells. (**B**) Caspase 3/7 activation was calculated in HT-1080 cells for each group. UL: live cells; UR: apoptotic cells; LR: apoptotic/dead cells; LL: dead cells. (**C-K**) Representative caspase 3/7-induced cell apoptotic diagrams were detected by flow cytometry. Cells were treated with DOX in solution or in DOX-loaded liposomes containing total DOX concentrations of 5 and 15 μg/mL for 24 h. These representative diagrams included non-treatment group (control, **C**), 5 μg/mL of DOX (**D**), cLip-DOX (**E**) R_9-Lip-DOX (**F**) and Int PMA-R_9-Lip-DOX (**G**), 15 μg/mL of DOX (**H**), cLip-DOX (**I**), R_9-Lip-DOX (**J**) and Int PMA-R_9-Lip-DOX (**K**). Data are shown as the mean ± SD (n = 3).