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An injectable thermosensitive hydrogel loading with theranostic nanoprobe for synergetic chemo-photothermal therapy of multidrug-resistant hepatocellular carcinoma

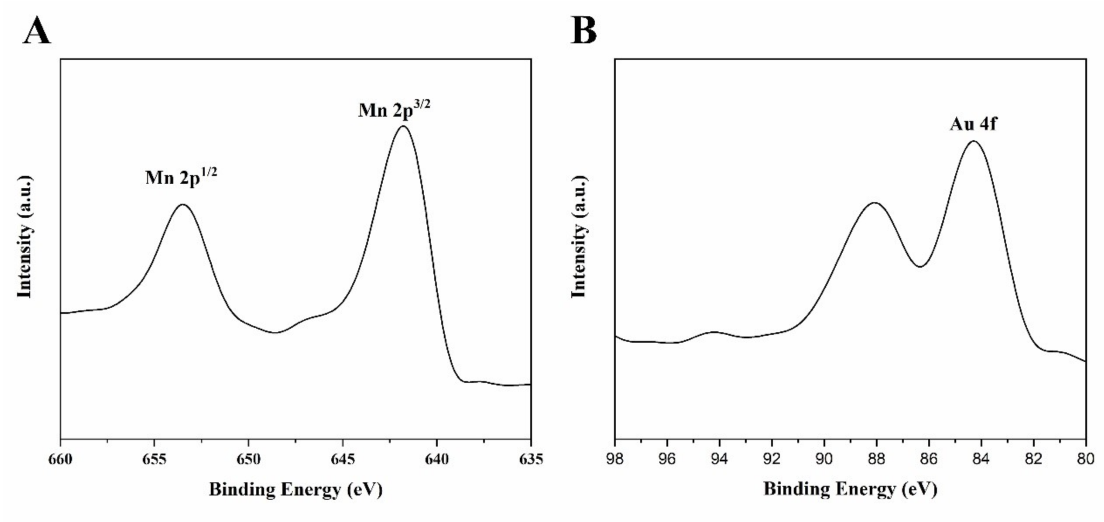

Fig. S1. The valence state of Mn (A) and Au (B).

Table S1. The analysis of element content in Au-MnO NPs measured by ICP-AES.

Element	Content (mean ± sd, wt%)
Mn	14.51 ± 0.85
Au	60.04 ± 1.47

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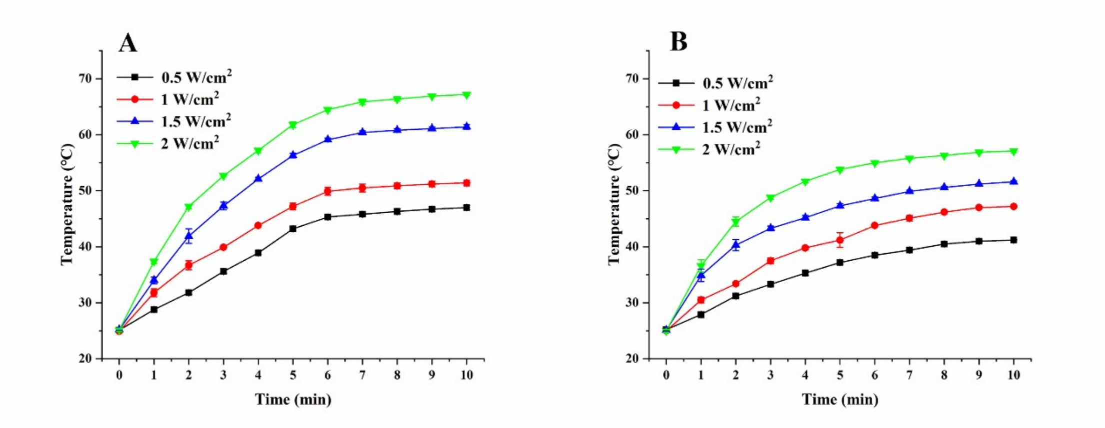

Fig. S2. The temperature change of DOX@Au-MnO-L NPs (A) and DAML/H (B) at various intensity during NIR laser irradiation for 10 min.

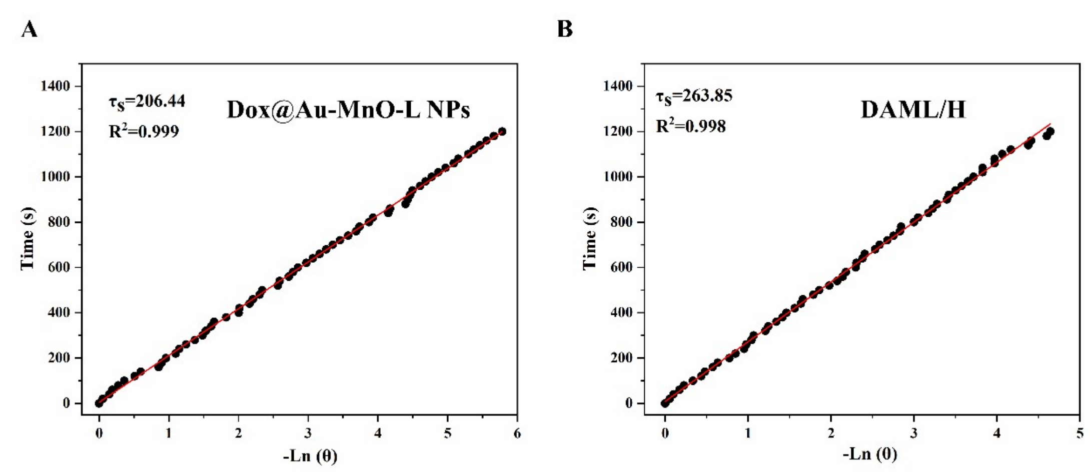

Fig. S3. Plot of cooling time versus negative natural logarithm of the driving force temperature obtained from a cooling stage to calculate time constant (τs) for heat transfer of DOX@Au-MnO-L NPs (A) and DAML/H (B).

A more detailed NIR-responsive release study of DOX from DOX@Au-MnO-L NPs and DAML/H was investigated (Fig. S4). Compared with non-NIR-irradiation, the DOX release rate of DOX@Au-MnO-L NPs or DAML/H was much faster under NIR laser irradiation.

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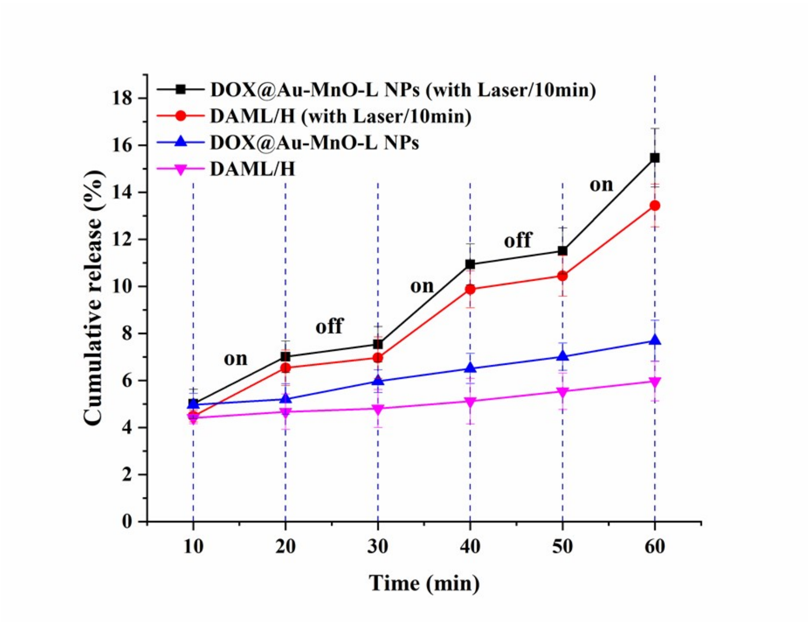

Fig. S4. *In vitro* cumulative DOX released from DOX@Au-Au-MnO-L NPs and DAML/H with or without NIR laser irradiation (808 nm, 1 W/cm^2, 10 min).

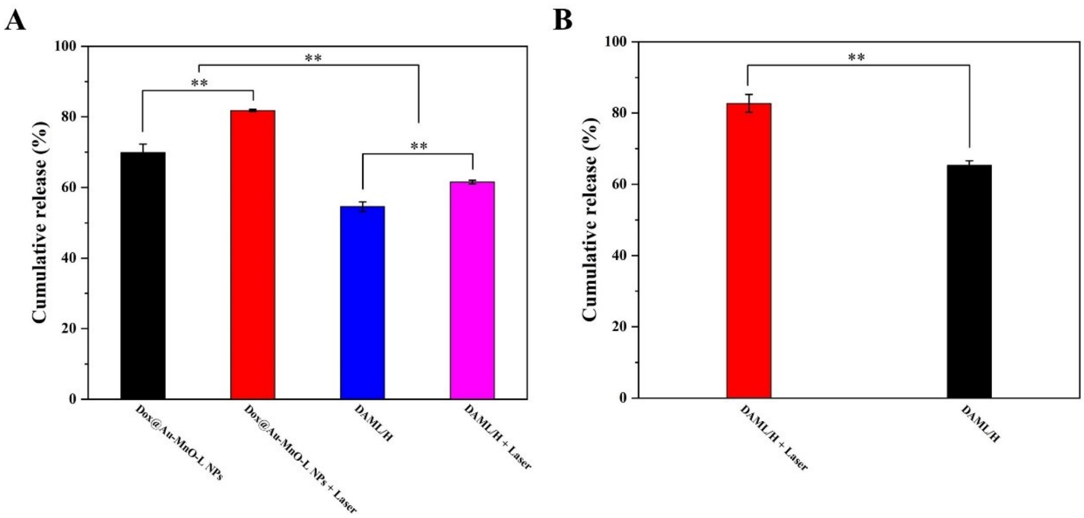

Fig. S5. (A) Cumulative DOX released from DOX@Au-Au-MnO-L NPs and DAML/H at 48 h, corresponding to Fig. 3A. (B) Cumulative DOX released from DAML/H on day 16, corresponding to Fig. 3B.

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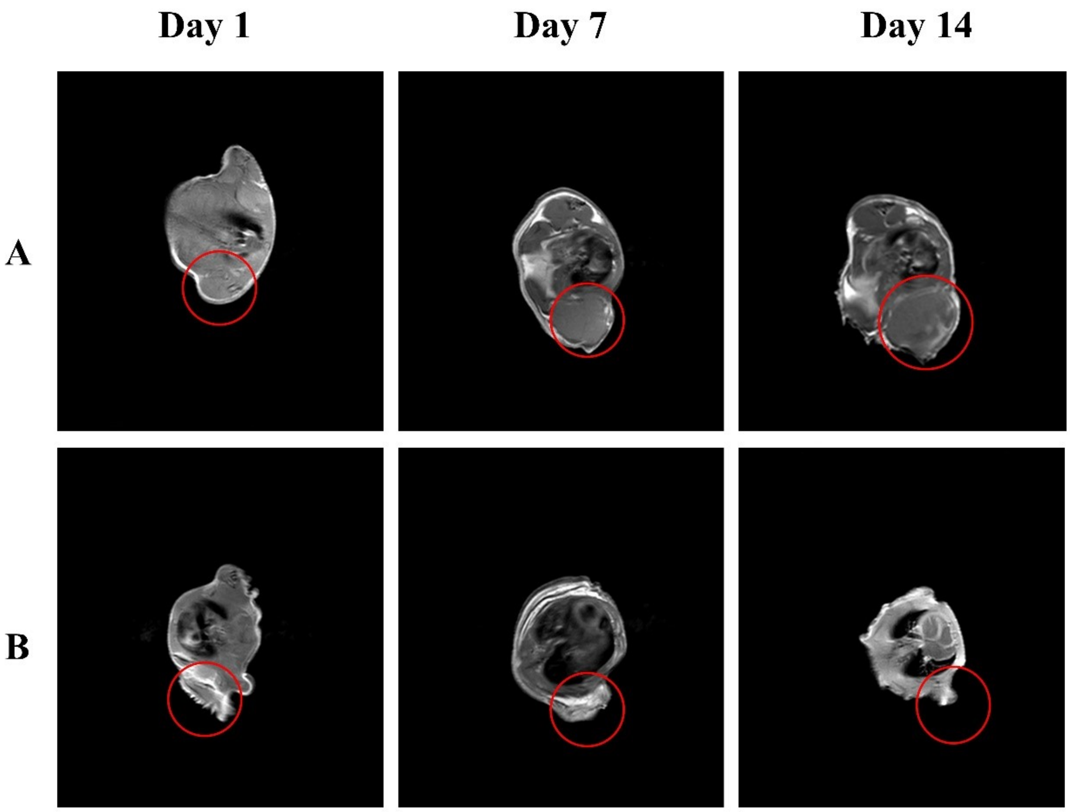

Fig. S6. *In vivo* MR images of HepG2/ADR-bearing mice at Day 1, 7 and 14. The mice were treated were treated with NIR radiation (808 nm, 1 W/cm^2, 10 min) every day: (a) PBS and (b) DAML/H.

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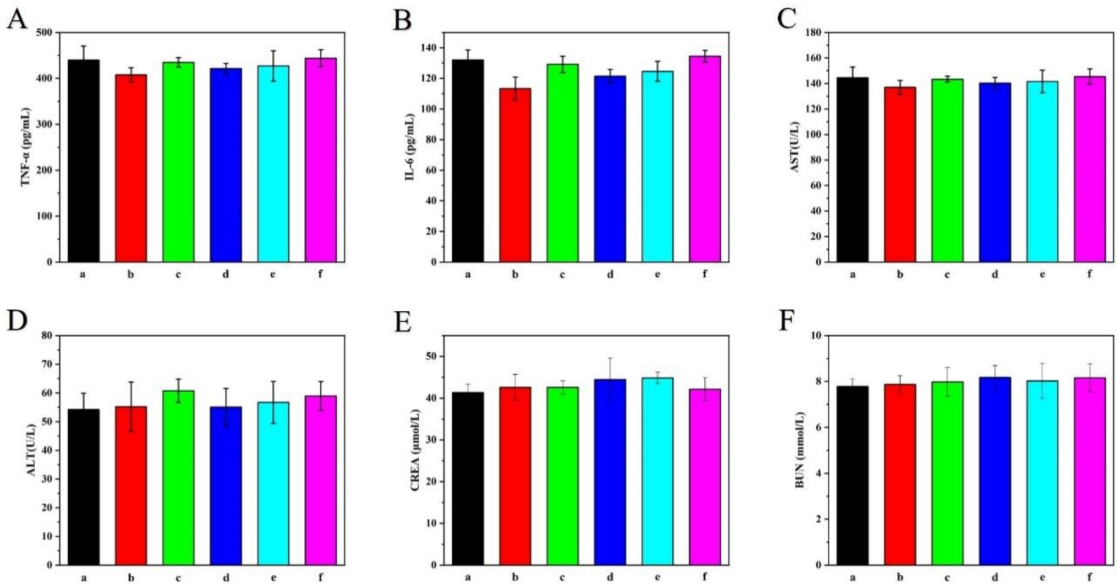

Fig. S7. Blood test results of mice received intra-tumoral injection. Mice in the PBS (control), DOX (a), DOX@Au-MnO-L NPs (b), and DOX@Au-MnO-L NPs + laser (d) groups were injected intratumorally with a dosage of 100 □L every other day, while mice in the DAML/H (c) and DAML/H + laser (e) groups were received only one intratumoral injection on the first day. The DOX@Au-MnO-L NPs + laser (d) group was subjected to a NIR laser treatment every other day, while the DAML/H + laser (e) group was subjected to a NIR laser treatment every day. The NIR laser parameter was set to 808 nm, 1 W/cm^2, 10 min.

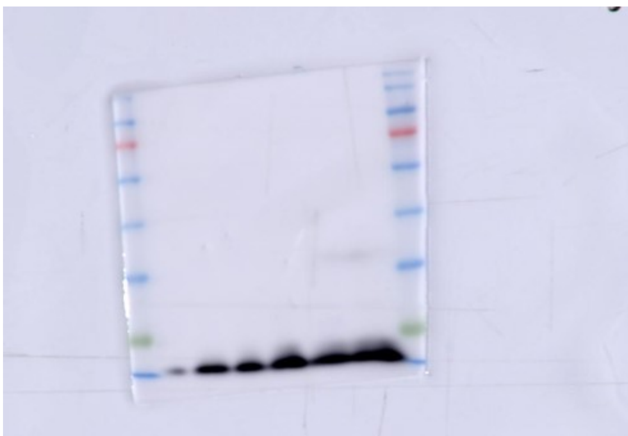

Fig. S8(a). Bax Panel: Marker, Control, a, b, c, d, e, marker

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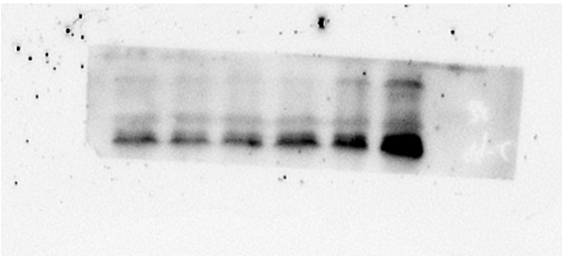

Fig. S8(b). Bax Panel: Control, a, b, c, d, e

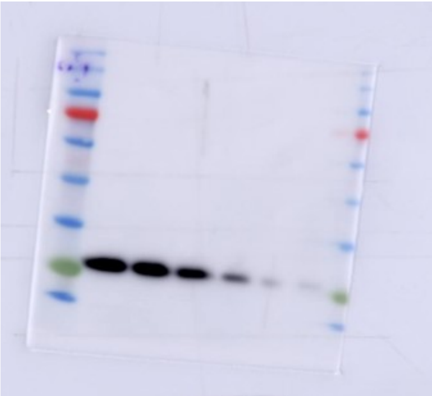

Fig. S9(a). BCL-2 Panel: Control, a, b, c, d, e

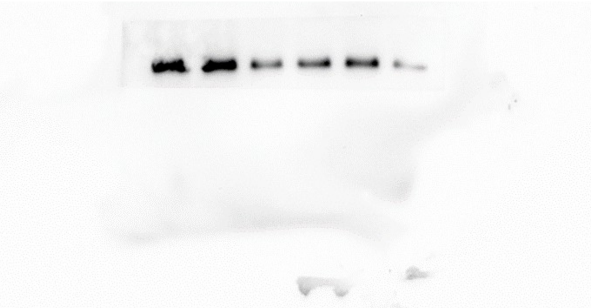

Fig. S9(b). BCL-2 Panel: Control, a, b, c, d, e

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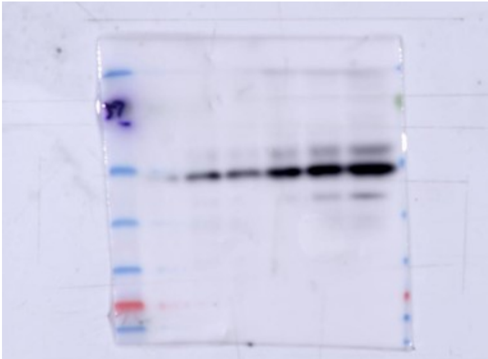

Fig. S10(a). Capase-3 Panel: Control, a, b, c, d, e

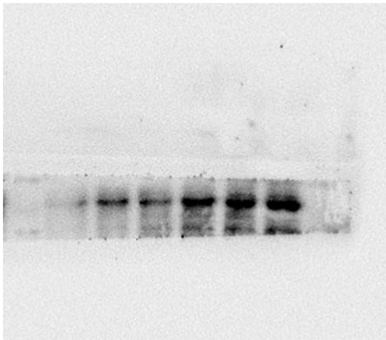

Fig. S10(b). Capase-3 Panel: Control, a, b, c, d, e

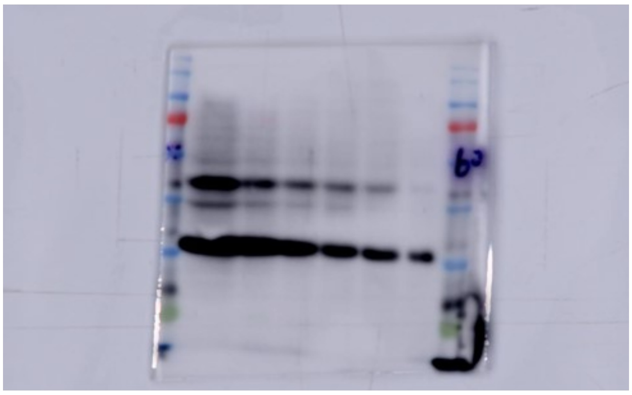

Fig. S11(a). P53 Panel: Control, a, b, c, d, e

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Fig. S11(b). P53 Panel: Control, a, b, c, d, e

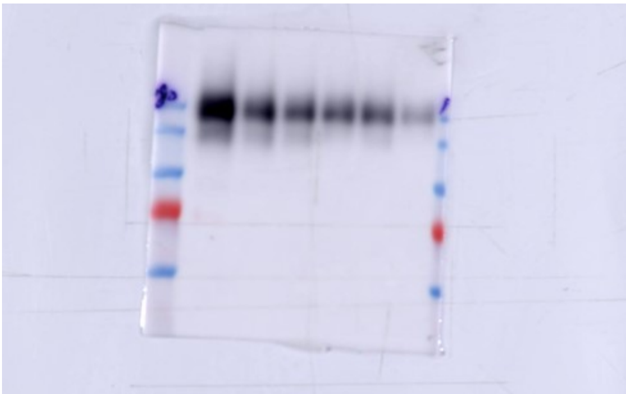

Fig. S12(a). P-gp Panel: Control, a, b, c, d, e

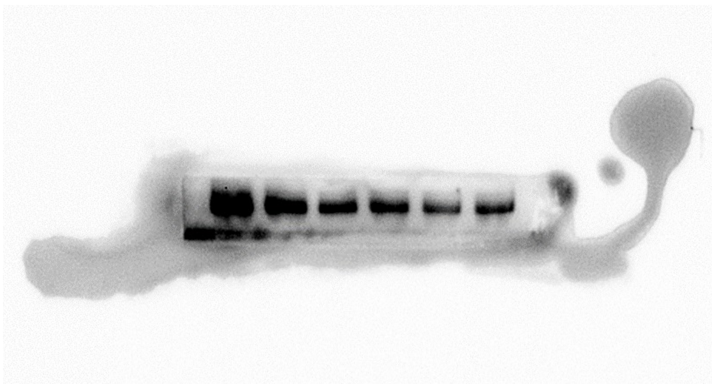

Fig. S12(b). P-gp Panel: Control, a, b, c, d, e

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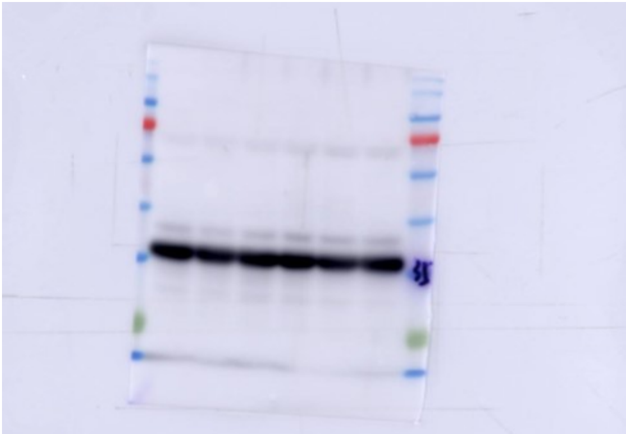

Fig. S13(a). GAPDH Panel: Control, a, b, c, d, e

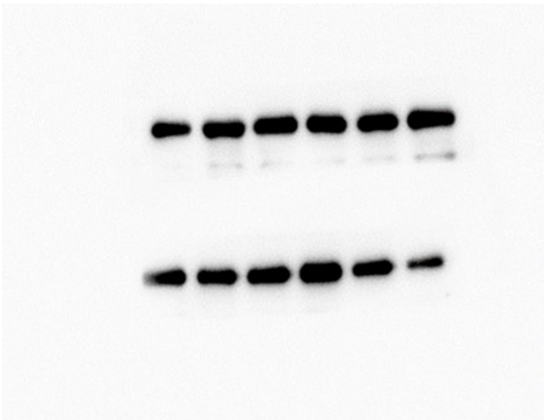

Fig. S13(b). GAPDH Panel: Control, a, b, c, d, e

Method and Results:

Photothermal conversion efficiency of DOX@Au-Mno-L NPs and DAML/H

The photothermal conversion efficiency of DOX@Au-Mno-L NPs and DAML/H was measured according to previous report [1]. DOX@Au-Mno-L NPs and DAML/H underwent continuous irradiation of 808 nm laser (1W/cm^2) until steady state temperature was reached. Then the laser was turn off, and the aqueous solution was naturally cooled to the environment temperature. The η value was calculated as follows:

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$$\eta = \frac{hA\Delta T - Qs}{I(1-10^{-A808})} \times 100\% \quad (1)$$

Here h is the heat transfer coefficient, A is the surface area of the container, and ΔT is the temperature change, which is defined as $T\text{-}T_{sur}$ (T and T_{sur} are the solution temperature and ambient temperature of the surroundings, respectively).

Qs is the heat associated with the light absorbance of the solvent, I is the laser power, A_{808} is the absorbance of sample at 808 nm, and η is the conversion efficiency. hA can be determined by applying the linear time data from the cooling period vs –lnθ

$$hA = \frac{mC_p}{\tau_s} \quad (2)$$

where m and Cp are the mass and heat capacity of solvent (water), respectively.

A dimensionless parameter θ was calculated as followed:

$$\theta = (T - T_{sur})/(T_{max} - T_{Sur}) \quad (3)$$

A sample system time constant τs could be calculated as followed:

$$t = -\tau s \ln(\theta) \quad (4)$$

Table1 Parameters of the calculation of η value

The maximum steady temperature of DOX@Au-Mno-L NPs (T_{max})	51.0 ℃
The maximum steady temperature of DAML/H (T_{max})	48.9 ℃
Environmental temperature (T_{Sur})	25℃
The absorbance of DOX@Au-Mno-L NPs at 808 nm (A_{808})	0.48
The absorbance of DAML/H at 808 nm (A_{808})	0.64
The mass of the sample (m)	0.5 g

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The laser power for irradiation (*I*)	1 W/cm^2
heat capacity of solvent (Cp)	4.2 J/g °C
Q_S	0.0252 W

QS was heat dissipated from the light absorbed by the solvent and container. τ_s of DOX@Au-Mno-L NPs and DAML/H was calculated to be 206.44 and 263.85, respectively. In addition, m was 0.5 g and c_p was 4.2 J/g °C. Thus, according to Equation (2), the *h*A of DOX@Au-Mno-L NPs and DAML/H was calculated to be 0.0101 W/°C and 0.0079 W/°C, respectively. Qs was heat dissipated from the light absorbed by the container itself, which was determined independently to be 0.0252 W using a container containing pure water. Thus, substituting the values of each parameters to Equation (1), the 808 nm laser photothermal conversion efficiency (η) of the DOX@Au-Mno-L NPs and DAML/H could be calculated to be 35.77% and 21.41%, respectively.