# Supporting information

## Materials and Reagents

Hexadecyltrimethylammonium chloride (CTAC), triethanolamine (TEA), (3-aminopropyl)triethoxysilane (APTES), all-trans-retinoic acid (ATRA), cyclohexane and ammonia solution were purchased from Aladdin, China. 2-dioleoyl-snglycero-3-phosphocholine (DOPC), cholesterol and 1,2-distearoylsn-glycero-3-phosphoethanolamine-N- [methoxy(polyethylene glycol)-2000] (DSPE-PEG2000) were purchased from Avanti Polar Lipids lnc, USA. Recombinant murine IL-2 was purchased from Peprotech, USA. Doxorubicin hydrochloride (DOX) was purchased from Beijing Huafeng United Technology Co., China. Dulbecco's modified eagle medium (DMEM), penicillin-streptomycin, fetal bovine serum (FBS) and trypsin without EDTA were purchased from Hyclone, USA. 3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) was purchased from Biosharp, China. Cyanine5-amine ester was purchased from Lumiprobe, USA. Anti-mouse monoclonal antibodies against CD16/CD32, CD11b, Gr-1, CD86, CD11c, CD3e, CD4, CD8a, CD69, NK1.1 and IFN-γ were purchased from BD Pharmingen™, USA. Mouse lymphocyte isolating solution was purchased from Dakewe biotech, China. The solvents including anhydrous methanol, ethanol, acetic acid, hydrochloric acid, diethyl ether, chloroform, tetraethylorthosilicate (TEOS) and dimethyl sulfoxide (DMSO) were of analytical grade and purchased from Sinopharm, China. Methanol and acetonitrile of chromatographic grade were purchased from Sigma-Aldrich, USA.

**Cell Culture and Animals**

Murine melanoma cell line B16F10 (syngeneic with C57BL/6) and L929 fibrosarcoma cells were cultured in DMEM supplemented with 10% FBS, 100 IU/mL of penicillin, and 100 μg/mL of streptomycin in a humidified atmosphere incubator with 5% $CO_2$ at 37$^{o}$C. Female 4-5 weeks C57BL/6 mice were purchased from Hubei Provincial Center for Disease Control and Prevention. SD rats (200 ± 20 g) were obtained from the Laboratory Animal Resources of Huazhong University of Science and Technology (HUST). All animals were maintained under specific pathogen-free condition in the Animal Center of HUST. All the animal experiments were performed with the approval of local ethical committee and animals were treated according to the National Institutes of Health guide for the care and use of Laboratory animals.

**Synthesis of $NH_2$-dHMSN**

dHMSN and 0.2 mL of APTES were mixed in 20 mL of absolute ethanol, and then refluxed at 88ºC for 12 h. After that, the mixture was centrifuged and washed with ethanol to remove residual APTES. The obtained $NH_2$-modified dHMSN ($NH_2$-dHMSN) was dispersed in DMSO directly for ATRA loading.

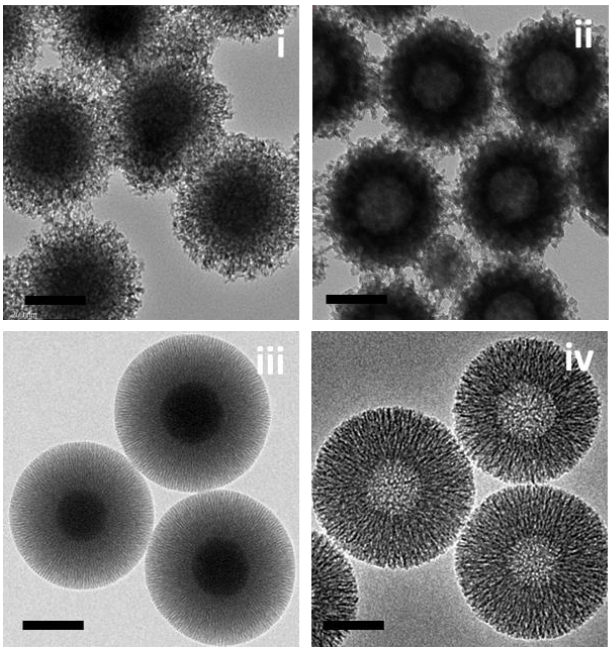


**Figure S1.** The protection effect of CTAC in etching process (50°C, 0.2 M $Na_2CO_3$). (i) 0.5 h, CTAC removed; (ii) 1 h, CTAC removed; (iii) 0.5 h, CTAC protection; (iv) 1 h, CTAC protection. All scale bars are 100 nm.

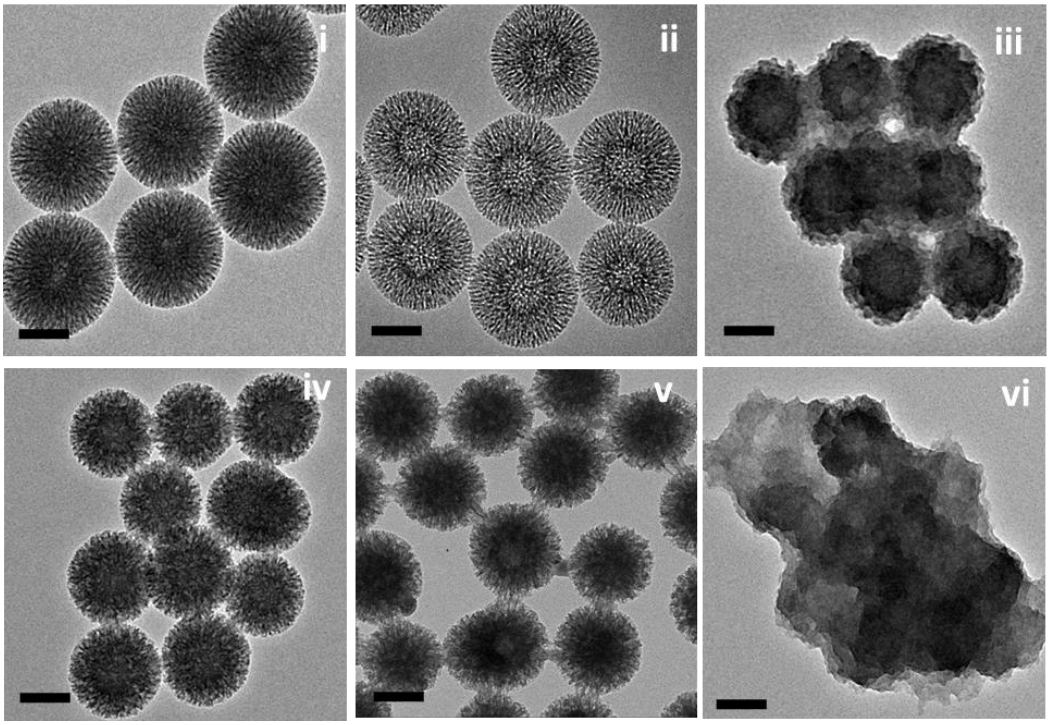


**Figure S2.** The effect of $Na_2CO_3$ concentration and etching duration on fabrication of dHMSN. (i) 0.2 M, 0.5 h; (ii) 0.2 M, 1 h; (iii) 0.2 M, 2 h; (iv) 0.4 M, 0.5 h; (v) 0.4 M, 1 h; (vi) 0.4 M, 2 h. All scale bars are 100 nm.

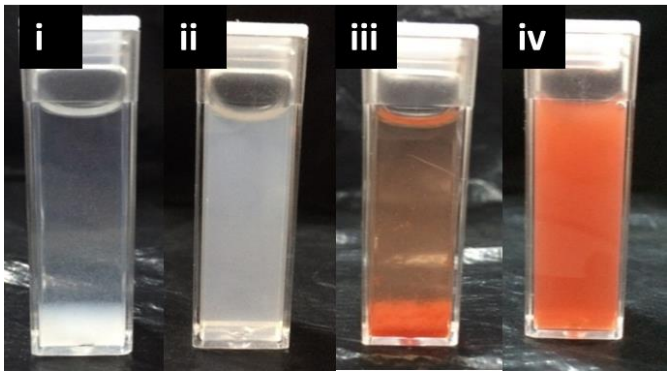


**Figure S3.** *In vitro* stability of dHMSN and dHMLB in PBS after 2 h. (i) dHMSN, (ii) dHMLB, (iii) A/D/I-dHMSN, (iv) A/D/I-dHMLB.

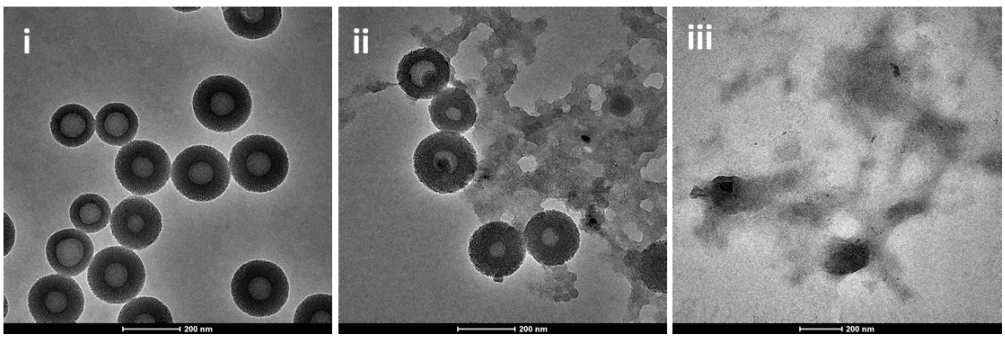


**Figure S4.** The biodegradation property of $NH_2$-dHMSN in PBS. (i) day 0, (ii) day 3, (iii) day 7.

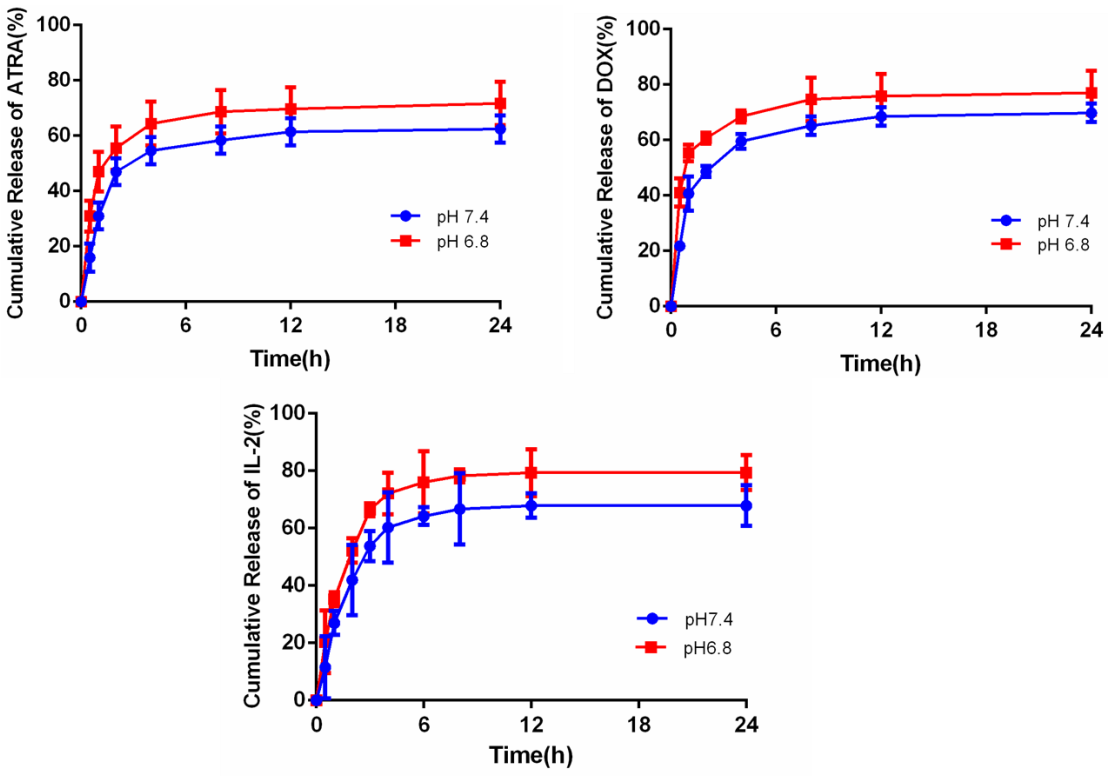


**Figure S5.** *In vitro* release of ATRA, DOX and IL-2 from A/D/I-dHMLB at different pH.

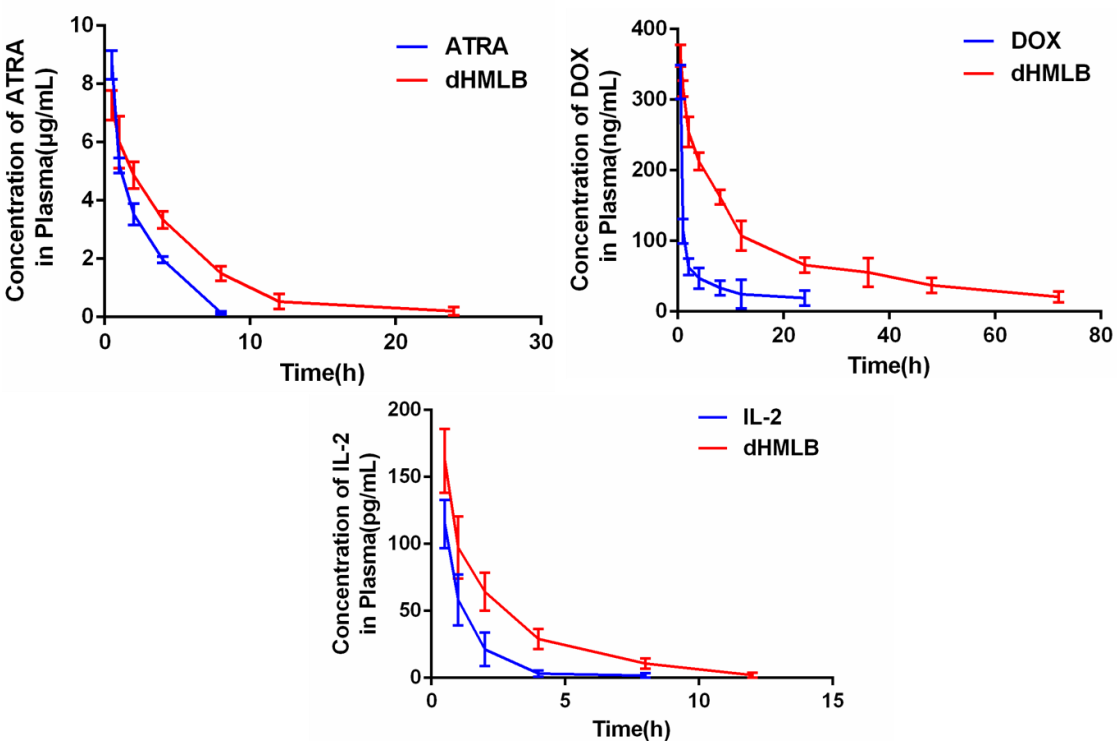


**Figure S6.** Pharmacokinetics behaviors after *i.v.* injection to SD rats of ATRA, DOX, IL-2 and A/D/I-dHMLB at equivalent dose of all agents.

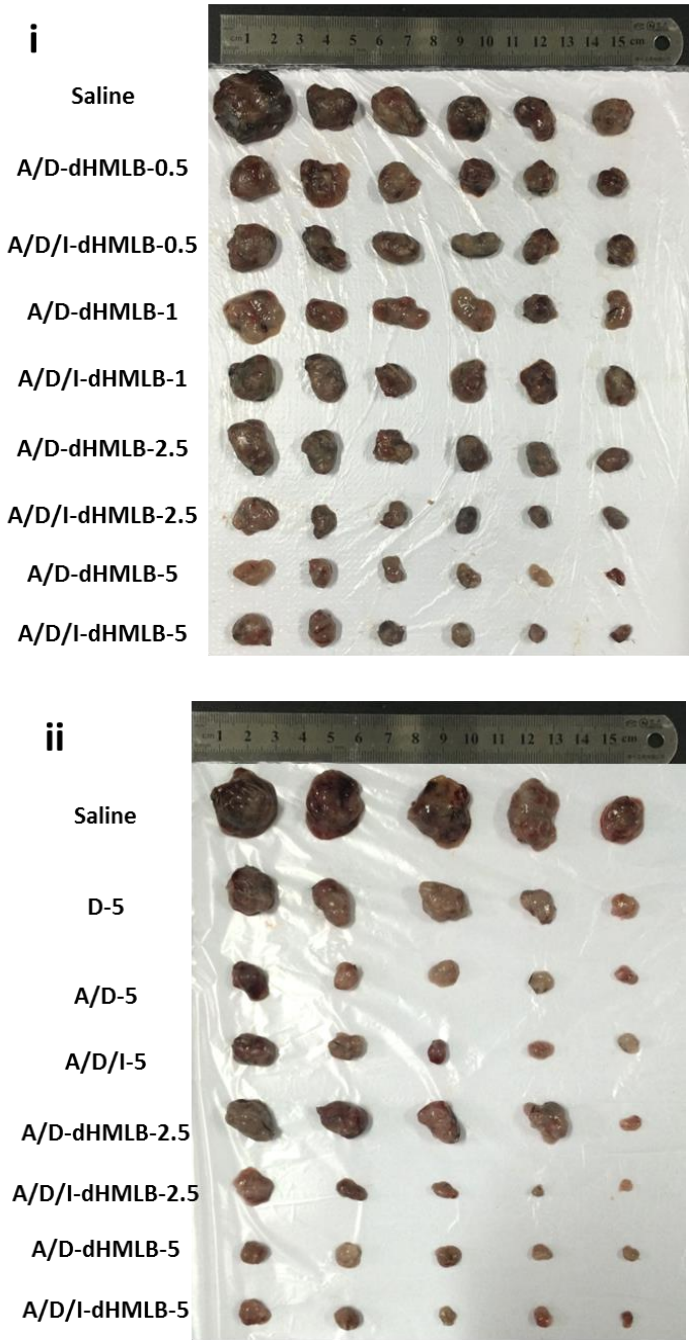


**Figure S7.** Dosage exploration for tumor inhibition. Tumor-bearing mice were injected with different dose of (i) drug-loaded dHMLB of which *0.5, 1, 2.5, 5* represent the dose of DOX (mg/kg), and (ii) free drugs, A/D-dHMLB and A/D/I-dHMLB. The dosage ratio of ATRA/DOX is 3/1 and the dose of IL-2 is 2.5 μg/kg.

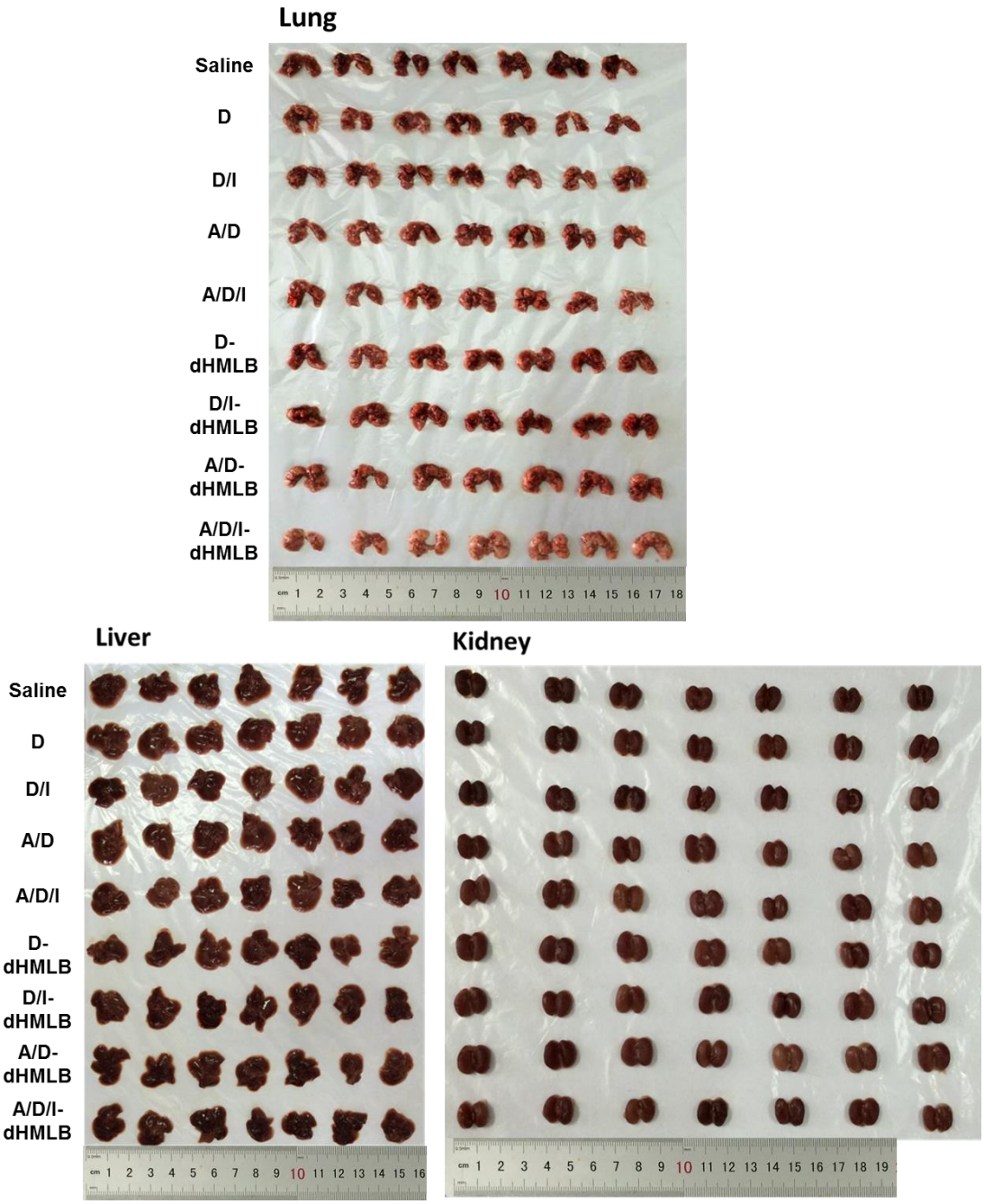


**Figure S8.** Lungs, livers and kidneys were harvested for image in the B16F10 metastasis inhibition experiment. Livers and kidneys showed no apparent metastasis in all groups.

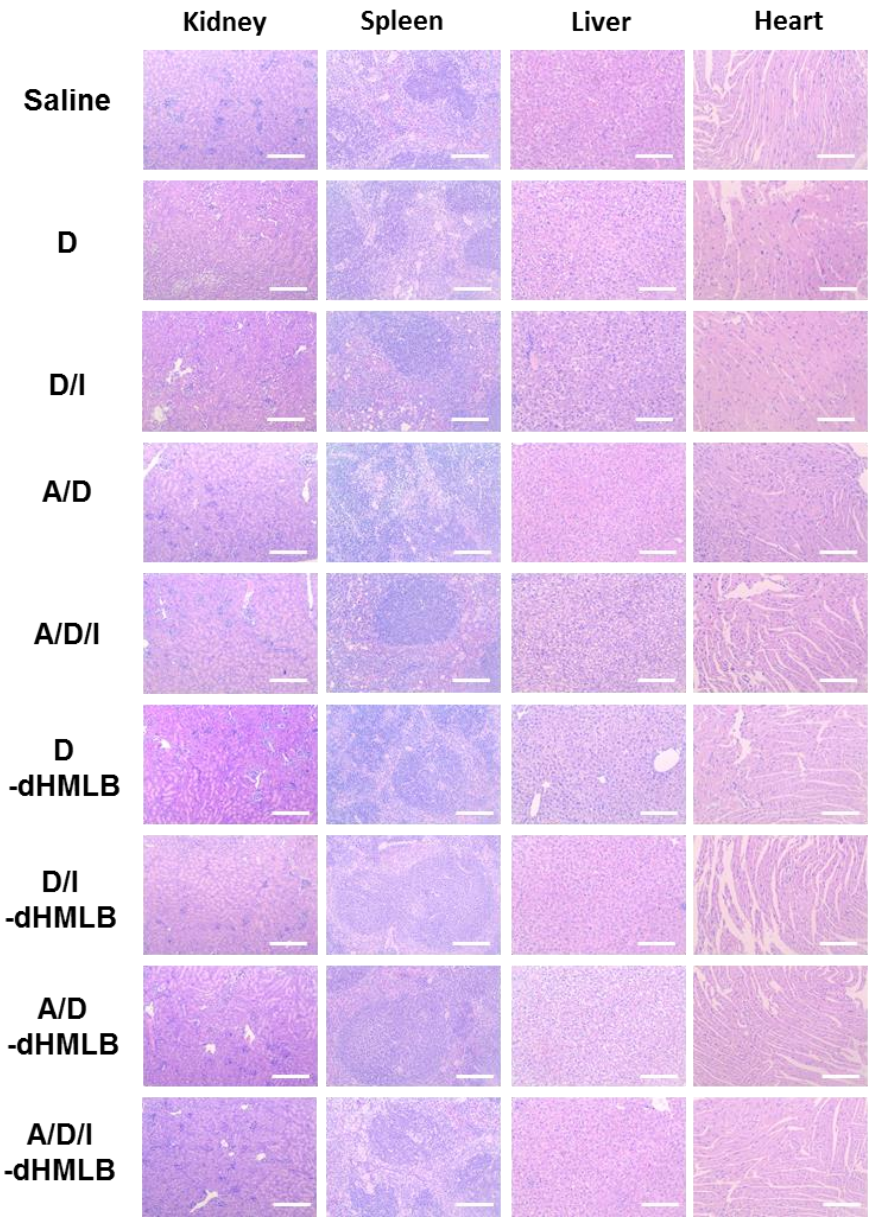


**Figure S9.** Kidney, spleen, liver and heart of all groups were excised for H&E staining, showing no apparent lesion (Magnification: 100×). All scale bars are 250 μm.

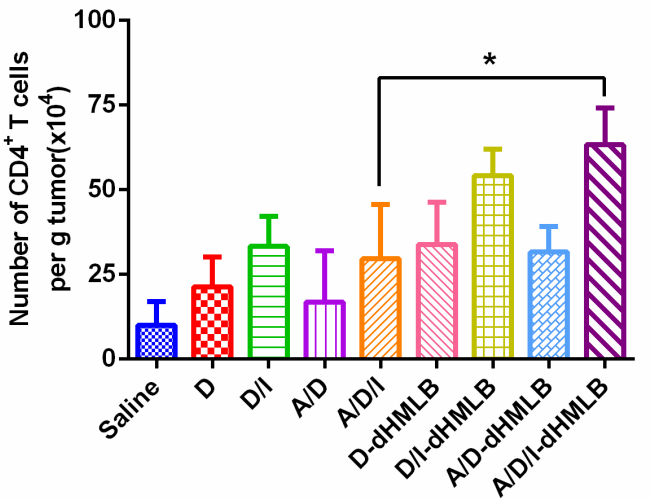


**Figure S10.** Number of $CD4^+$ T cells ($CD3^+CD4^+$) per gram of tumor.

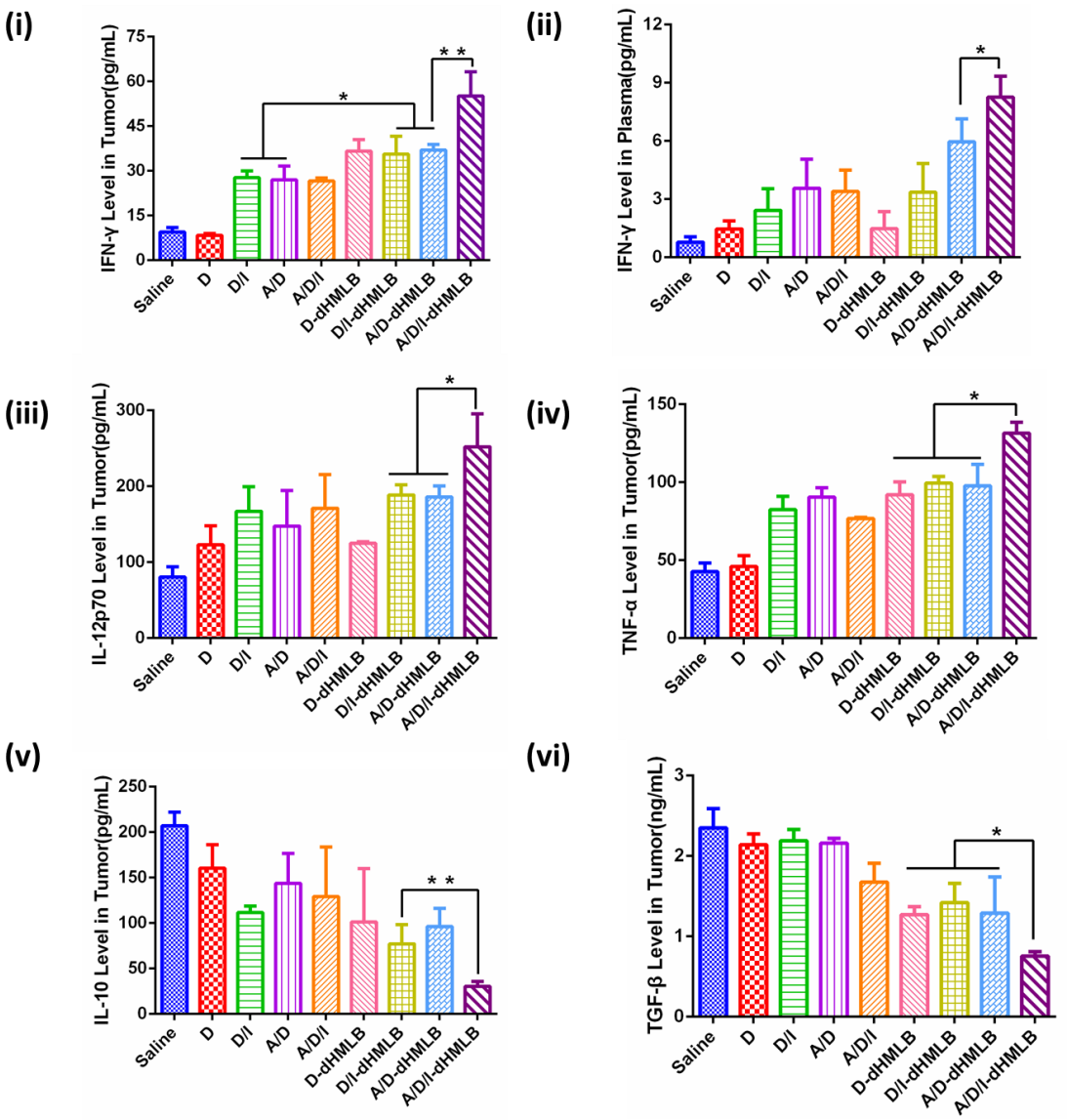


**Figure S11.** (i) IFN-γ level in tumor. (ii) IFN-γ level in plasma. (iii-vi) Secretion of IL-12p70, TNF-α , IL-10 and TGF-β in tumor.

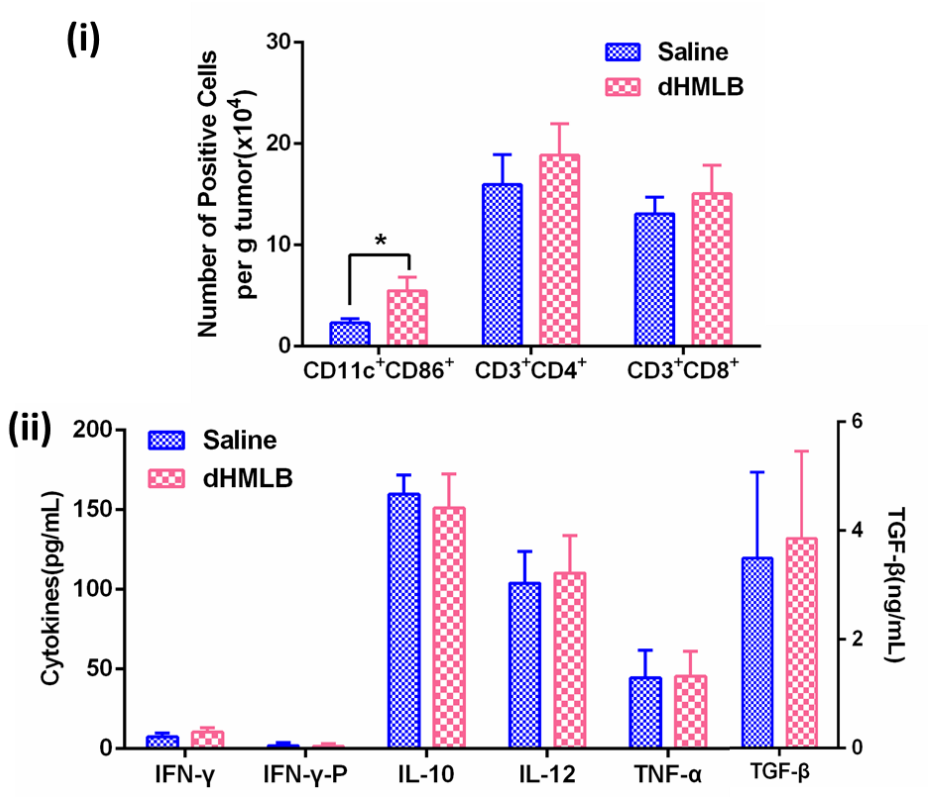


**Figure S12.** Immune response and cytokine analysis of dHMLB. (i) Flow cytometric analysis of mature DC ($CD11c^+CD86^+$) and T cell ($CD3^+CD4^+$ and $CD3^+CD8^+$) in tumor microenvironment. (ii) Cytokine analysis of IFN-γ, IL-10, IL-12, TNF-α, TGF-β in tumor microenvironment and IFN-γ in plasma (marked as IFN-γ-P).