

Supplementary Information

Mitochondrial targeting and cell penetrating peptides co-modified HPMA copolymers for enhancing therapeutic efficacy of α -tocopheryl succinate

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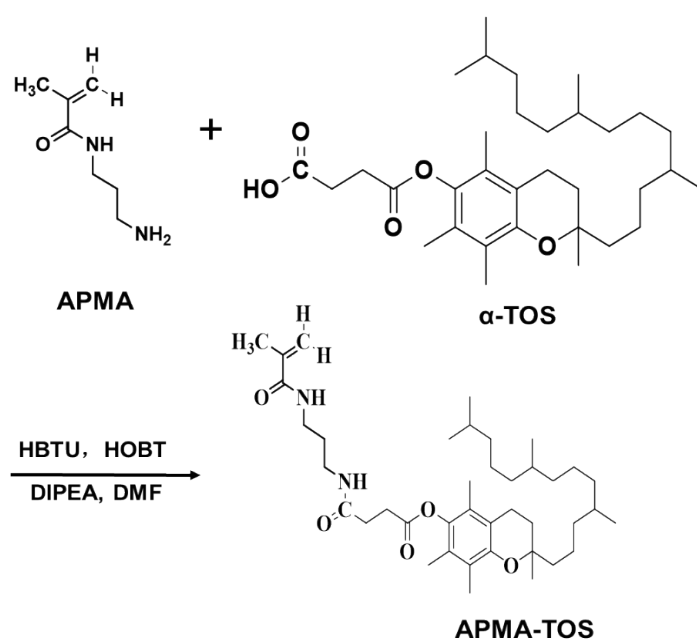
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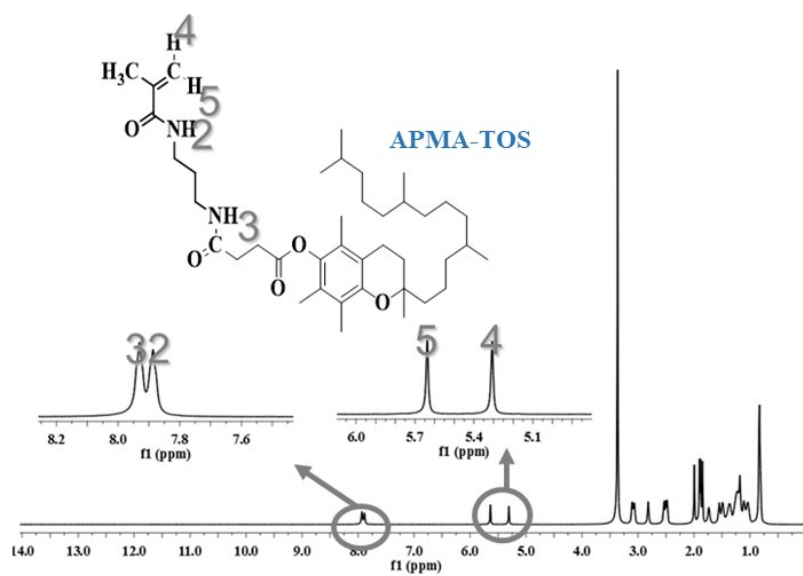
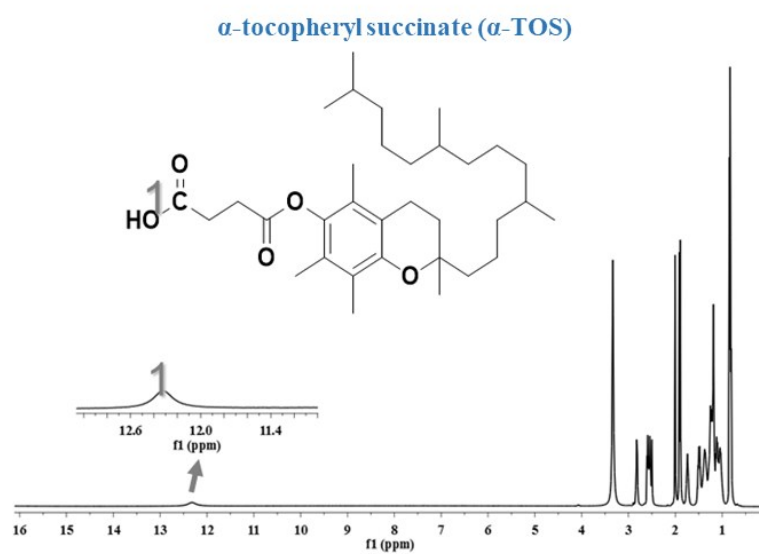
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Scheme S1. Synthesis of α -tocopheryl succinate derivative (APMA-TOS).



Scheme S2. ^1H NMR spectrum of α -tocopheryl succinate (α -TOS) and APMA-TOS.

Table S1. Key characteristics of HPMA copolymers synthesized with different functional groups.

Polymer NO.	HPMA copolymers	Mw (kDa)	PDI	FITC (wt%)	TOS (wt%)	SS20 peptide content (μmol/g)	dNP2 peptide content (μmol/g)
1	P-FITC	22.6	1.43	4.84	-	-	-
2	P-FITC-SS20	26.6	1.50	3.86	-	198	-
3	P-FITC-SS20-dNP2	31.7	1.24	3.14	-	195	70
4	P-FITC-dNP2	28.9	1.65	3.71	-	-	72
5	P-TOS	25.9	1.53	-	7.65	-	-
6	P-TOS-SS20	28.4	1.34	-	6.47	193	-
7	P-TOS-SS20-dNP2	35.3	1.65	-	5.14	189	68

Abbreviations: Mw, weight-averaged molecular weight; PDI, polydispersity index; TOS, α-tocopheryl succinate.

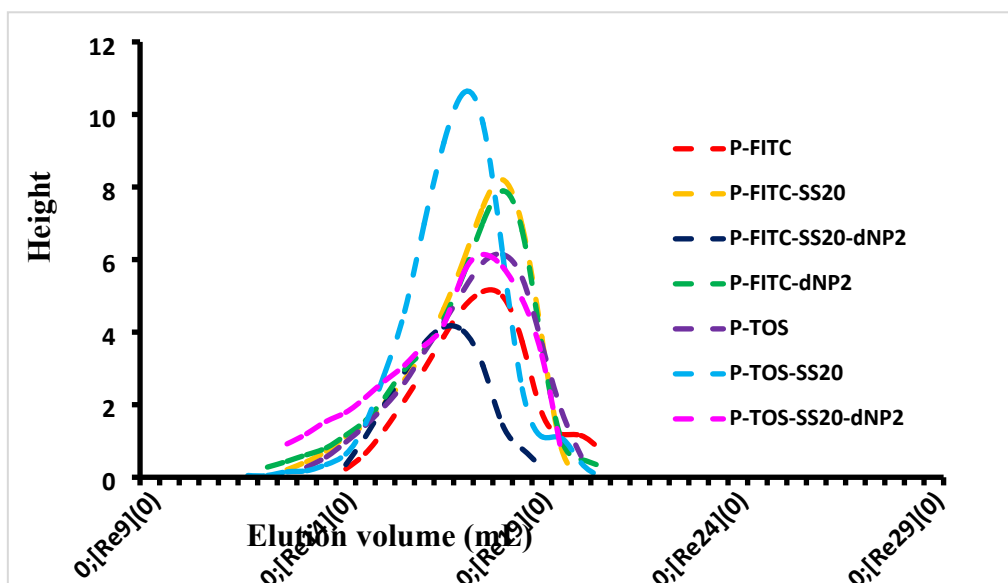


Figure S1. Size-exclusion chromatography (SEC) profiles of synthesized HPMA copolymer conjugates.

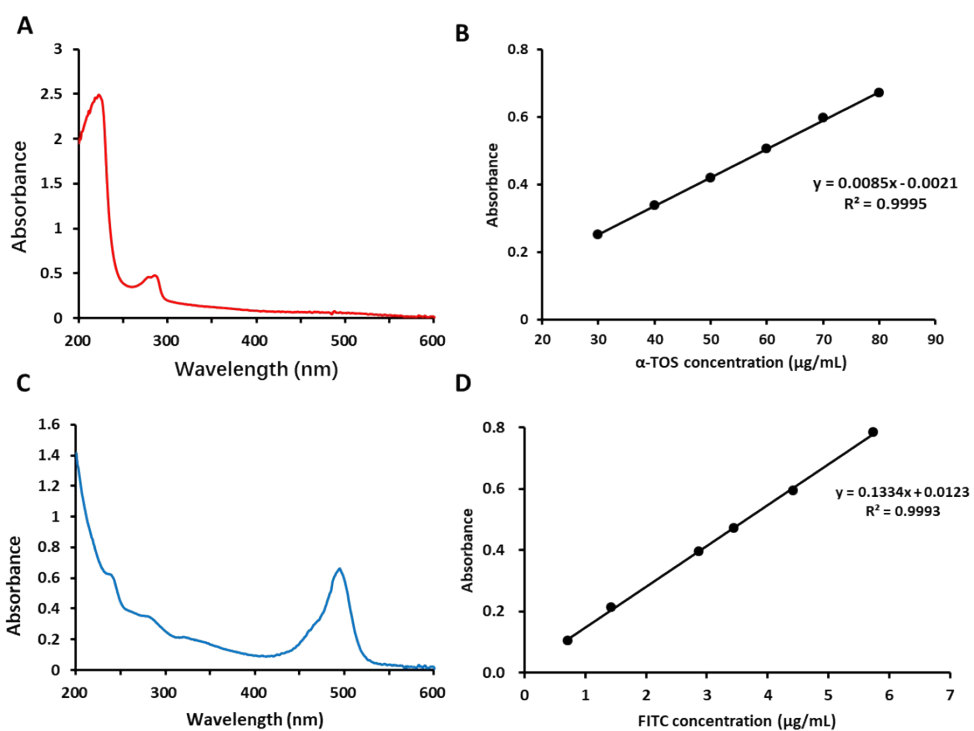


Figure S2. (A) UV-vis spectrum of free α -TOS and (B) concentration versus absorbance calibration graph of α -TOS determined by UV-vis spectroscopy. (C) UV-vis spectrum of FITC and (D) concentration versus absorbance calibration graph of FITC determined by UV-vis spectroscopy.

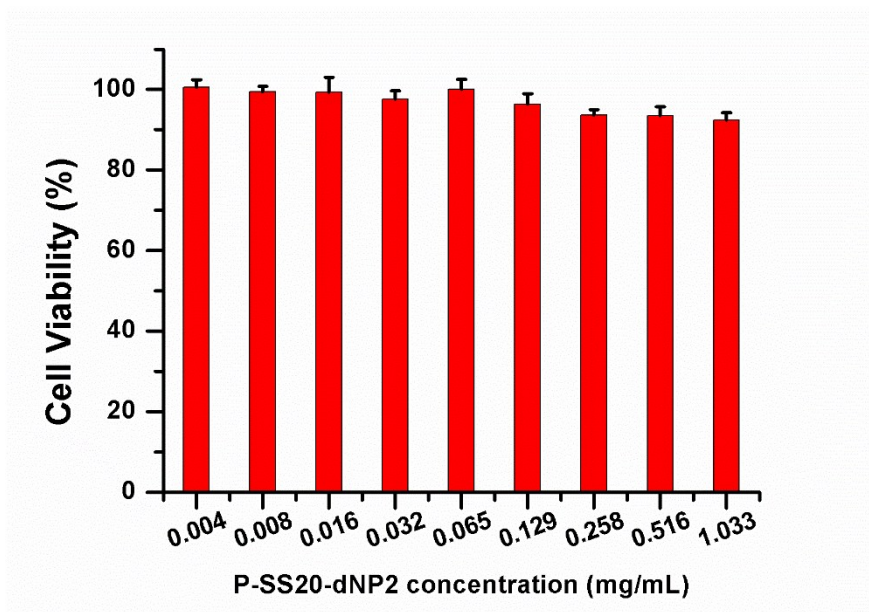


Figure S3. *In vitro* cytotoxicity of various concentrations of drug-free P-SS20-dNP2 copolymer on HeLa cells for 48 h (n=5).

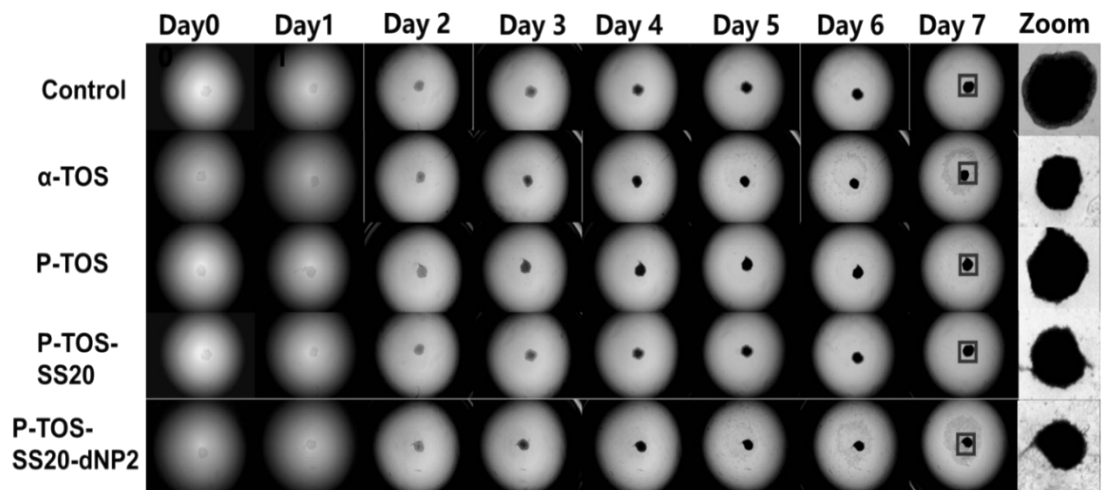


Figure S4. The growth inhibition of HeLa three-dimensional multicellular tumor spheroids treated with α -TOS, P-TOS, P-TOS-SS20 and P-TOS-SS20-dNP2 (α -TOS equivalent concentration 200 μ M).

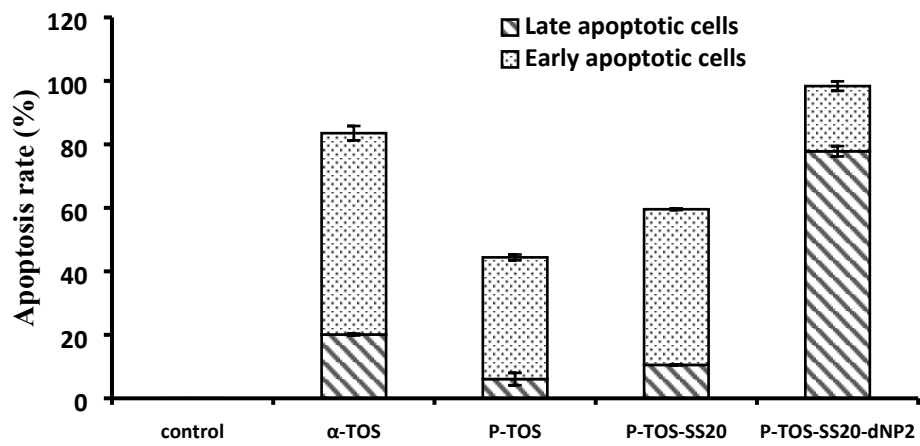


Figure S5. Apoptosis rate of HeLa cells treated with α -TOS, P-TOS, P-TOS-SS20 and P-TOS-SS20-dNP2. (n=3)

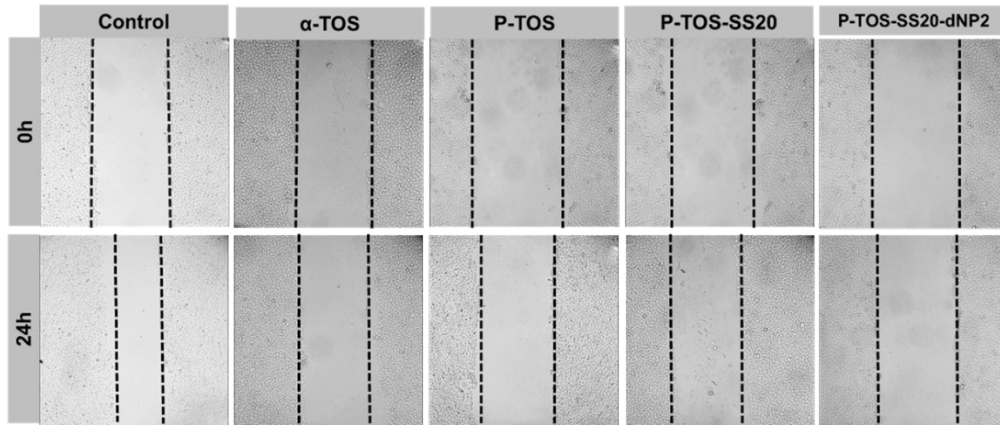


Figure S6. The migration images of HeLa cells mediated by α -TOS, P-TOS, P-TOS-SS20 and P-TOS-SS20-dNP2.