Supplementary materials

Plasmonic gold-titania-curcumin nanoantennas for synergistic quadruple photodynamic/mild photothermal/radiodynamic/chemo therapy of non-small cell lung cancer

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Supplementary material S1: A summary of some studies of cancer treatment using Au/Ti-based nanoplatforms in combination with photo/radio/sono therapy.

Nanoformulations	E_g / eV	Cell type	Therapeutic modality, activation source	Key mechanism in cancer treatment	Ref.
Au-$H_2Ti_3O_7$ nanotubes	3.37	A549, LNCap	PDT/PTT; 532 nm with an energy fluence of 450 J cm^{-2}, 635 nm with an energy fluence of 72.5 J cm^{-2} and 365 J cm^{-2}, 808 nm with an energy fluence of 214.2 J cm^{-2}	Au plasmon-assisted ROS generation, photothermal heating, apoptosis	1
TiO_2-Au nanosheets	2.8	Breast cancer	SDT by US irradiation at 1.0 MHz, 50% duty cycle, 1.5 W cm^{-2}	ROS generation, 4.7-fold increase in apoptosis	2
TiO_2-Au-PEG-curcumin	2.4	HeLa	SDT by US irradiation at 1.0 MHz, 50% duty cycle, 1.5 W cm^{-2}	Reducing IC_{50} to 38 μg mL^{-1} under US irradiation, inhibiting cell migration and 3D spheroid formation	3
Black TiO_2 NPs	2.9-3.15	Bladder cancer	Phototherapy by 808-nm light irradiation	ROS generation	4
Au-TiO_2@doxorubicin	-	MCF-7	PDT at 150 mW cm^{-2}	ROS generation, metastasis and apoptosis	5
TiO_2-$Au_{10.5}$	2.8	4T1 breast cancer	US irradiation at 1.0 MHz, 50% duty cycle, 1.5 W cm^{-2}	ROS generation, apoptosis in vitro	6
Titania-coated 2D gold nanoplates	-	HeLa	PTT + SDT; in vitro: 1 W cm^{-2}, 5 min, 1064 nm + 0.5 W cm^{-2}, 3 MHz, 4 min on/1 min off, repeated 5 times; in vivo: 1 W cm^{-2}, 5 min, 1064 nm + 0.5 W cm^{-2}, 20 min with 4 min on/1 min off,	PTT/SDT synergistic therapy and ROS generation in vitro; complete tumor elimination in vivo	7

			repeated 5 times		
TiO_2-Au-triphenylphosphine NPs	-	MCF-7	RDT with 4 Gy X-ray irradiation	Mitochondrial targeting, ROS generation, mitochondrial collapse, and apoptosis in vitro; tumor suppression with a single dose of radiation therapy in vivo	8
PGTCNA	2.4	A549	PDT + mild PTT + RDT + chemotherapy. 808-nm light + 6 Gy X-ray	ROS generation and mitochondrial disruption	This work

Sonodynamic therapy: SDT
Ultrasound: US

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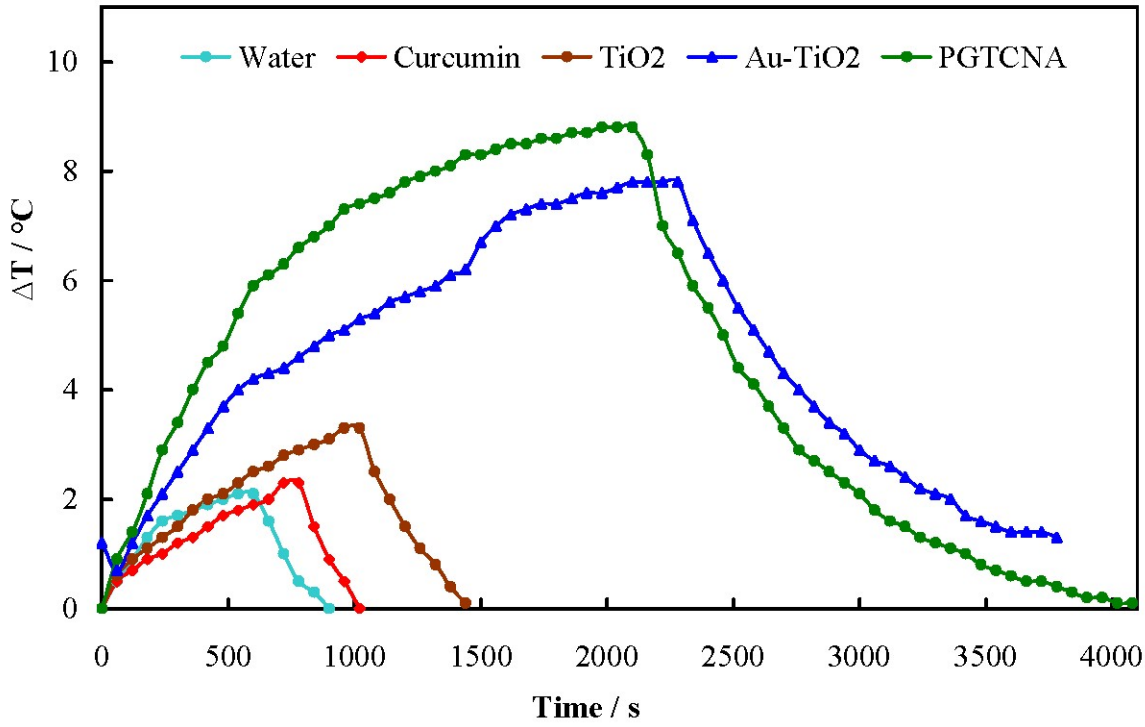
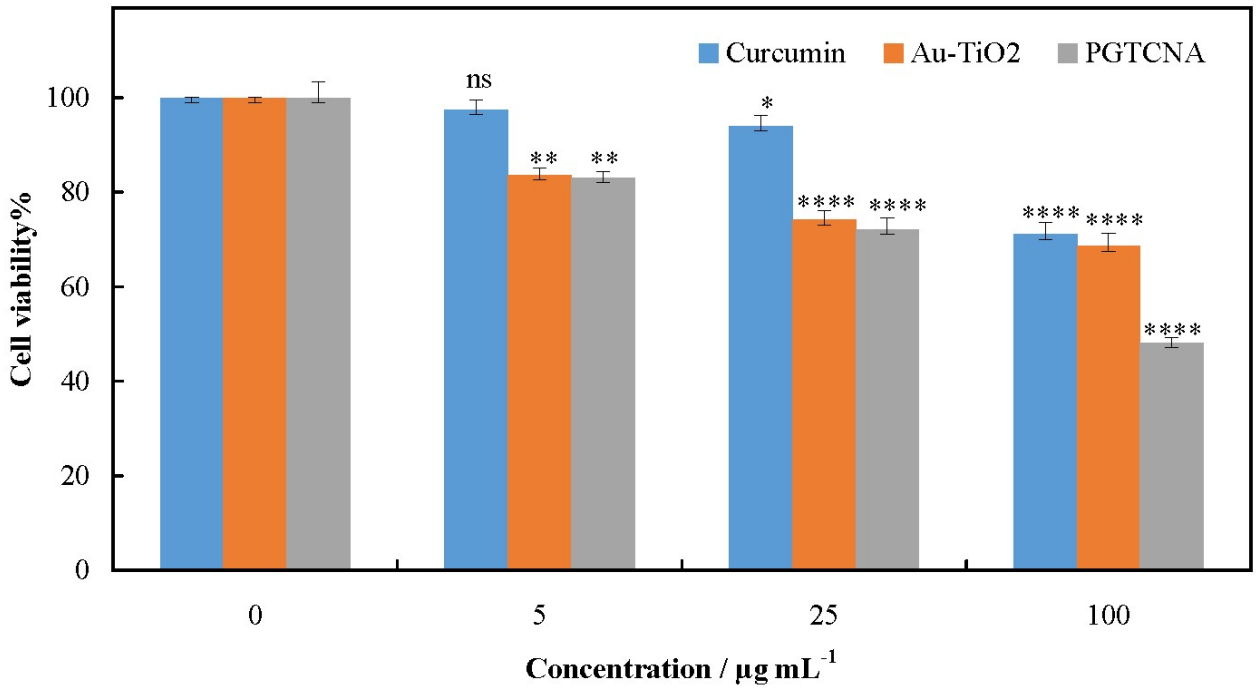
Supplementary material S2: Treatment groups of NSCLC tumorspheres were categorized into the following groups:
L-/R-/PGTCNA -: Untreated tumorspheres (control)
L-/R-/PGTCNA+: Tumorspheres treated with PGTCNA at a concentration of 100 μg mL^{-1} (without any radiation)
L+/R-/PGTCNA-: Tumorspheres exposed to laser light radiation (without PGTCNA treatment or X-ray radiation)
L-/R+/PGTCNA-: Tumorspheres exposed to X-ray radiation (without PGTCNA treatment or laser light radiation)
L+/R+/PGTCNA-: Tumorspheres exposed to laser light radiation and then X-ray radiation with one hour interval (without PGTCNA treatment)
L+/R-/PGTCNA+: Tumorspheres treated with PGTCNA at a concentration of 100 μg mL^{-1} and then exposed to laser light radiation at a one-hour interval (without X-ray radiation)
L-/R+/PGTCNA+: Tumorspheres treated with PGTCNA at a concentration of 100 μg mL^{-1} and then exposed to X-ray radiation at a one-hour interval (without laser light radiation)
L+/R+/PGTCNA+: Tumorspheres treated with PGTCNA at a concentration of 100 μg mL^{-1} and then exposed to laser light radiation at a one-hour interval, and ultimately exposed to X-ray radiation at a one-hour interval

Supplementary material S3: Temperature changes of DI-water, curcumin, TiO_2, and Au-TiO_2 dispersion, and PGTCNA dispersion (100 μg mL^{-1}) upon the laser light radiation followed by radiation off and cooling.



Supplementary material S4: Cytotoxicity of curcumin, Au-TiO2, and PGTCNA against cancer lung cell lines (A549). ** indicates very significant differences (n=3, P-value < 0.01). *** indicates high significant differences (n=3, P-value < 0.001), for biological replicates.



Supplementary material S5: A summary of applications of 808-nm laser/RT in preclinical and translational studies on NSCLC treatment.

Formulation	Laser parameters	X-ray dose	Cell type	Key outcomes	Ref.
Au@SiO_2 nanomaterials	808 nm, 1.0 W cm^{-2}, 10 min, CW	-	MCF-7	Strong anti-cancer effects, mild PTT by an HSP-70 inhibitor operated at a low temperature (~45 °C)	1
A programmed death-ligand 1 antibody@lipid gel	808 nm, 1.0 W cm^{-2}, 10 min, CW	-	B16F10	Controlled mild hyperthermia and triggered immunotherapy, to convert cold tumors into immunologically active hot ones	2
Mesoporous Fe_3O_4 nanoparticles loaded with perfluoropentane and glucose oxidase	808 nm, 1.0 W cm^{-2}, 10 min, CW	-	4T1	Temperature increment to ~44 °C, synergistic effects of mild hyperthermia and chemotherapy	3
-	-	18 Gy × 3 (SBRT)	Clinical NSCLC	100% local tumor control	4
-	-	6 Gy/fraction	A549 (NSCLC)	Amplifying radiation-induced DNA damage and apoptosis with delay in its repair	5
PGTCNA	808 nm, 1.0 W cm^{-2}, 10 min, CW	6 Gy	A549 (NSCLC)	Combined mild photothermal/photodynamic effects with X-rays to enhance ROS generation	This study

Abbreviations:
CW, continuous wave; SBRT, stereotactic body radiotherapy

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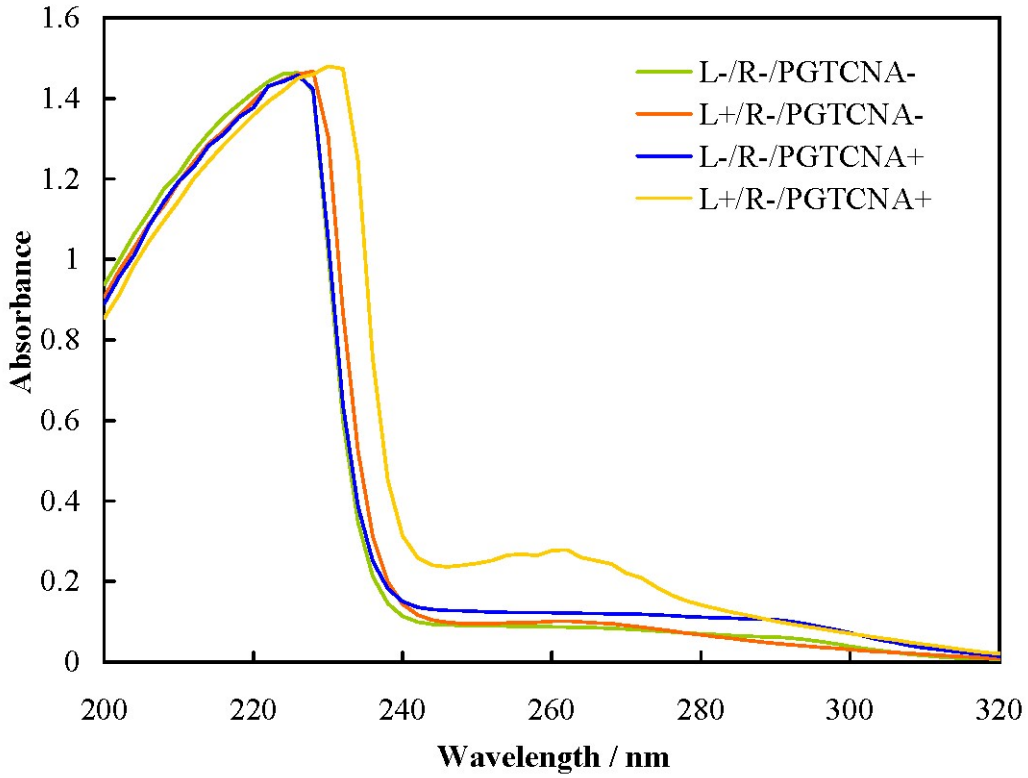
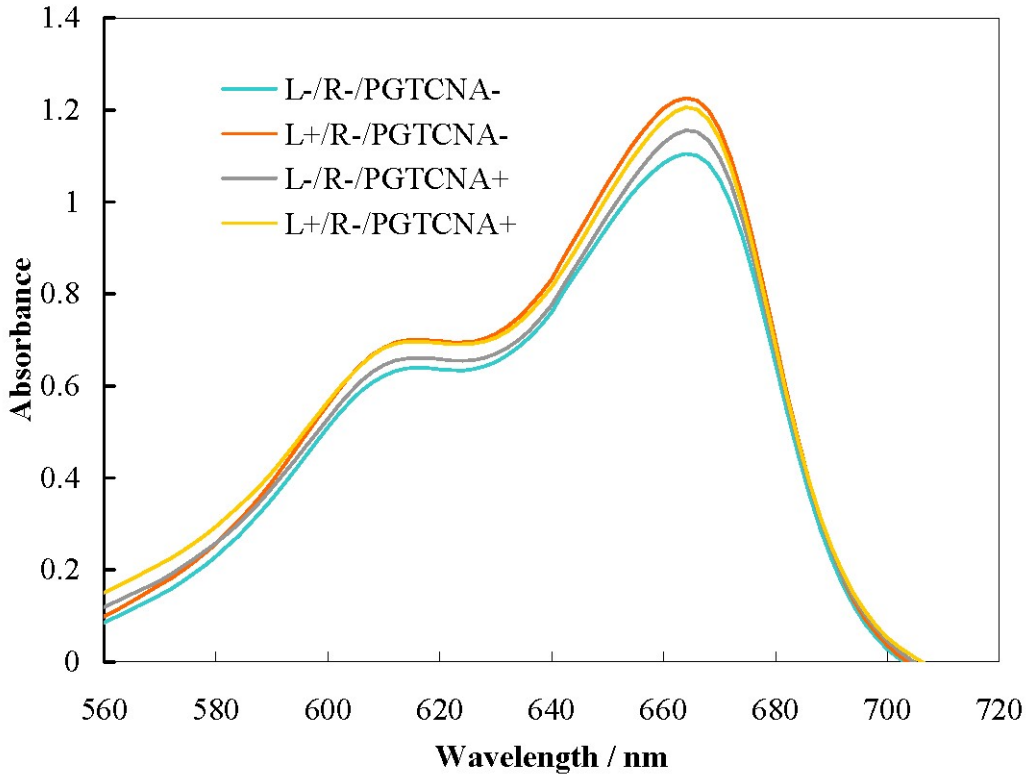
Supplementary material S6: Absorbance spectra for NBT upon radiation by laser light in the absence or presence of PGTCNA.



Supplementary material S7: Absorbance spectra for MB upon radiation by laser light in the absence or presence of PGTCNA.



Supplementary material S8: $^1O_2$ generation by PGTCNA upon the laser light radiation in different treatment groups, that evaluated by measuring the 420 nm absorbtion as DPBF degradation ratios, for L-/R-/PGTCNA-, L+/R-/PGTCNA-, L-/R-/PGTCNA+, L+/R-/PGTCNA+ groups, and after the addition of sodium azide as singlet oxygen scavenger as L+/R-/PGTCNA+/scavenger group.