Supporting Information

Light-facilitated Drug Delivery System from Pseudo-protein/Hyaluronic Acid Nanocomplex with Improved Anti-Tumor Effect

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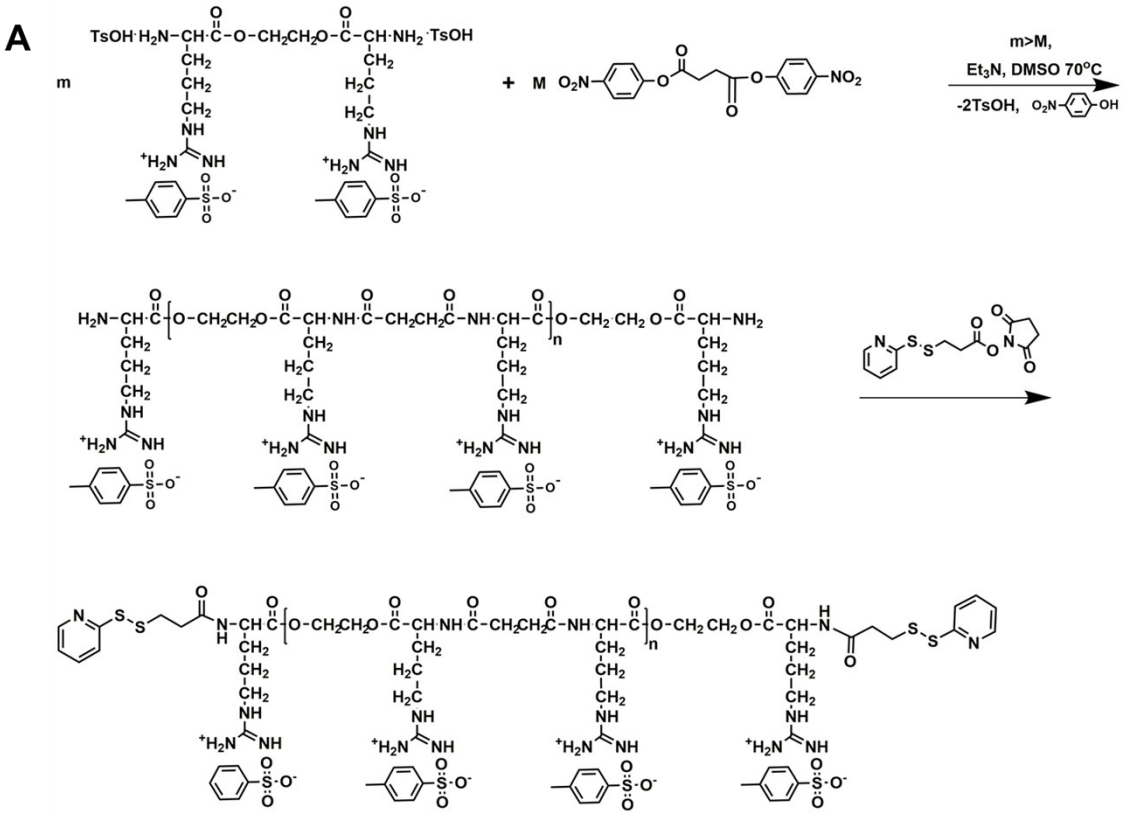


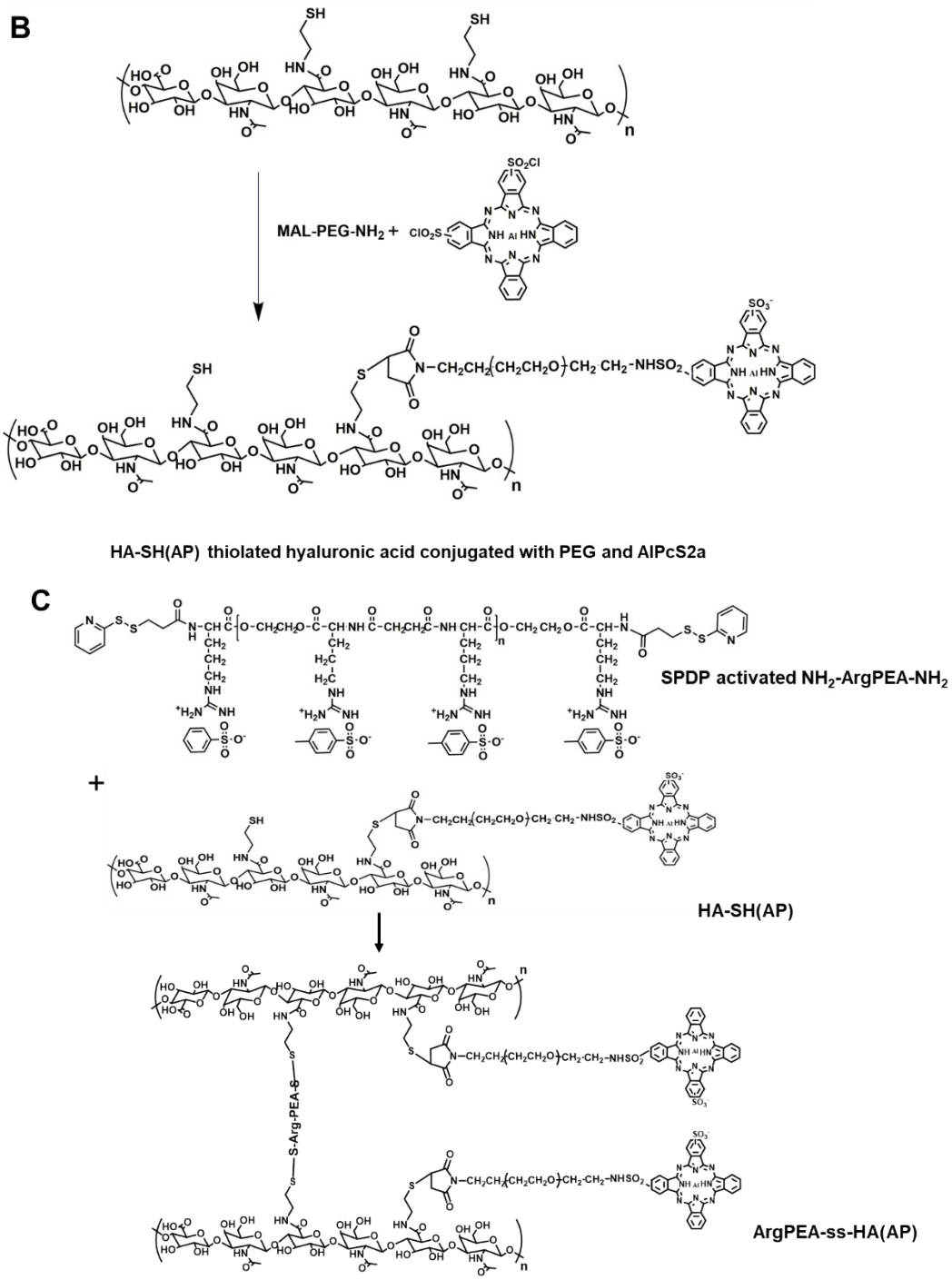


Figure S1. Synthesis scheme for A) arginine based poly(ester amide)s (ArgPEA) with amino end groups (NH_2-ArgPEA-NH_2), and activation of amino groups with SPDP crosslinker; B) thiolated hyaluronic acid (HA-SH) functionalized with polyethylene glycol (PEG) and AlPcS2a photosensitizer (HA-SH (AP)); and C) the formation of reduction-sensitive nanocomplex ArgPEA-ss-HA(AP) from NH_2-ArgPEA-NH_2 activated by SPDP and HA-SH(AP) via disulfide linkage.

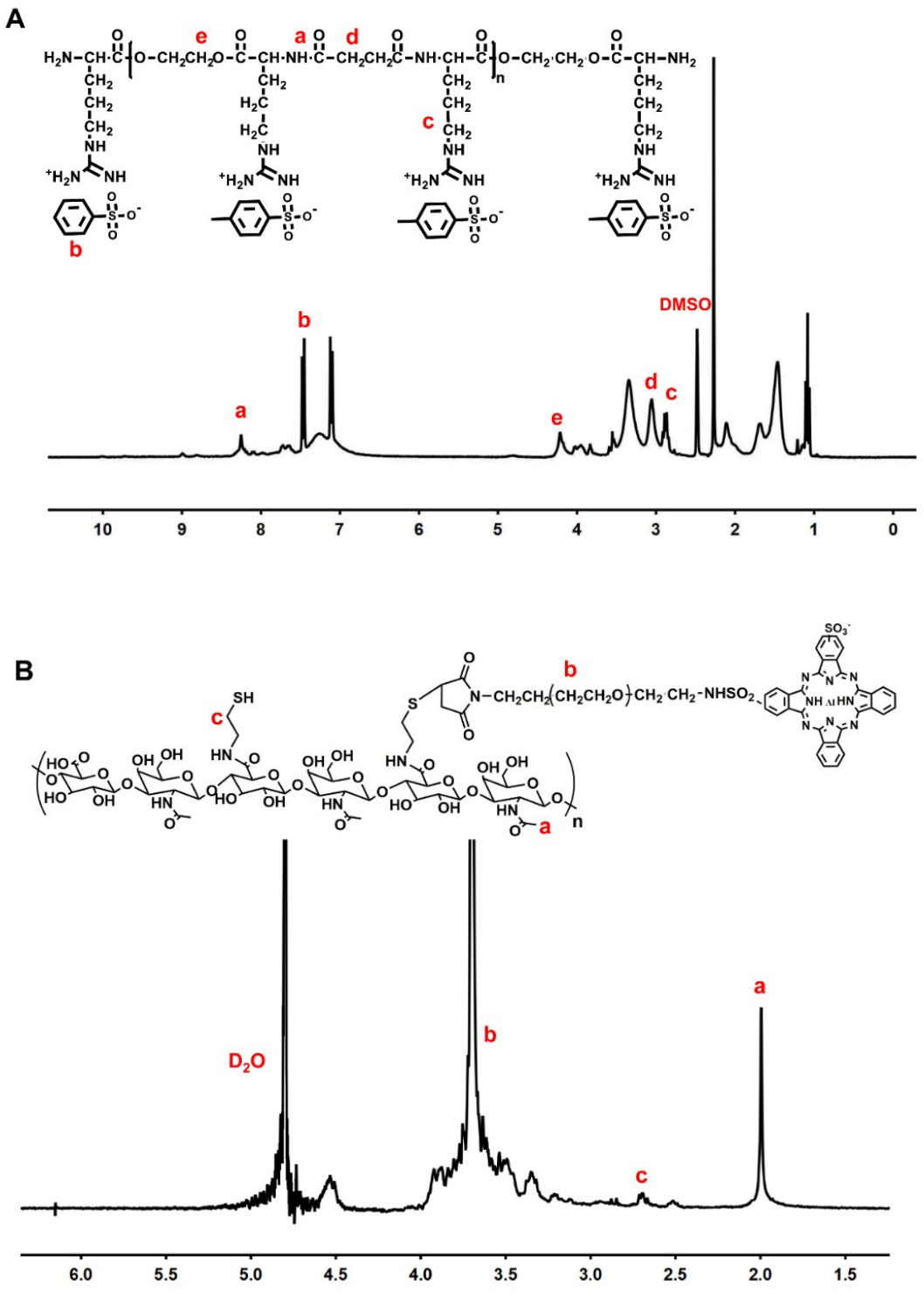


Figure S2. ^{1}H NMR spectra of A) NH_2-ArgPEA-NH_2; B) HA-SH functionalized with PEG and AlPcS2a (HA-SH(AP)).

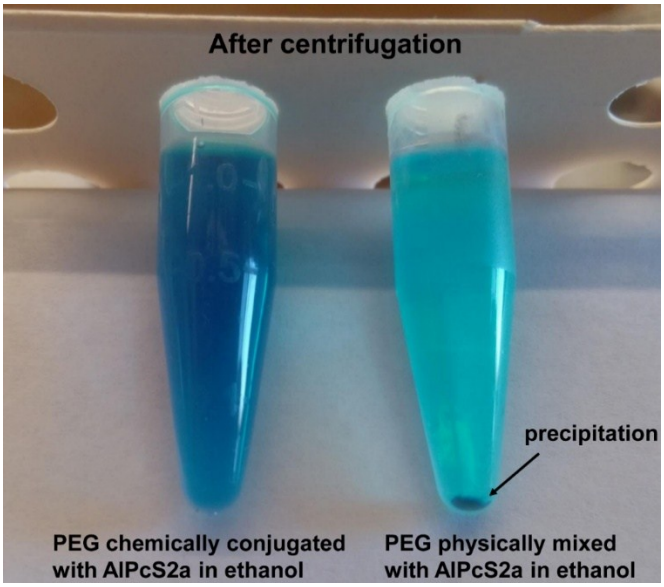
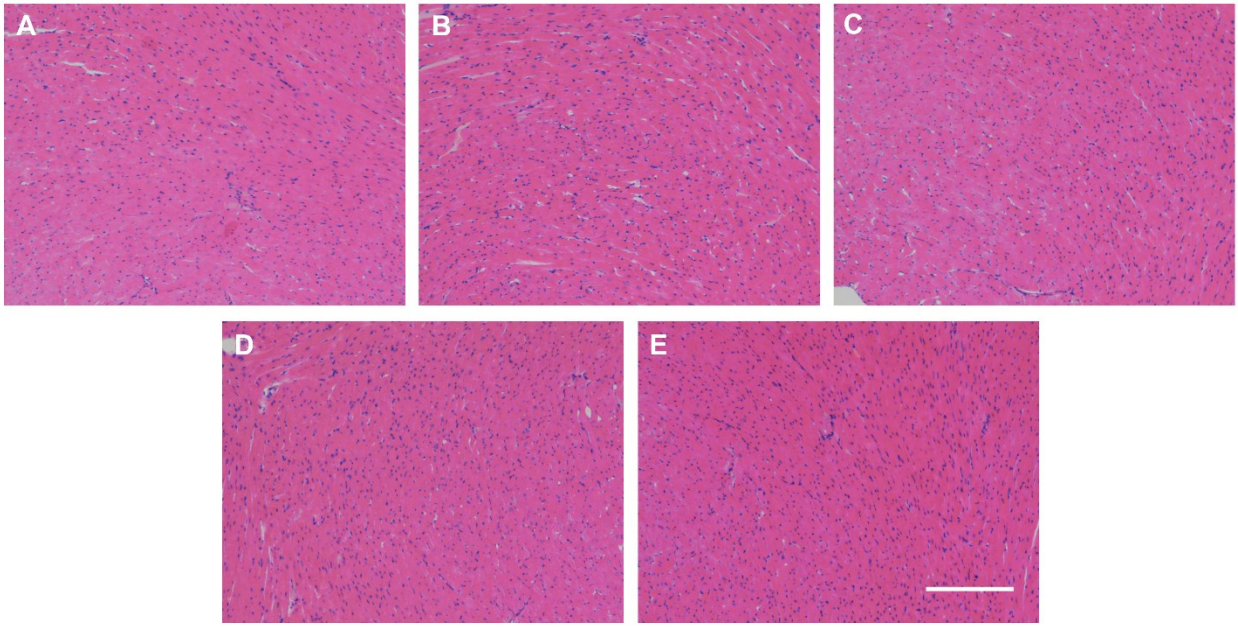
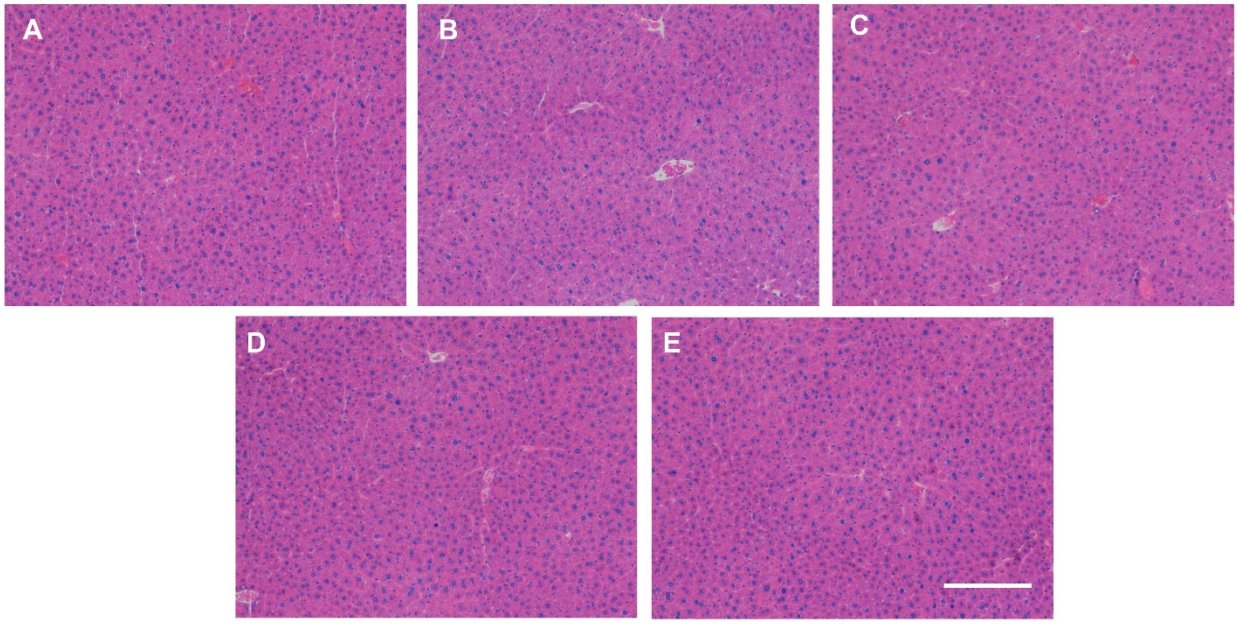


Figure S3. To further proved the chemical reaction between MAL-PEG-NH_2 and AlPcS2a, AlPcS2a conjugated with PEG or AlPcS2a physically mixed with PEG were dispersed in ethanol with equivalent AlPcS2a concentration of 10 μM and centrifuged at 10, 000 rcf for 20 min. Due to the poor solubility of free AlPcS2a in ethanol, significant precipitation was observed in the physical mixture. However, uniform solution was observed after centrifugation in the case of AlPcS2a conjugated with PEG, as PEG improved the solubility of the photosensitizer. Dispersion of AlPcS2a conjugated with PEG or AlPcS2a physically mixed with PEG were dispersed in ethanol and centrifuged at 10,000 rcf for 20 min. The image of the two samples right after centrifugation was recorded.

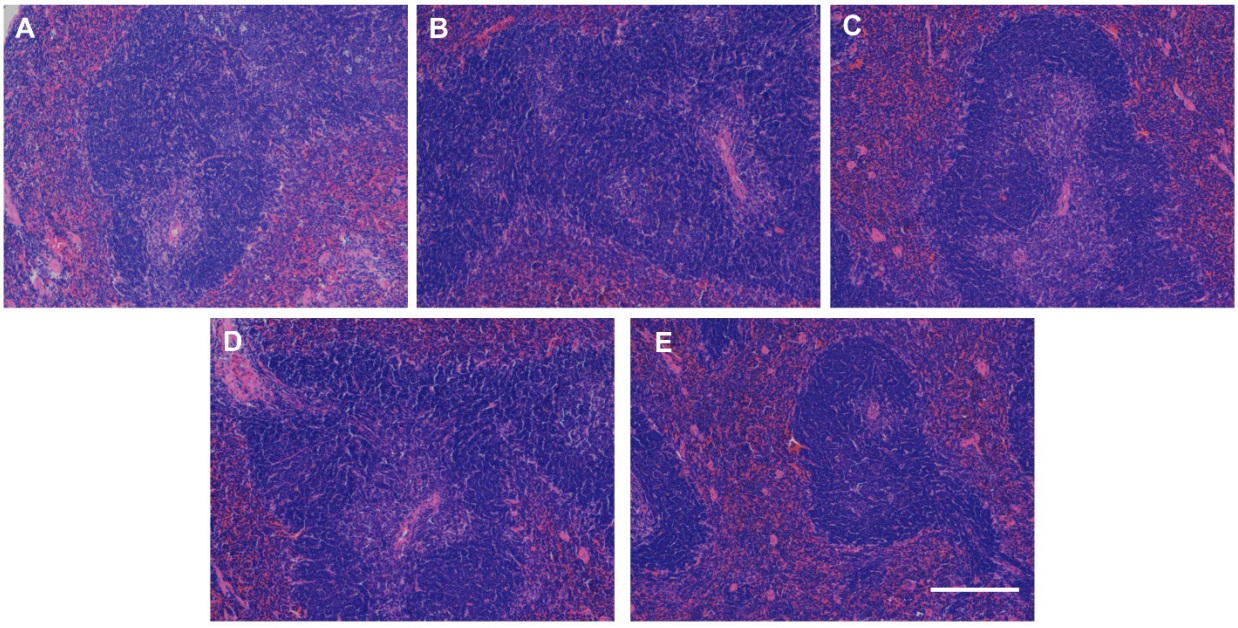
Heart



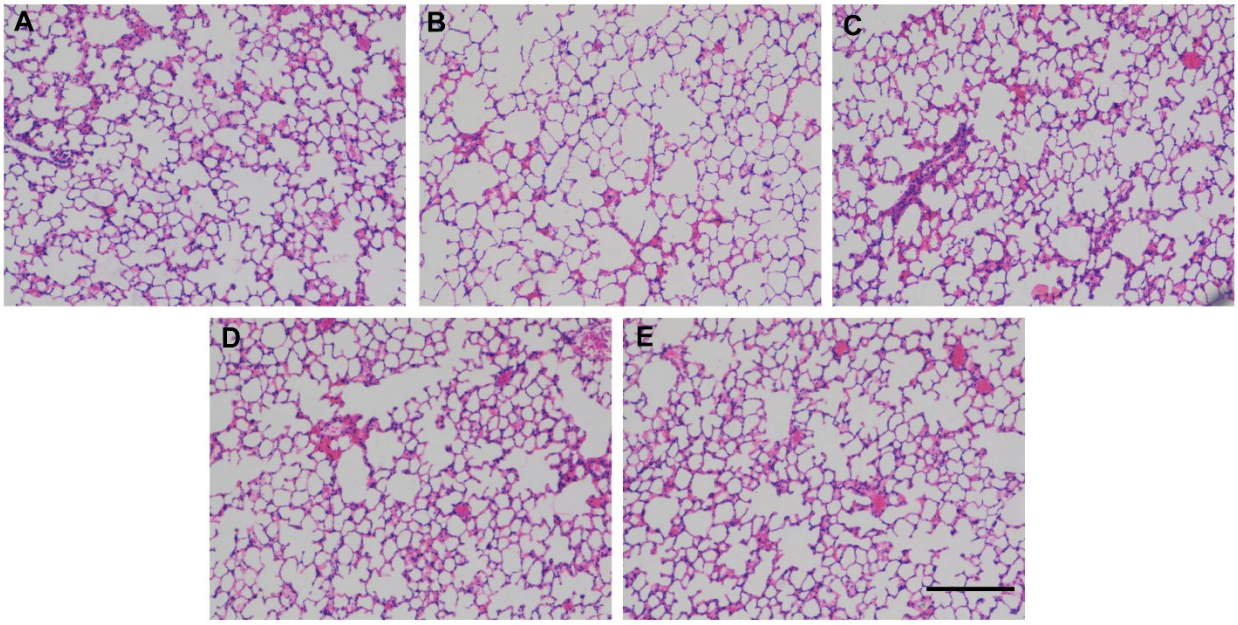
Liver



Spleen



Lung



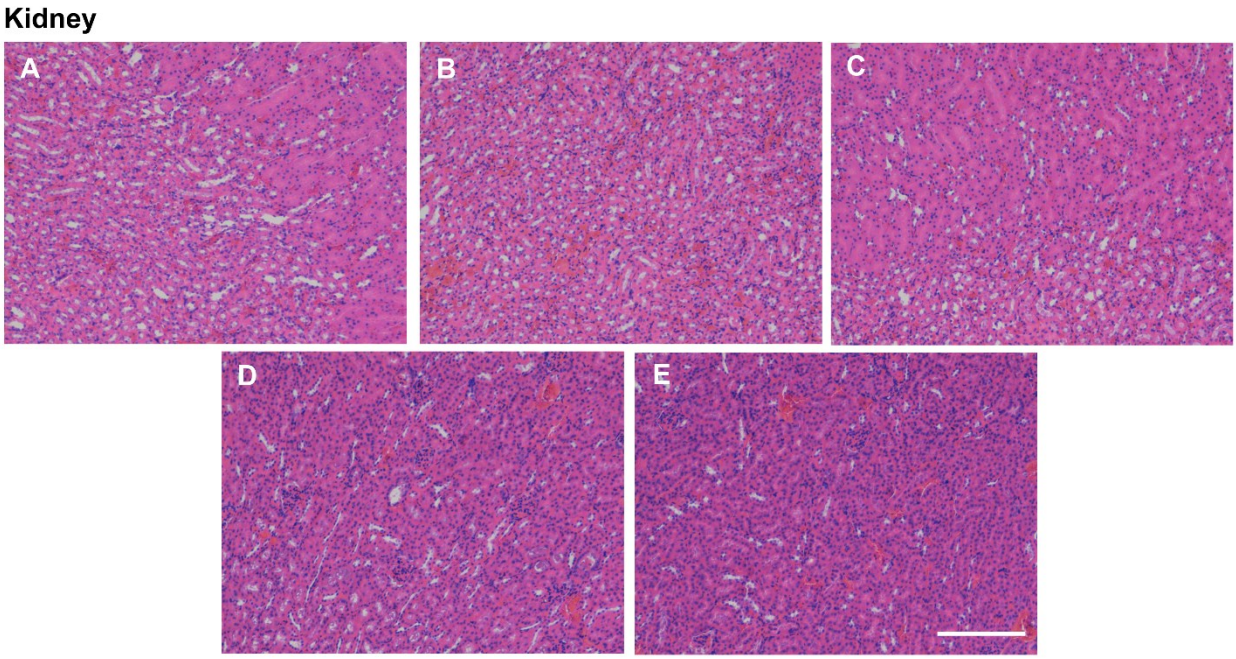


Figure S4. H&E staining of major organs (heart, liver, spleen, lung and kidney) from tumor bearing mice on day 28 treated with: A, Saline; B, free DOX; C, blank ArgPEA-ss-HA(AP) with irradiation; D, DOX-loaded ArgPEA-ss-HA(AP) without irradiation; E. DOX-loaded ArgPEA-ss-HA(AP) with irradiation. Scale bar represented 200 μm. Histological examination was applied to examine the toxicology of DOX-loaded nanocomplex. Tumor bearing mice were injected with saline, free DOX, blank ArgPEA-ss-HA(AP) nanocomplex with irradiation, DOX-loaded ArgPEA-ss-HA(AP) nanocomplex (with equivalent DOX dosage of 2 mg/kg/week) with or without light irradiation. 3 injections were given at day 1, day 8 and day 15. And 24 hrs post-injection, tumor tissues were irradiated by 671 nm He-Ne laser (100 mW/cm^2, 50 J/cm^2). At day 28, all mice were sacrificed and the weight of the tumor was measured. The major organs (heart, liver, spleen, lung, kidney) were collected and sectioned at 5-10 μm. The specimen was fixed with 4% paraformaldehyde, embedded in paraffin and subjected to haematoxylin and eosin (H&E) staining. In H&E staining, haematoxylin stained the nuclei and eosin stained the intracellular and extracellular protein component. As indicated in Figure S2, compared to saline-treated control. we didn't observe any swelling of cells in heart, or any void/lesion in lung and liver. Abnormality or noticeable organ damage was absent on all the studied organs when compared to the saline-treated group. The treatment of DOX-loaded ArgPEA-ss-HA(AP) nanocomplex with or without light irradiation was well-tolerable on tumor bearing mice. The results showed consistency with the result of body weight in Figure 9B, which further supported the good biocompatibility of the DOX-loaded nanocomplex.