Supporting information for

Acidic pH-Triggered Drug Eluting Nanocomposites for MRI Monitored Intra-Arterial Drug Delivery to Hepatocellular Carcinoma

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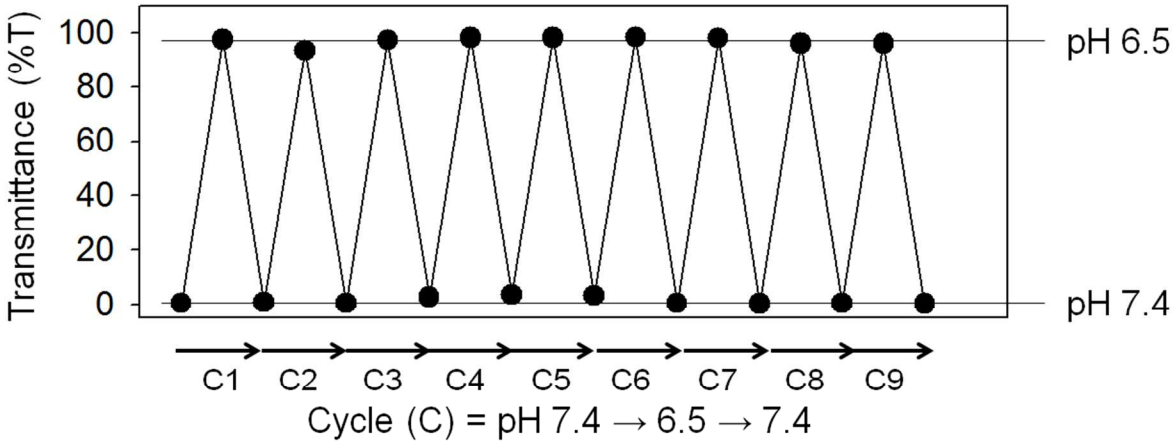

Figure S1. Reversible change of light transmittance (λ = 500 nm) of pH-ADT aqueous solution between pH 7.4 and 6.5 at room temperature.

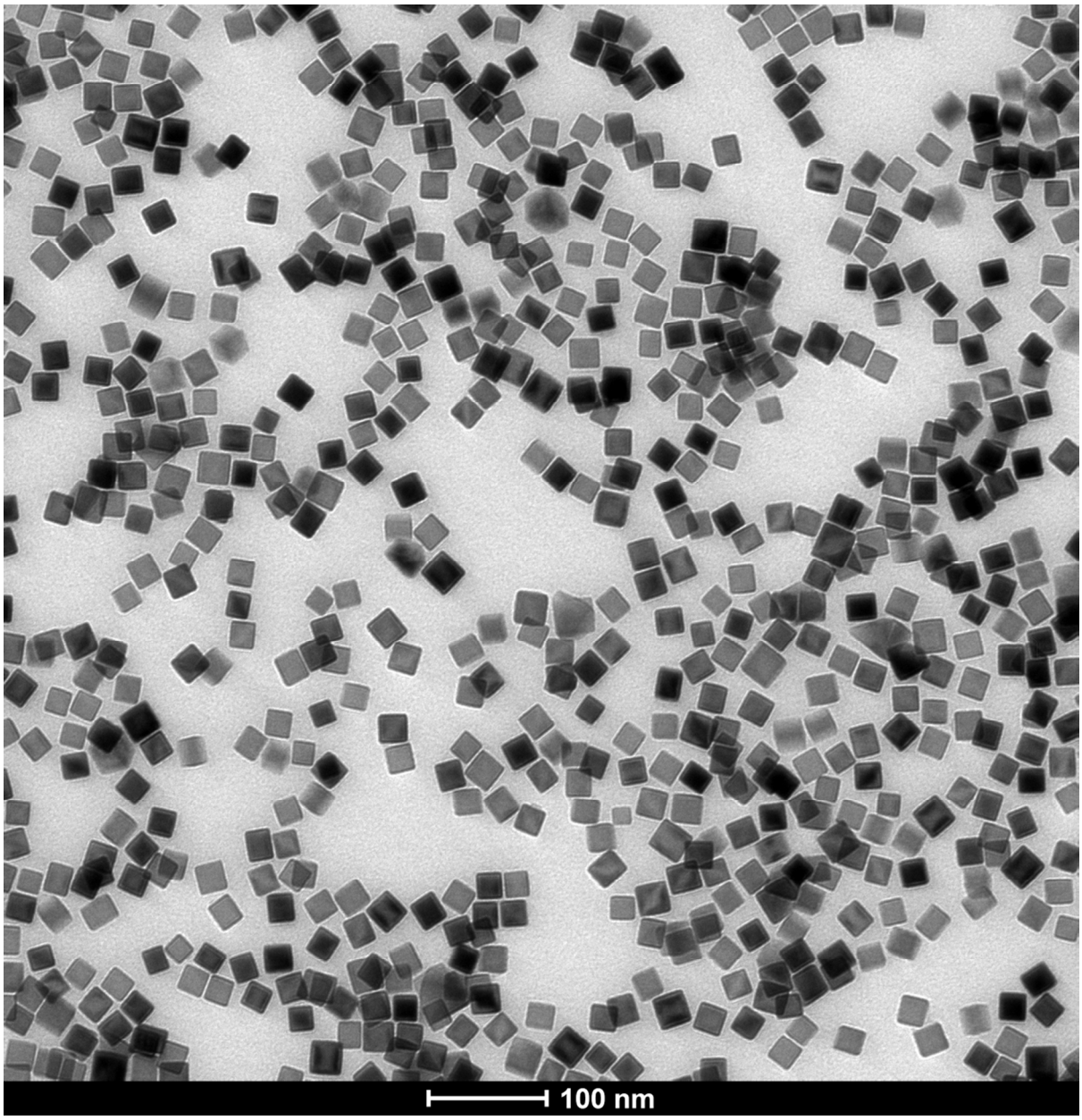

Figure S2. A low magnification TEM image of IONCs.

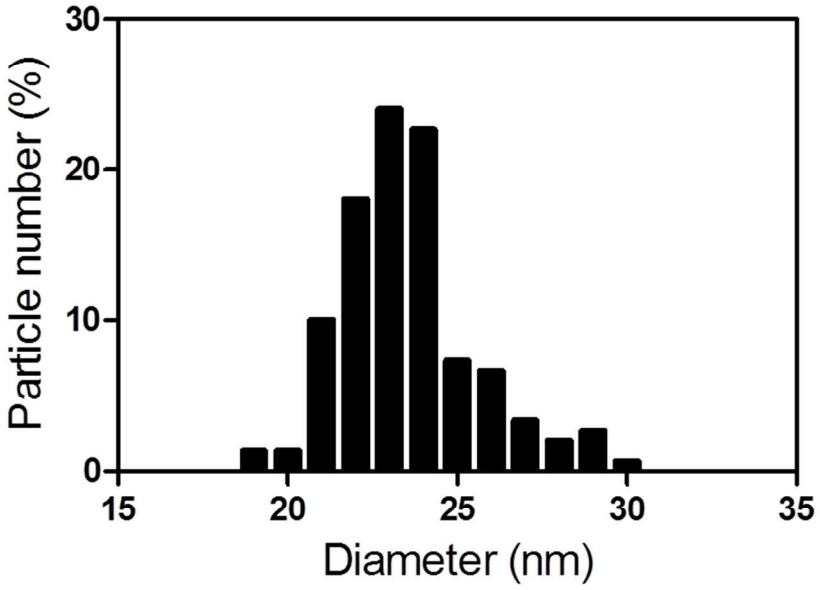

Figure S3. Size distribution of IONCs.

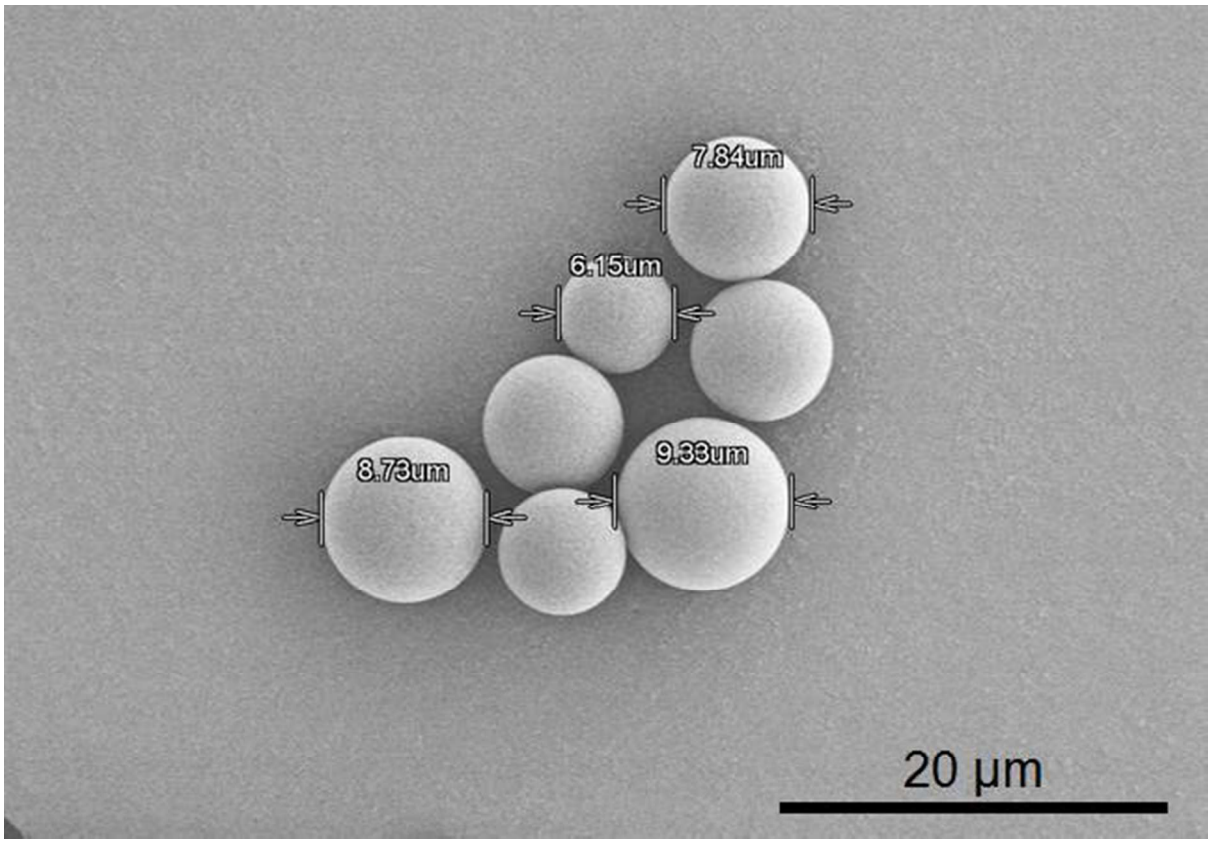

Figure S4. High-magnification SEM image of pH-DENs.

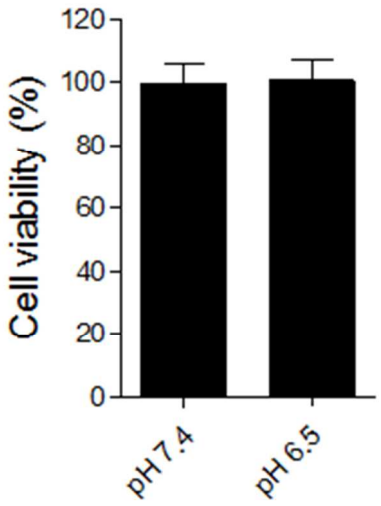

Figure S5. Cell viability of McA-RH7777 hepatoma cells cultured in media at pH 7.4 or pH 6.5 for 24 h.

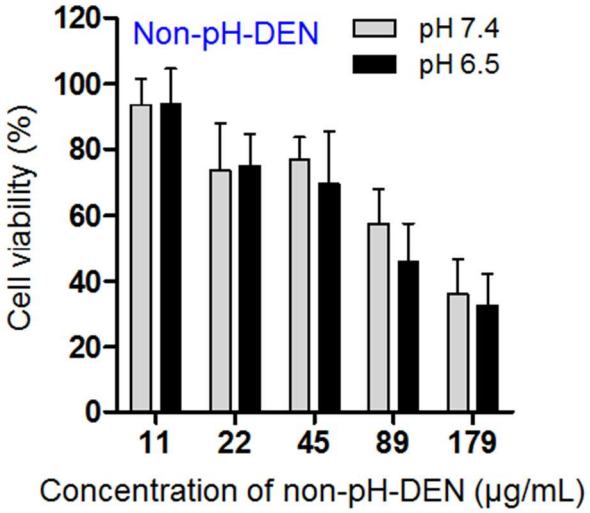

Figure S6. Cell viability of McA-RH7777 hepatoma cells treated with Non-pH-DEN (control) at pH 7.4 or pH 6.5 (n = 4).

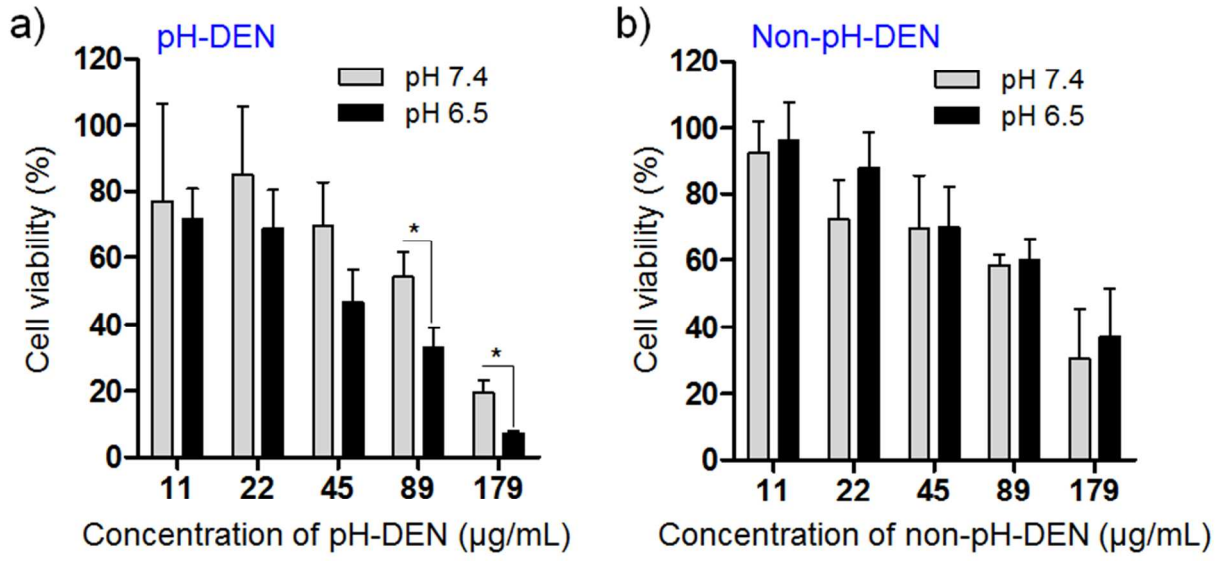

Figure S7. Cell viability of Clone 9 (Normal liver) cells treated with a) pH-DEN or b) Non-pH-DEN (control) at pH 7.4 or pH 6.5 (*$P < 0.02$, $n = 4$).

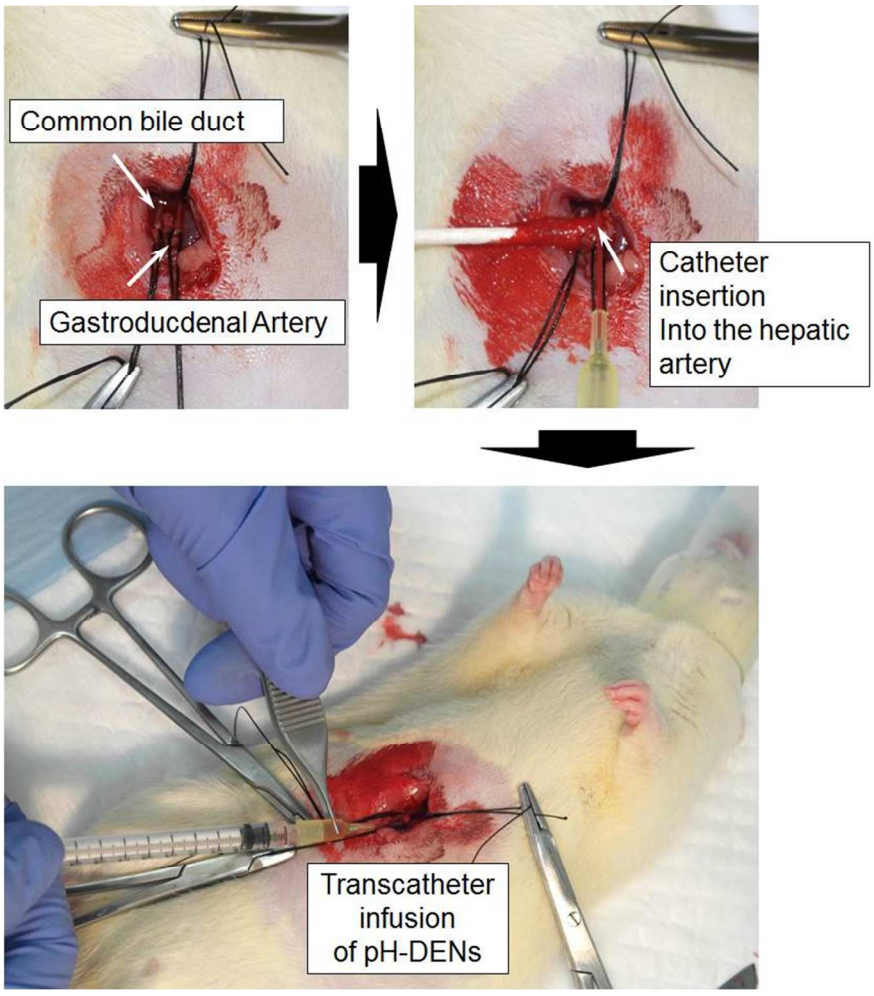

Figure S8. Hepatic intra-arterial catheterization of pH-DENs in an orthotopic HCC rat model: The following steps were used to invasively catheterize the left hepatic artery (LHA) for selective infusion of the pH-DENs in each animal. First, rats were anesthetized with an isoflurane induction dose (mixture of 5% isoflurane and oxygen at 3 L/min). After laparotomy, a cotton-tipped applicator was used to expose the common hepatic artery (CHA), proper hepatic artery (PHA), and gastroduodenal artery (GDA). A micro bulldog clamp was placed on the CHA (World Precision Instruments, Sarasota, FL, USA) to prevent bleeding during catheterization. 4-0 Vetacryl absorbable polyglycolic acid suture (Webster Veterinary, Devens, MA, USA) was then used to ligate the GDA distally to control retrograde bleeding during catheterization. Next, a 24G SureFlash polyurethane catheter (Terumo Medical Co., Somerset, NJ, USA) was inserted into the GDA, advanced into the PHA and then distally into the LHA. After selective catheterization, 0.1mL of heparin was infused before infusing the pH-DENs (20 mg in 200 uL); each infusion was followed by a 0.2mL saline flush. The catheter was then withdrawn, and a 3-0 suture used to permanently ligate the GDA above the insertion position. Finally, abdomen was closed using two-layer technique. The animals were then moved to the 7 T MRI scanner (Clinscan, Bruker, Billerica, MA, USA) located adjacent to the surgical suite.

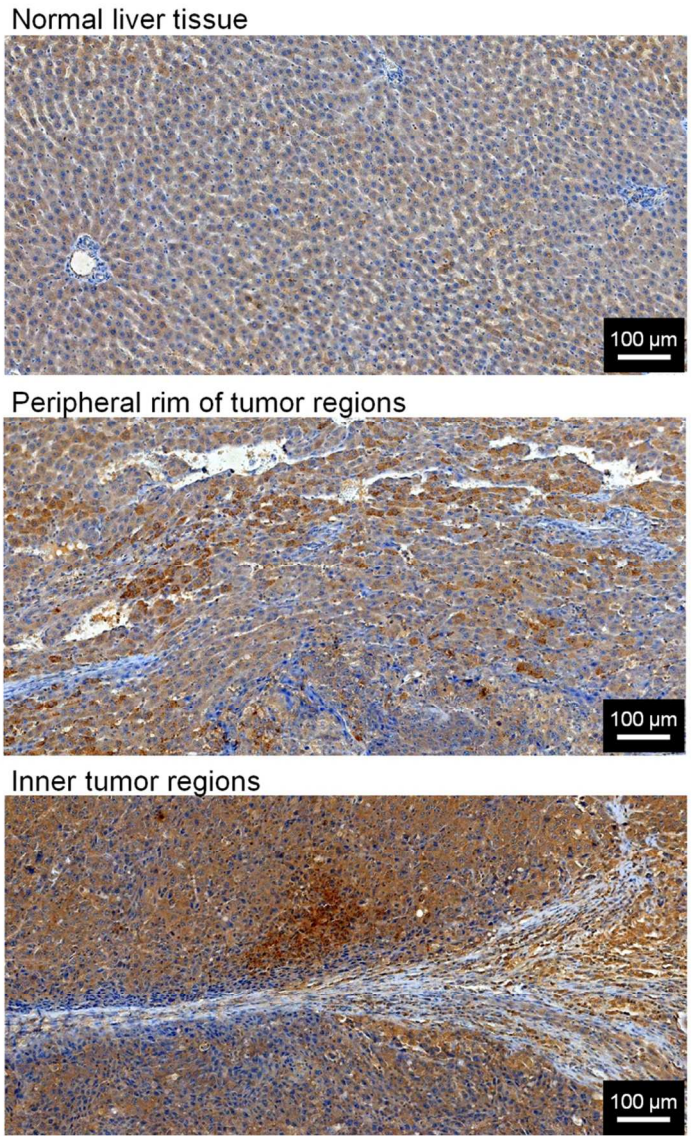

Figure S9. IHC-staining of hydrogen/potassium ATPase beta in normal liver, peripheral rim of tumor, and inner tumor regions (brown, positive staining; blue, nuclear countering staining Scale bar: 100 μm) of rats. Highly overexpressed hydrogen/potassium ATPase was observed in the peripheral rim and inner tumor regions, compared to normal liver tissue.

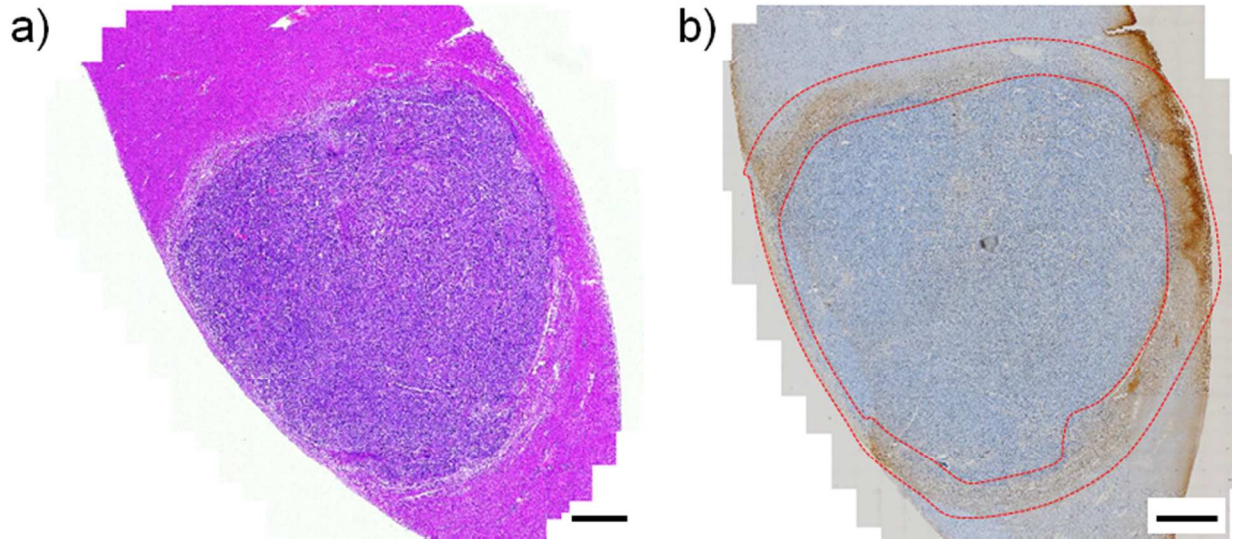

Figure S10. Representative photographs of extracted tumor-bearing liver from non-pH-DENs-treated group. a) H&E and b) TUNEL staining of tumor tissue sections to assess the efficacy of treatment. The brown color (in red-dot line) indicates TUNEL-positive apoptotic cells (Scale bar: 1 mm).

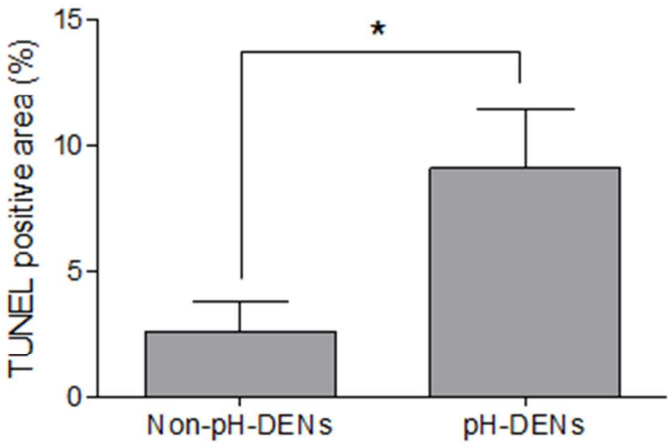

Figure S11. Quantitative analysis of TUNEL positive area from TUNEL stained tumor tissues treated with non-pH-DENs or pH-DENs (n=3, *p<0.02). The quantitative analysis was performed by Image J (National Institute of Health, USA) software.