

## Supporting Information

### **Low intensity focused ultrasound (LIFU) triggered drug release from Cetuximab-conjugated phase-changeable nanoparticles for precision theranostics against anaplastic thyroid carcinoma**

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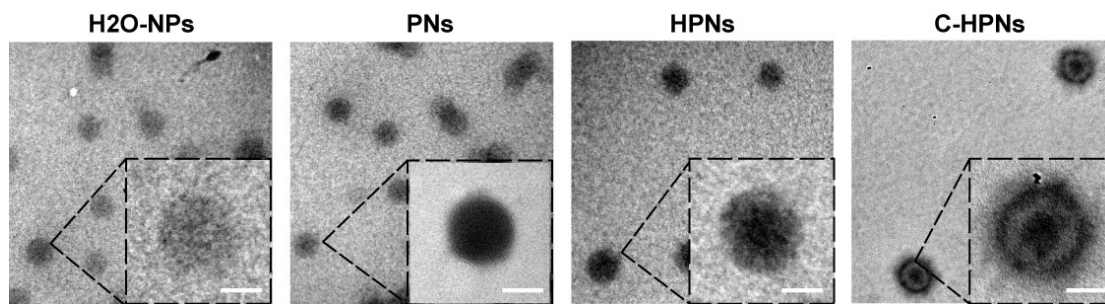
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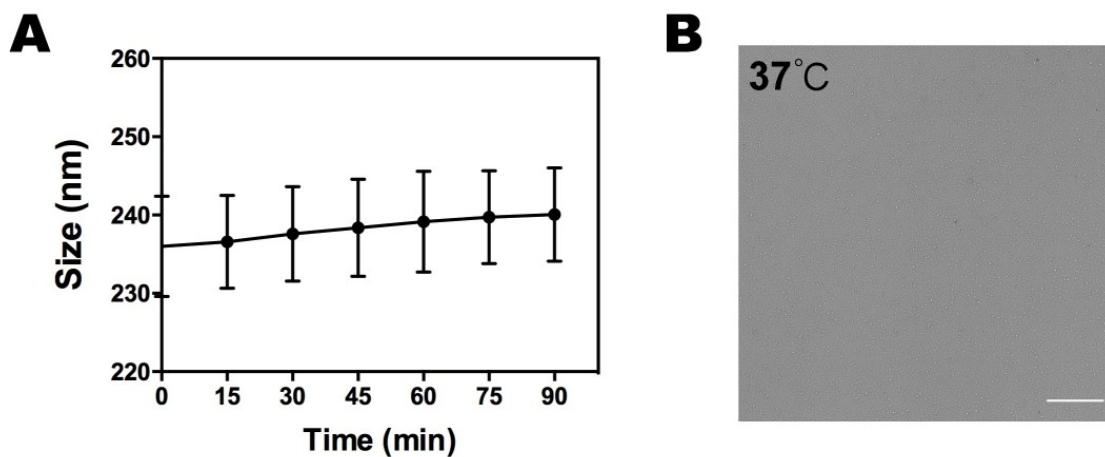
**Table S1** The particle size, PDI and zeta potential of different formulations of NPs determined by DLS. (The data was shown as mean  $\pm$  SD, n=3 per group).

| Groups | Particle<br>Size (nm) | PDI             | Zeta             |
|--------|-----------------------|-----------------|------------------|
|        |                       |                 | Potential (mV)   |
| PNs    | 163.5 $\pm$ 7.25      | 0.54 $\pm$ 0.28 | -1.19 $\pm$ 0.33 |
| C-PNs  | 175.8 $\pm$ 11.75     | 0.1 $\pm$ 0.02  | -2.48 $\pm$ 0.53 |
| HPNs   | 204.3 $\pm$ 3.84      | 0.26 $\pm$ 0.07 | -2.2 $\pm$ 0.77  |
| C-HPNs | 241.7 $\pm$ 4.04      | 0.19 $\pm$ 0.03 | -3.28 $\pm$ 0.91 |

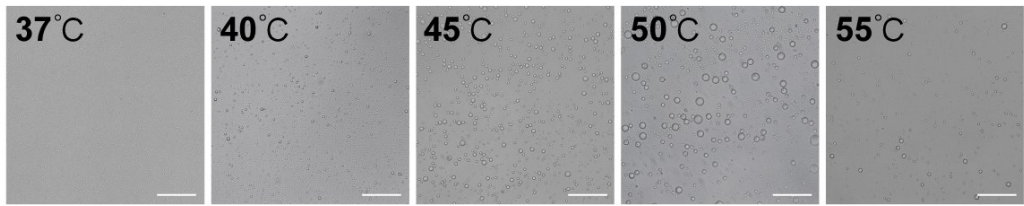
**Figure S1** TEM images of H<sub>2</sub>O-NPs, PNs, HPNs, and C-HPNs. The scale bar is 100 nm.



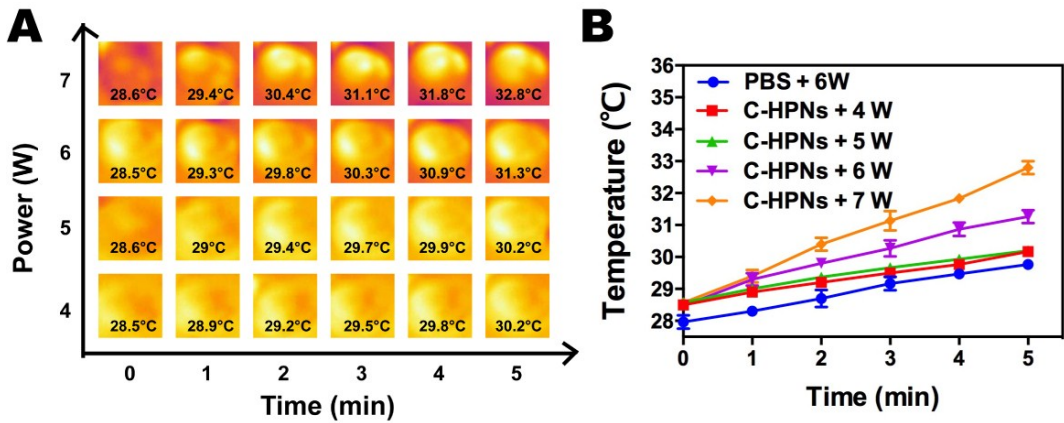
**Figure S2** (A) The size changes of C-HPNs at 37°C for 90 min. (B) Optical microscopic image of C-HPNs at 37°C. (The data was shown as mean  $\pm$  SD, n=3 per group, scale bar = 10  $\mu$ m).



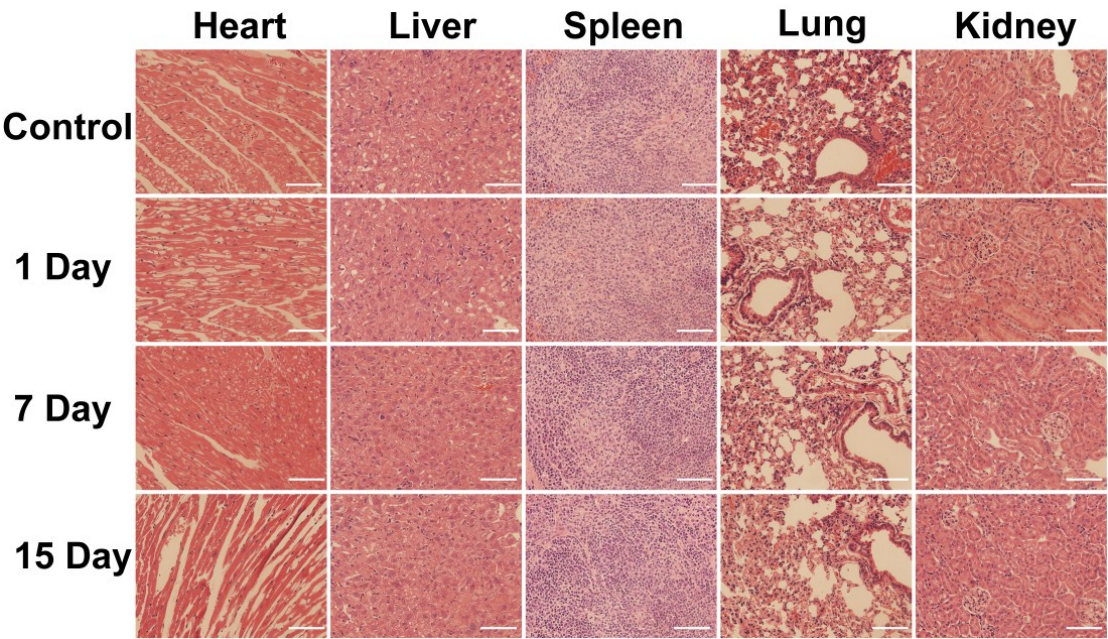
**Figure S3** Optical microscopic images of C-HPNs heated to different temperatures. The scale bar is 10  $\mu\text{m}$ , n=3 per group.



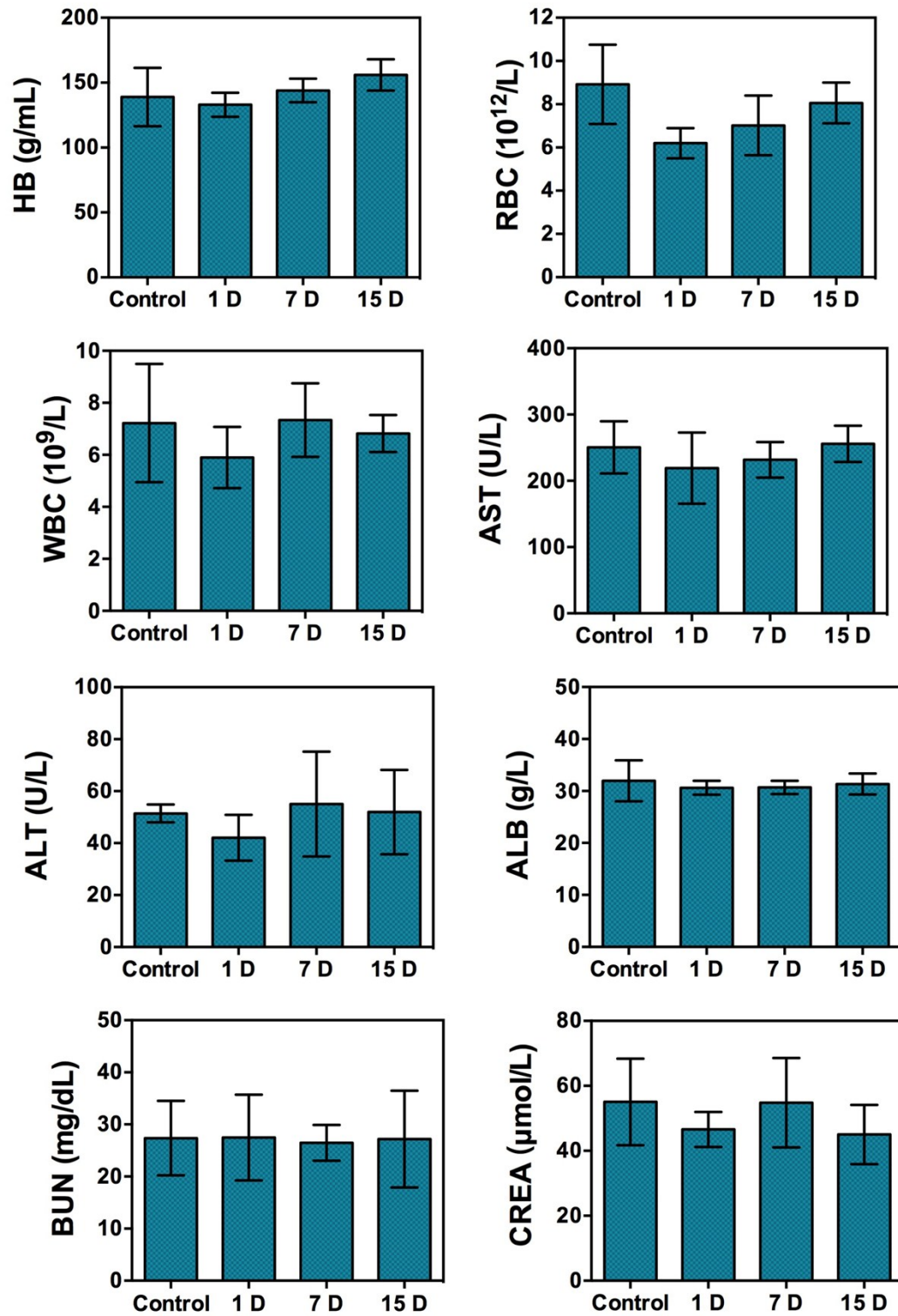
**Figure S4** The average temperature at different parameters of LIFU (A), and the temperature increase curves after LIFU irradiation.



**Figure S5** H&E staining of major organs of the control group and the experimental groups 1, 7, 15 days after intravenous administration of C-HPNs. The scale bar is 100  $\mu\text{m}$ .



**Figure S6** Blood biochemical examination of mice at 1, 7, 15 days after intravenous injection of C-HPNs. (The data was shown as mean  $\pm$  SD, n=3 per group).



**Table S2** Mean tumor weight and mean percentage tumor inhibition in each group after treatment for 17 days. (The data was shown as mean  $\pm$  SD, n=5 per group).

| <b>Group</b>          | <b>Tumor weight<br/>(mg)</b> | <b>Mean tumor inhibition<br/>rate (%)</b> |
|-----------------------|------------------------------|-------------------------------------------|
| <b>Saline control</b> | 627.94 $\pm$ 50.77           | -                                         |
| <b>Saline + LIFU</b>  | 604.08 $\pm$ 64.09           | 3.92 $\pm$ 4.67                           |
| <b>C-PNs</b>          | 543.3 $\pm$ 50.99            | 13.41 $\pm$ 5.4                           |
| <b>C-PNs + LIFU</b>   | 504.48 $\pm$ 39.51           | 19.64 $\pm$ 0.7                           |
| <b>HPNs</b>           | 433.84 $\pm$ 40.22           | 30.61 $\pm$ 8.0                           |
| <b>HPNs + LIFU</b>    | 386.34 $\pm$ 30.91           | 39.13 $\pm$ 5.4                           |
| <b>10-HCPT</b>        | 381.22 $\pm$ 32.17           | 38.18 $\pm$ 6.9                           |
| <b>10-HCPT + LIFU</b> | 356.18 $\pm$ 21.56           | 43.08 $\pm$ 4.3                           |
| <b>C-HPNs</b>         | 291.98 $\pm$ 23.67           | 53.36 $\pm$ 4.3                           |
| <b>C-HPNs + LIFU</b>  | 117.22 $\pm$ 24.83           | 81.24 $\pm$ 4.0                           |

**Table S3** Blood biochemical examination of mice after different treatment. (The data was shown as mean  $\pm$  SD, n=5 per group).

| □                                   | Without LIFU    |                 |                 |                      |                 | With LIFU       |                 |                 |                      |                 |
|-------------------------------------|-----------------|-----------------|-----------------|----------------------|-----------------|-----------------|-----------------|-----------------|----------------------|-----------------|
|                                     | Contr<br>ol     | C-<br>PNs       | HPNs            | 10-<br>HCP<br>T      | C-<br>HPNs      | Contr<br>ol     | C-<br>PNs       | HPNs            | 10-<br>HCP<br>T      | C-<br>HPNs      |
| <b>HB</b><br>(g/mL)                 | 120 $\pm$ 8.7   | 123 $\pm$ 6.2   | 124 $\pm$ 7.5   | 126.4 $\pm$ 4.7      | 124.8 $\pm$ 9.5 | 122 $\pm$ 9.9   | 123 $\pm$ 4.9   | 132.3 $\pm$ 2.0 | 123.4 $\pm$ 1.3      | 120.4 $\pm$ 9.9 |
| <b>RBC</b><br>(10 <sup>12</sup> /L) | 6.2 $\pm$ 0.7   | 6.6 $\pm$ 0.5   | 7.2 $\pm$ 1.6   | 8.2 $\pm$ 1.6        | 8 $\pm$ 1.6     | 6.6 $\pm$ 1.0   | 7.5 $\pm$ 1.2   | 7.6 $\pm$ 1.0   | 6.8 $\pm$ 0.5        | 6.8 $\pm$ 0.6   |
| <b>WBC</b><br>(10 <sup>9</sup> /L)  | 7.4 $\pm$ 0.7   | 7 $\pm$ 0.3     | 6.9 $\pm$ 0.8   | 3.6 $\pm$ 0.4<br>*   | 7.8 $\pm$ 0.5   | 6.9 $\pm$ 1.4   | 7.1 $\pm$ 1.2   | 7.1 $\pm$ 1.5   | 3.7 $\pm$ 0.4<br>*   | 7.1 $\pm$ 1.2   |
| <b>AST</b><br>(U/L)                 | 248.8 $\pm$ 8.0 | 238.9 $\pm$ 2.0 | 230.6 $\pm$ 1.9 | 238.3 $\pm$ 8.5      | 219.5 $\pm$ 3.5 | 220.6 $\pm$ 3.4 | 243.9 $\pm$ 3.9 | 227.7 $\pm$ 1.9 | 245.5 $\pm$ 1.4      | 240.4 $\pm$ 2.6 |
| <b>ALT</b><br>(U/L)                 | 49.1 $\pm$ 6.5  | 55.8 $\pm$ 17.5 | 50.1 $\pm$ 10.5 | 141.3 $\pm$ 2.3<br>* | 49.1 $\pm$ 9.3  | 46.8 $\pm$ 9.2  | 48.7 $\pm$ 6.0  | 45.9 $\pm$ 7.9  | 156.3 $\pm$ 2.8<br>* | 52.8 $\pm$ 7.9  |
| <b>ALB</b><br>(g/L)                 | 29.8 $\pm$ 1.5  | 32.1 $\pm$ 1.9  | 30.7 $\pm$ 1.6  | 32.5 $\pm$ 4.2       | 34.4 $\pm$ 3.8  | 31.7 $\pm$ 3.0  | 32.1 $\pm$ 2.5  | 32.1 $\pm$ 2.3  | 31.8 $\pm$ 3.1       | 31.2 $\pm$ 2.9  |
| <b>BUN</b><br>(mg/dL)               | 24.8 $\pm$ 3.9  | 26.1 $\pm$ 6.1  | 24.4 $\pm$ 3.3  | 44.4 $\pm$ 3.9<br>*  | 29.9 $\pm$ 4.6  | 26.9 $\pm$ 2.8  | 29.1 $\pm$ 5.9  | 23.8 $\pm$ 3.0  | 52.9 $\pm$ 4.6<br>*  | 28.6 $\pm$ 6.7  |
| <b>CREA</b><br>( $\mu$ mol/L)       | 43.5 $\pm$ 3.6  | 38.7 $\pm$ 6.5  | 38.0 $\pm$ 4.4  | 38.8 $\pm$ 3.1       | 44.9 $\pm$ 6.9  | 40.5 $\pm$ 10.7 | 47.2 $\pm$ 9.6  | 47.3 $\pm$ 7.1  | 46.4 $\pm$ 5.9       | 45.3 $\pm$ 4.4  |