

Supporting Information for *Nanoscale*

Fluorine-Free Preparation of Titanium Carbide MXene Quantum Dots with High Near-infrared Photothermal Performances for Cancer Therapy

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S1. Materials. The bulk Ti_3AlC_2 powders were purchased from a commercial supplier (Forsman, China). 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT) was bought from Sigma-Aldrich. PBS (pH=7.4), fetal bovine serum (FBS), DMEM, trypsin-EDTA, and penicillin-streptomycin were purchased from Gibco Life Technologies (AG, Switzerland). PEG-NH₂ was purchased from Shanghai Ponsure Biotech, Inc., China. All other chemicals used in this work were analytical reagent grade and used without further purification.

S2. Preparation of MXene QDs. The MXene QDs were prepared using a fluorine-free method developed in this research. Specifically, the preparation of MXene QDs was based on a facile liquid exfoliation technique involving ultrasound probe sonication followed by bath sonication of powders of bulk Ti_3AlC_2 . In brief, Ti_3AlC_2 powders (25 mg), TBAOH (10mL), and water (25 mL) were added into a sealed conical tube (with a volume of 50 mL). The mixture was sonicated with a sonic tip for 6 h at a power of 480 W. The ultrasonic frequency was from 19 to 25 kHz and the ultrasound probe worked in a 2s ON and 4s OFF fashion. The dispersions were further bath sonicated continuously for another 10 h at a power of 300 W. The resulting dispersion was centrifuged for 20 min at 7,000 rpm, and the supernatant containing MXene QDs was collected gently. Later, the MXene QDs were precipitated out from the supernatant solution by centrifuging for 30 min at 12,000 rpm. The precipitate, which contains MXene QDs was repeated water rinsing and re-suspended in PBS or ultrapure water for further use. In our work, the MXene QDs were dispersed in water based media. Specifically, for NIR optical absorption characterization, the solvent is water. For the cell and animal experiments, the solvent is PBS, which is a standard media for biological experiments.

S3. Modifications of MXene QDs with PEG. To coat PEG on MXene QDs, the MXene QDs (1 mg) dispersed in H₂O (5 mL) was mixed with of PEG-NH₂ (5 mg). After ultra-sonication for 20 min and stirring for 4 h, excess PEG molecules were removed by centrifugation at 12,000 rpm and repeated water rinsing. The final PEG-modified MXene QDs were re-suspended in PBS or ultrapure water for further use.

S4. Characterization. SEM images and EDS mapping of the as-received bulk Ti₃AlC₂ powders were taken on a field emission SEM (FESEM, 5.0 kV, HITACHI SU8010, Japan). TEM images, STEM images and EDS mapping of MXene nanosheets and QDs were taken on the Tecnai G² F30 S-Twin TEM at an electron acceleration voltage of 300 kV. AFM studies were performed on the drop-casted MXene samples on Si/SiO₂ substrates (Bruker Dimension® IconTM). X-ray photoelectron spectroscopy (XPS) measurements were conducted on the Thermo Fisher ESCALAB 250Xi XPS. UV–vis–NIR absorption spectra were recorded on an Infinite M200 Pro TECAN GENIOS with QS-grade quartz cuvettes at room temperature. The concentrations of MXene QDs were determined by ICP-AES (7000DV, PerkinElmer).

S5. Photothermal evaluation of MXene QDs. To assess the photothermal effect of the as-synthesized MXene QDs, various concentrations of MXene QD solutions were irradiated under an 808 nm laser at a power density of 1.0 W/cm² for 300s. An IR thermal imaging camera (FLUKE Ti25) was used to record temperatures of the solution at different times. To evaluate the NIR stability of MXene QDs, MXene QDs (50 ppm) were irradiated for 10 min at a power density of 1.0 W/cm² and then the laser was turned off. This procedure was repeated for five times to assess the photostability of MXene QDs.

S6. Calculations of photothermal conversion efficiency. Following Roper et al.'s report,¹ the total energy balance of the system can be considered as

$$\sum_i m_i C_{pi} \frac{dT}{dt} = Q_{QD} + Q_{Dis} - Q_{Surr} \quad (1)$$

where m and C_p are the mass and heat capacity of water, T is the temperature of water, Q_{QD} is the energy inputted by MXene QDs, Q_{Dis} is the energy entrance by the sample cell, and Q_{Surr} is heat conduction away from the system. Q_{QD} , represents heat dissipated on the MXene QDs surface under the irradiation of 808 nm laser:

$$Q_{QD} = I(1 - 10^{-A_{808}})\eta \quad (2)$$

Where I is laser power incidentally (in unit of mW), A_{808} is the absorbance of the MXene QDs at a wavelength of 808 nm, and η is the photothermal conversion efficiency from incident light energy from laser to thermal energy. In addition, Q_{Dis} is heat dissipated from light absorbed by the sample cell itself, and it can be measured independently by a sample cell containing pure water without MXene QDs. Q_{QD} is linear relationship with temperature for the outgoing thermal energy, as the following equation:

$$Q_{Surr} = hS(T - T_{Surr}) \quad (3)$$

where h is heat transfer coefficient, S is the surface area of the sample cell, and T_{Surr} is the temperature of the surroundings.

Once the power of the laser is defined, the heat input ($Q_{QD} + Q_{Surr}$) will be finite. Since the heat output Q_{QD} is increased along with the temperature increasing according to the equation (3), the system temperature will increase to a maximum when the heat input is equal to heat output:

$$Q_{Dis} = Q_{Surr-Max} = hS(T_{Max} - T_{Surr}) \quad (4)$$

where $Q_{Surr-Max}$ is the heat conduction away from the system by air when the temperature of sample cell reaches equilibrium, and T_{MAX} is the equilibrium temperature. The 808 nm laser

photothermal conversion efficiency (η) can be determined by substituting equation (2) for Q_{QD} into equation (4) and rearranging to get

$$\eta = \frac{hS(T_{Max}-T_{Surr})-Q_{Dis}}{I(1-10^{-A_{808}})} \quad (5)$$

where Q_{Dis} was measured independently, the $T_{Max}-T_{Surr}$ was 20 °C according to Fig. S4a, A_{808} is the absorbance of MXene QDs at 808 nm. Thus, only the hS remains unknown for calculating η . In order to get the hS , a dimensionless driving force temperature, θ has a relation with the maximum system temperature, T_{Max}

$$\theta = \frac{T-T_{Surr}}{(T_{Max}-T_{Surr})} \quad (6)$$

and a sample system time constant τ_s

$$\tau_s = \frac{\sum_i m_i C_{P,i}}{hS} \quad (7)$$

which is substituted into equation (1) and rearranged to yield

$$\frac{d\theta}{dt} = \frac{1}{\tau_s} \left[\frac{Q_{QD}+Q_{Dis}}{hS(T_{Max}-T_{Surr})} - \theta \right] \quad (8)$$

At the cooling period of MXene QDs aqueous dispersion, the light source was shut off,

The $Q_{QD} + Q_{Dis} = 0$, reducing the following equation

$$dt = -\tau_s \frac{d\theta}{\theta} \quad (9)$$

and integrating, giving the expression

$$t = -\tau_s \ln \theta \quad (10)$$

Therefore, time constant for heat transfer from the system can be determined by applying the linear time data coming from the cooling stage versus negative natural logarithm of driving force temperature (Fig. S4b). In addition, the m is 1 g and the C is 4.2 J/g. Thus, according to equation (7), the hS is deduced to be 18.3 mW/°C. Substituting this value of hS into equation (5), the 808 nm laser photothermal conversion efficiency (η) of MXene QDs can be calculated to be 52.2%.

S7. Cell culture. HeLa, MCF-7, U251, and HEK 293 cells were cultured in DMEM medium. All the cell culture media were supplemented with 10% fetal bovine serum (FBS) and 1% streptomycin/penicillin. Cells were kept at 37 °C in a humidified atmosphere with 5% CO₂.

S8. *In vitro* toxicity and safety studies. HeLa cells were seeded at a density of 5,000 cells/well in 96-well plates and incubated overnight. Then, the cells were incubated with MXene QDs solution at different concentrations (6.25, 12.5, 25, 50, and 100 ppm) for 48 h. After that, the excess MXene QDs were removed by washing twice with PBS. A standard MTT assay was used to analyze the cell viabilities. Similar experiments were carried out on MCF-7, U251, and HEK 293 cells to further evaluate the safety of MXene QDs on different types of cells.

S9. PA Imaging. To evaluate the linearity of the PA signals as a function of the concentrations of MXene QDs, different concentrations of MXene QDs dissolved in purified water were used for *in vitro* PA signal detection. As for *in vivo* PA imaging, experimental mice were administrated with MXene QDs solution (1 mg/mL, 50 µL) via *i.t.* injection. PA imaging was carried out both prior to and after each injection.

S10. *In vitro* PTT. The HeLa cells were treated with MXene QDs with the concentrations of 25 and 50 ppm for 12 h before laser irradiation. Different laser power densities were used to irradiate the cells. After irradiation, a standard MTT assay was used to calculate the relative cell viabilities.

S11. *In vivo* PTT. Female Balb/c mice (5 weeks old) were purchased from Guangdong Medical Laboratory Animal Center Co. Ltd. The Administrative Committee on Animal Research in Tsinghua University approved the protocols for all animal assays in this study.

The tumor model was generated by subcutaneously injecting 100 μL of PBS containing 1×10^6 HeLa cells into the back of each mouse. The tumor volume was calculated according to the formula: tumor volume (mm^3) = $1/2 \times \text{length} \times \text{width}^2$.

When the tumor volume reached about 100 mm^3 , the mice were divided into three groups ($n = 5$ in each group) including group 1: PBS, group 2: MXene QDs, and group 3: MXene QDs followed with irradiation by an 808 nm NIR laser at a power of 0.5 W/cm^2 . For group 1, the mice were received an *i.t.* injection of $20 \mu\text{L}$ of PBS. For group 2 and group 3, the mice were received an *i.t.* injection of $20 \mu\text{L}$ of MXene QDs (0.5 mg/kg), respectively. For the PTT treatments group 3, after injection, the mice were irradiated by the 808 nm laser at a power density of 0.5 W/cm^2 for 5 min. During the irradiation, the local temperature of tumor was monitored using thermal infrared imaging camera. The tumor volume and body weight were recorded every two days.

S12. Hematocilin and eosin (H&E) stained histology. The MXene QDs ($200 \mu\text{L}$, 10 mg/kg) were injected separately into the mice via the tail vein. The mice were randomly divided into 3 groups and subjected to variable conditions. This include (i) Control group without any treatment, (ii) MXene QDs being directly *i.v.* injected into the mice, (iii) MXene QDs being directly *i.v.* injected into the mice followed by 808nm laser irradiation for 5 min. Then, the mice were killed at various time points after injection (1, 7, and 14 days, five mice per group at each time point). The major organs (heart, liver, spleen, lung, and kidney) were harvested, fixed in 10% neutral buffered formalin, processed routinely into paraffin, and sectioned at 8 mm for H&E staining.

S13. Blood routine test (BRT). The *in vivo* toxicity of MXene QDs was evaluated by BRT experiments. In brief, five healthy Balb/c mice without any treatment were used as the

controls. MXene QDs (200 μ L, 10 mg/kg) was *i.v.* injected into fifteen healthy Balb/c mice in three groups. After 1, 7, and 14 days of injection, all five mice in a group were sacrificed to collect blood (1 mL) for BRT experiments.

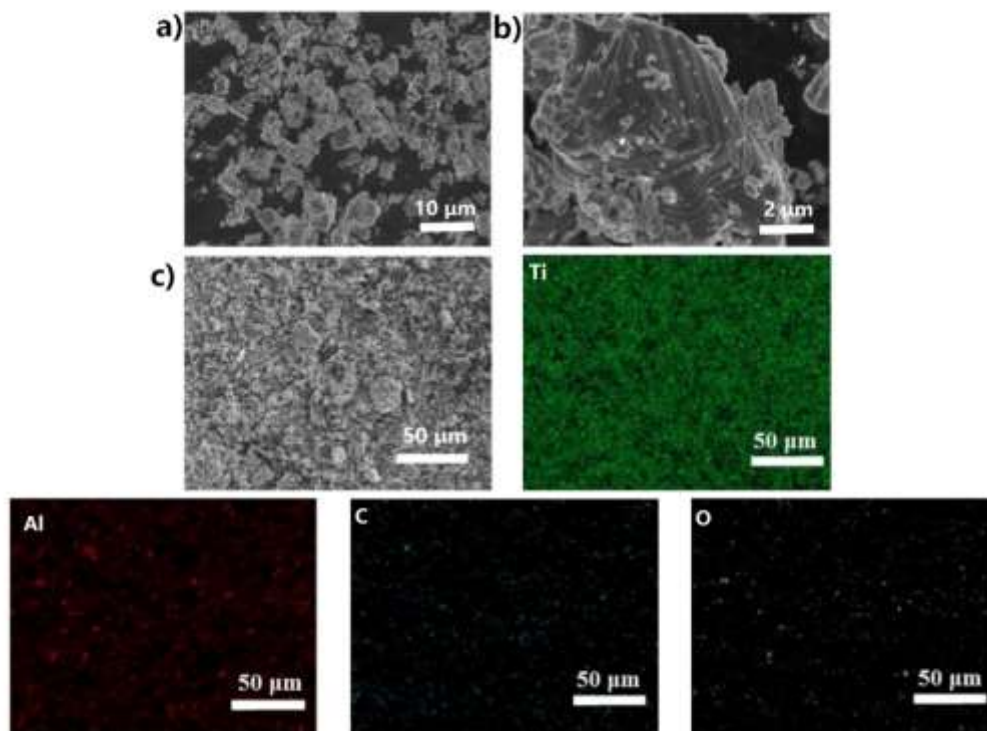


Fig. S1. a) Low and b) High magnification SEM images of as-received bulk Ti_3AlC_2 powders. c) An SEM image and corresponding elemental analysis of the as-received Ti_3AlC_2 powders, showing the presence of Ti, Al, C, and O.

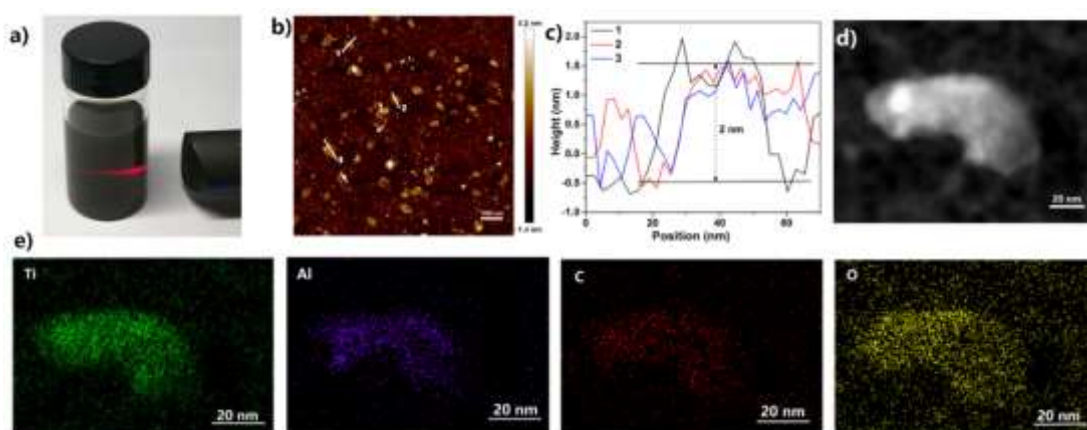


Fig. S2. a) Photograph of the MXene nanosheets dispersion in water showing an apparent Tyndall effect. b) An AFM image of MXene nanosheets. c) Height profiles along the white lines in the AFM image, showing an average height of ~ 2 nm for MXene nanosheets. d) STEM (scale bar = 20 nm). e) EDS mapping (scale bar = 20 nm) of MXene nanosheets.

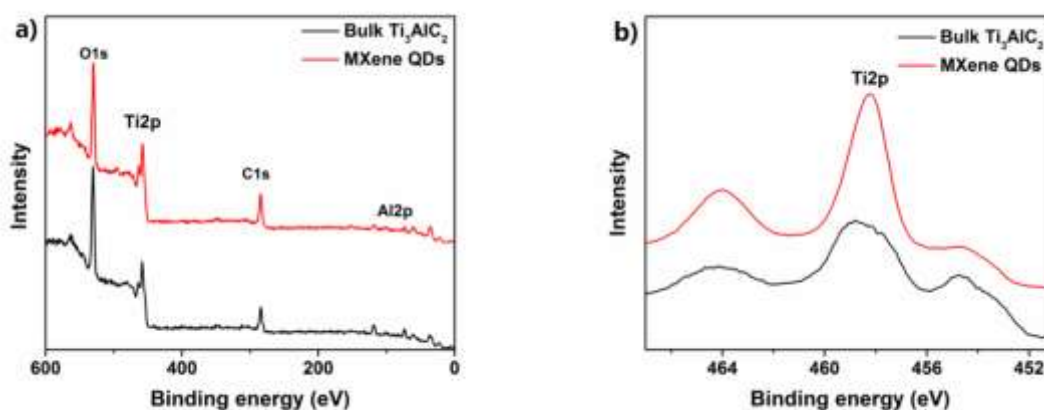


Fig. S3. XPS spectra of bulk Ti_3AlC_2 powders (black curves) and MXene QDs (Red curves).

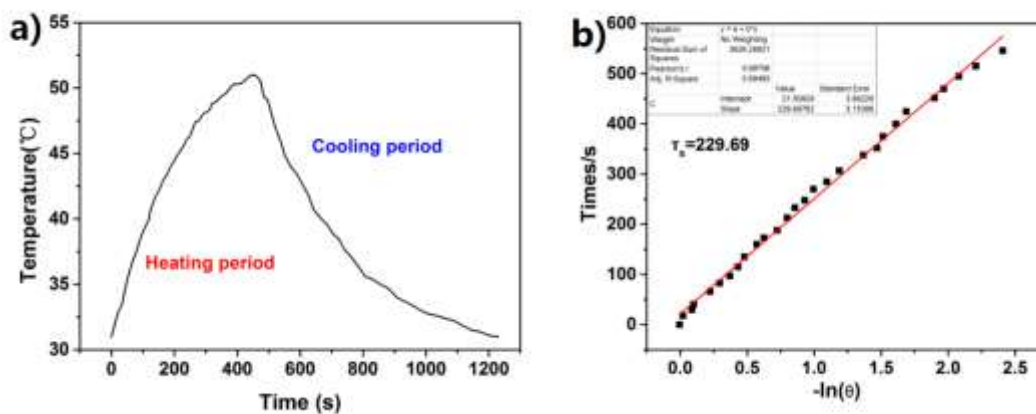


Fig. S4. a) Photothermal effect of aqueous dispersion of MXene QDs under irradiation with the NIR laser (808 nm, 1.0 W/cm^2), in which the irradiation lasted for 455 s, and then the laser was shut off. b) Time constant for heat transfer from the system is determined to be $\tau_s = 229.69$ s by applying the linear time data from the cooling period (after 455 s) versus negative

natural logarithm of driving force temperature, which is obtained from the cooling period in the panel a.

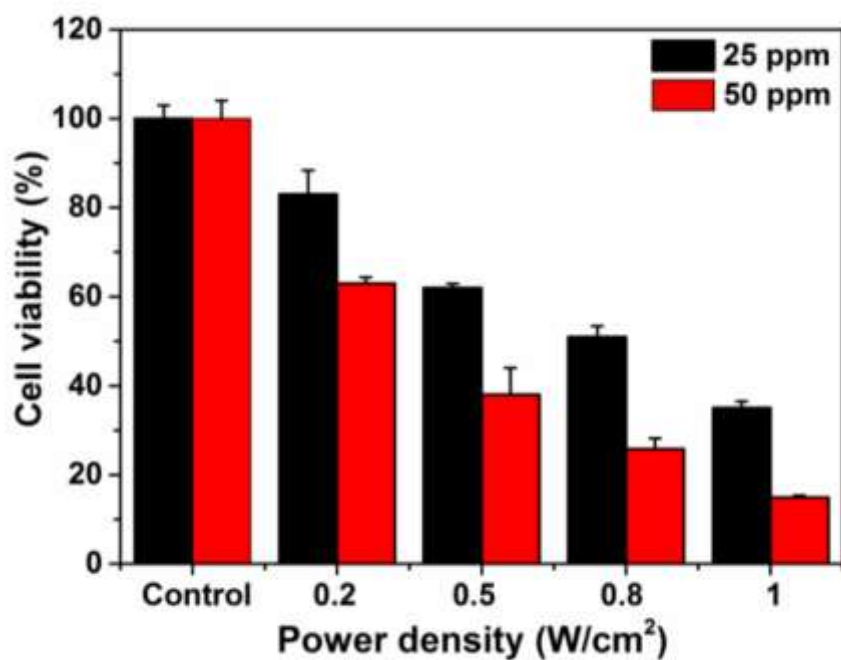


Fig. S5. Relative viability of HeLa cells after photothermal ablation induced by MXene QDs at different power densities. The concentrations of MXene QDs was 25 ppm and 50 ppm.

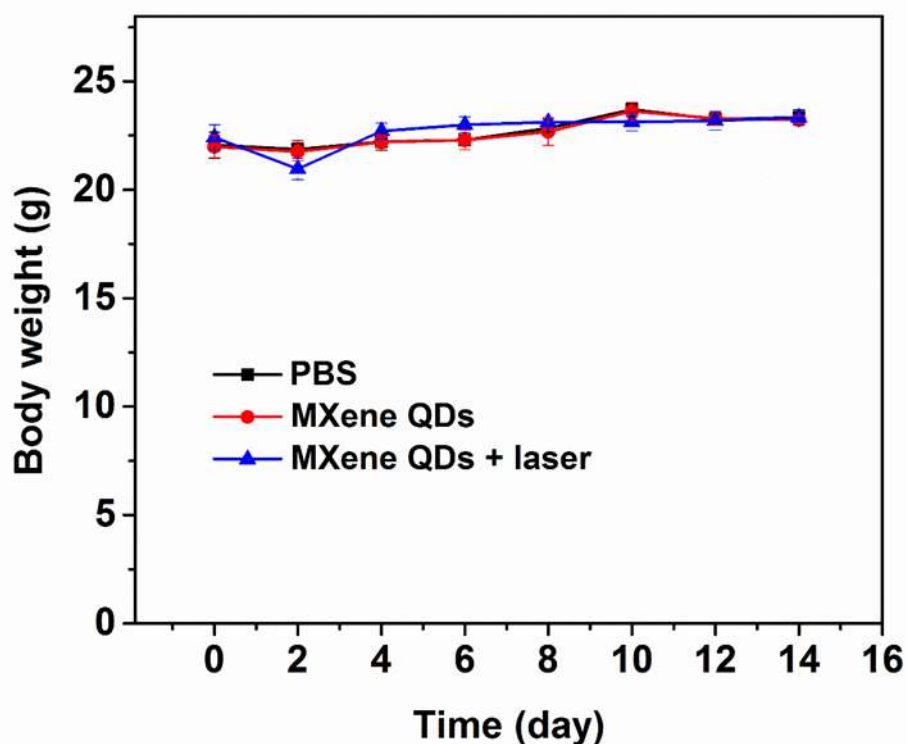


Fig. S6. Body weight of nude mice taken at every two days after various treatments with PBS (control), MXene QDs, and MXene QDs followed with 808 nm 0.5 W/cm² NIR laser irradiation.

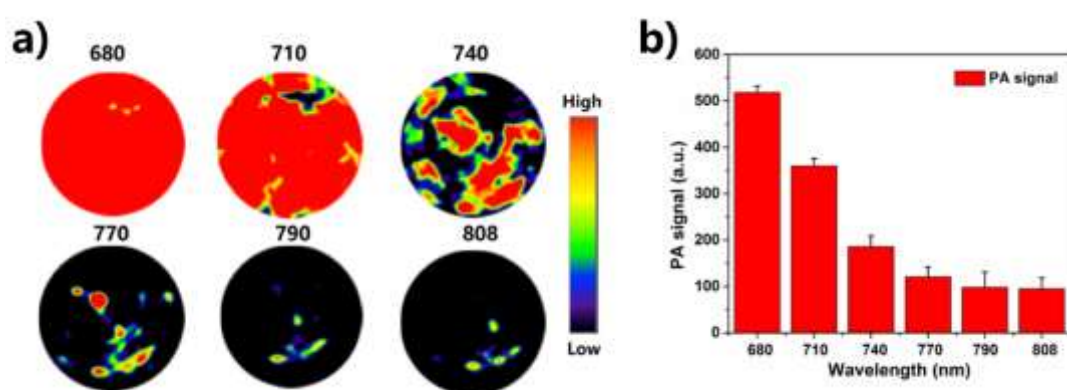


Fig. S7. a) PA images of MXene QDs at different excitation wavelengths (680, 710, 740, 770, 790, and 808 nm). b) PA signals and corresponding absorption intensities of MXene QDs at

different excitation wavelengths. The data also suggests that the optimal PA signal occurs at the wavelength of 680 nm which is used in the subsequent PA experiments.

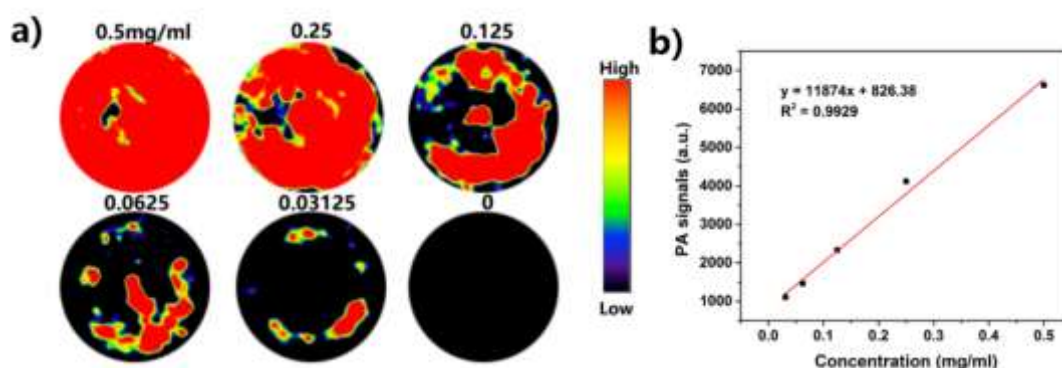


Fig. S8. a) PA images of the MXene QDs for different optical densities at 680 nm. b) Corresponding PA signal intensities of the MXene QDs for different concentrations at 680 nm. The PA signal of MXene QDs greatly enhanced with the increase of MXene QDs concentrations and correlated linearly with MXene QDs concentrations, indicating that MXene QDs should be a promising candidate for PA imaging.

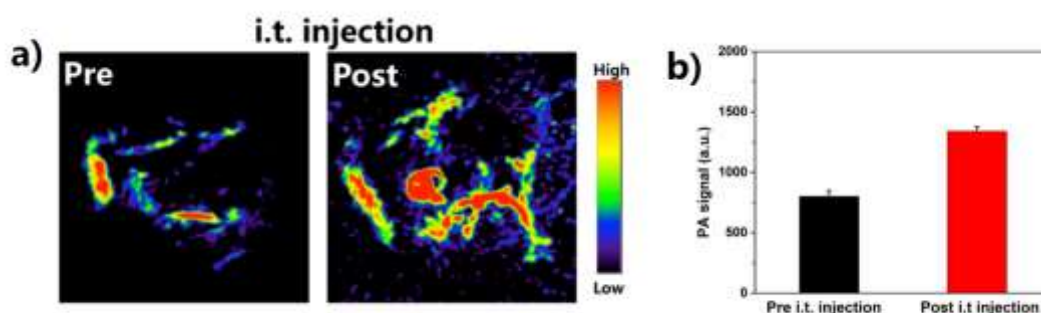


Fig. S9. a) PA images and b) PA signal intensities of tumors at 680 nm obtained before and after administration of MXene QDs. Our result indicated the great promise MXene QDs as highly efficient contrast agents for PA imaging guided cancer treatment.

Table S1. A comparison of the mass extinction coefficients of several kinds of PPT agents.

PPT agents	Mass extinction coefficient ($\text{Lg}^{-1}\text{cm}^{-1}$)	Wavelength (nm)	References
Au nanorods	13.9	808	²
rGO	24.6	808	³
MoS ₂	29.2	800	⁴
WS ₂	23.8	808	⁵
BP QDs	14.8	808	⁶
TiS ₂	26.8	808	⁷
MoSe ₂ nanodots	17.4	785	⁸
Bi ₂ Se ₃ nanosheet	11.5	808	⁹

TiN NPs	28.6	808	¹⁰
Ta ₂ NiS ₅	25.6	808	¹¹
Graphene oxide(GO)	3.6	808	³
Bi ₂ Se ₃ nanodots	3.1	808	¹²
Cu _{2-x} Se Nanoparticles	8.5	808	¹³
FeS nanoplates	15.5	808	¹⁴
Bi ₂ S ₃ nanoflowers	20.5	808	¹⁵
Ti ₃ C ₂ nanosheets	25.2	808	¹⁶
Ti _x Ta _{1-x} S _y O _z Nanosheets	54.1	808	¹⁷
MXene QDs	52.8	808	This work

Table S2. A comparison of photothermal conversion efficiency of several kinds of PTT agents.

PTT agents	Photothermal conversion efficiency	Wavelength (nm)	References
Bi ₂ Se ₃ nanosheet	34.6%	808	⁹
BP QDs	28.4%	808	⁶
Ta ₂ NiS ₅	35%	808	¹¹
MoSe ₂ nanodots	46.5%	785	⁸
Bi ₂ Se ₃ nanodots	50.7%	808	¹²
Cu _{2-x} Se Nanoparticles	64.8%	808	¹³
TiN NPs	48%	808	¹⁰

Bi ₂ S ₃ nanoflowers	64.3%	808	¹⁵
Bismuth sulfide nanorods	28.1%	808	¹⁸
Ti ₃ C ₂ nanosheets	30.6%	808	¹⁶
Ti _x Ta _{1-x} S _y O _z Nanosheets	39.2%	808	¹⁷
MXene QDs	52.2%	808	This work

Table S3. Raw data for tumor volumes of HeLa tumors in different groups of nude mice treated with group 1: PBS, group 2: Mxene QDs only, and group 3: Mxene QDs + Laser

Group 1	PBS					
Time		No.1	No.2	No.3	No.4	No.5
0 d	Length (mm)	7.3	7.8	7.9	7.3	8.1
	Width (mm)	5.9	6.1	5.8	5.7	5.2
	Weight (g)	22.2	22.3	21.2	21.8	22.8
	Volume (mm ³)	127.057	145.119	132.878	118.589	109.512
2 d	Length (mm)	8.4	8.8	8.9	8.6	8.3
	Width (mm)	7.0	6.2	6.1	6.8	6.3
	Weight (g)	22.1	22.3	21.8	21.9	21.2
	Volume (mm ³)	205.8	169.136	168.582	198.832	164.714
4 d	Length (mm)	9.2	10.1	10.2	9.8	9.4
	Width (mm)	7.3	7.8	6.9	6.8	7.1
	Weight (g)	22.9	21.8	22.0	22.1	22.3
	Volume (mm ³)	245.134	307.242	242.811	226.579	236.927
6 d	Length (mm)	9.8	10.8	10.2	10.3	11.0
	Width (mm)	7.8	8.2	7.9	8.5	7.8
	Weight (g)	22.8	22.3	21.9	22.7	21.8
	Volume (mm ³)	298.116	363.096	318.291	328.088	334.662
8 d	Length (mm)	10.9	11.2	11.5	10.7	10.8

	Width (mm)	9.0	8.2	8.9	10.0	8.3
	Weight (g)	23.0	22.8	22.7	23.0	22.7
	Volume (mm ³)	441.45	376.544	445.458	535	372.006
10 d	Length (mm)	11.2	11.8	11.3	11.9	11.2
	Width (mm)	8.9	9.4	9.7	10.2	10.8
	Weight (g)	23.2	23.9	24.0	23.9	23.5
	Volume (mm ³)	443.576	521.324	531.609	619.038	653.184
12 d	Length (mm)	12.6	12.8	12.8	12.7	12.2
	Width (mm)	11.0	10.8	11.0	10.8	10.9
	Weight (g)	23.5	23.0	23.2	23.5	23.1
	Volume (mm ³)	762.3	746.496	774.4	740.664	724.741
14 d	Length (mm)	13.2	13.8	12.9	13.8	13.7
	Width (mm)	12.1	11.9	12.8	12.1	12.0
	Weight (g)	23.5	23.8	22.9	23.1	23.4
	Volume (mm ³)	996.306	977.109	1056.77	1010.23	986.4

Group 2	MXene QDs					
Time		No.1	No.2	No.3	No.4	No.5
0 d	Length (mm)	7.2	7.4	7.0	7.1	7.8
	Width (mm)	6.2	6.1	5.9	5.9	5.8
	Weight (g)	22.1	22.1	21.2	21.8	22.7
	Volume (mm ³)	138.384	137.677	121.135	123.576	131.196
2 d	Length (mm)	8.1	8.5	8.6	8.1	8.9
	Width (mm)	7.2	6.3	6.1	6.6	6.9
	Weight (g)	22.3	22.1	21.6	21.5	21.3
	Volume (mm ³)	209.952	168.683	160.003	176.418	211.865
4 d	Length (mm)	8.6	10.2	10.0	9.5	9.4
	Width (mm)	7.6	7.2	7.6	6.3	7.5
	Weight (g)	22.0	21.9	22.6	22.5	22.0
	Volume (mm ³)	248.368	264.364	288.8	188.528	264.375
6 d	Length (mm)	9.9	10.0	10.7	10.6	10.8
	Width (mm)	7.9	9.0	7.5	8.6	7.3
	Weight (g)	22.8	22.3	21.9	22.7	21.8
	Volume (mm ³)	308.93	405	300.938	391.988	287.766
8 d	Length (mm)	10.1	11.3	11.2	10.3	11.2
	Width (mm)	9.3	9.0	9.0	10.1	8.1
	Weight (g)	23.1	23.0	23.3	22.1	21.9

	Volume (mm ³)	436.755	457.65	453.6	525.352	367.416
10 d	Length (mm)	11.0	11.9	11.6	11.9	11.3
	Width (mm)	8.8	9.6	9.2	10.3	10.4
	Weight (g)	23.1	23.8	24.2	23.4	23.6
	Volume (mm ³)	425.92	548.352	490.913	631.236	611.104
12 d	Length (mm)	12.5	12.9	12.4	12.3	12.2
	Width (mm)	11.2	11.3	11.3	10.9	10.8
	Weight (g)	22.9	23.1	23.3	23.6	23.5
	Volume (mm ³)	784	823.601	791.618	730.682	711.504
14 d	Length (mm)	13.3	13.9	12.5	12.5	13.6
	Width (mm)	12.6	11.8	12.6	12.4	12.5
	Weight (g)	23.2	23.3	23.4	22.9	23.3
	Volume (mm ³)	1055.75	967.718	992.25	961	1062.8

Group 3	MXene QDs + Laser					
Time		No.1	No.2	No.3	No.4	No.5
0 d	Length (mm)	6.9	7.2	6.9	7.8	7.5
	Width (mm)	5.5	5.1	6.2	6.1	6.1
	Weight (g)	22.3	23.1	22.8	21.6	22.3
	Volume (mm ³)	104.363	93.636	132.618	145.119	139.538
2 d	Length (mm)	0	0	0	0	0
	Width (mm)	0	0	0	0	0
	Weight (g)	21.2	21.2	20.3	20.6	21.5
	Volume (mm ³)	0	0	0	0	0
4 d	Length (mm)	0	0	0	0	0
	Width (mm)	0	0	0	0	0
	Weight (g)	22.4	23.1	22.5	22.4	23.1
	Volume (mm ³)	0	0	0	0	0
6 d	Length (mm)	0	0	0	0	0
	Width (mm)	0	0	0	0	0
	Weight (g)	22.5	23.3	22.9	23.4	22.9
	Volume (mm ³)	0	0	0	0	0
8 d	Length (mm)	0	0	0	0	0
	Width (mm)	0	0	0	0	0

	Weight (g)	23.1	23.2	22.9	23.2	23.2
	Volume (mm ³)	0	0	0	0	0
10 d	Length (mm)	0	0	0	0	0
	Width (mm)	0	0	0	0	0
	Weight (g)	23.1	22.5	23.6	23.4	23.1
	Volume (mm ³)	0	0	0	0	0
12 d	Length (mm)	0	0	0	0	0
	Width (mm)	0	0	0	0	0
	Weight (g)	23.1	23.2	22.5	23.6	23.5
	Volume (mm ³)	0	0	0	0	0
14 d	Length (mm)	0	0	0	0	0
	Width (mm)	0	0	0	0	0
	Weight (g)	22.8	23.7	23.6	23.4	23.2
	Volume (mm ³)	0	0	0	0	0

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