Modulating Macrophage Clearance of Nanoparticles: Comparison of Small-Molecule and Biologic Drugs as Pharmacokinetic Modifiers of Soft Nanomaterials

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Nanomedicines are enormously beneficial in overcoming the limitations of conventional drug delivery systems by reducing side-effects, toxicity, and exhibiting tenable PK profile to improve the therapeutic window of small molecule drugs. Administration of nanoparticles (NPs) prompt induction of host inflammatory responses, eliminating up to 95% of the administered dose.[1] Here, we explore a drug pre-dosing strategy to transiently suppress the mononuclear phagocyte system (MPS),[2] subsequently improving the pharmacokinetic profile and biological behaviours exhibited by hyperbranched polymers (HBPs) in immunocompetent mice.[3] Pre-dosing of chloroquine (CQ) showed increased HBP retention in the blood at 24 h post administration by up to 24% using fluorescence imaging, compared to polymer injected alone. *Ex vivo* flow cytometry of isolated cells from spleen and liver tissue further demonstrated CQ to significantly reduce HBP association with myeloid cells by 23%. PET studies validated the promising ability of pre-dosed CQ to enhance the circulation time of HBP, with 64.5% higher blood levels at 19 hrs compared to the polymer alone (Fig. 1). The successful application of CQ in modulating PK and improving tumor delivery profiles of theranostic nanomedicines underscores its promise for optimizing 212Pb molecular radiopharmaceuticals in further studies.

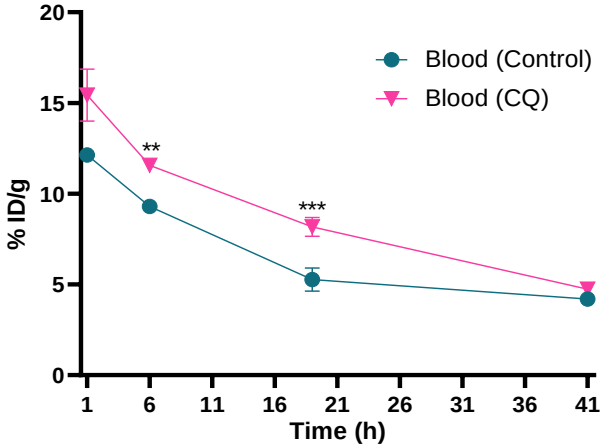

Figure 1 MPS pre-dosing nanomedicine delivery: The percent of injected dose per gram is shown for blood (from ROI imaging). PET/CT images obtained at 1, 6, 19 and 41 h post injection of ^{89}Zr labelled HBP. Mice were treated with CQ, 5 mg/kg (IV) for 3 days prior to injection of HBP. CQ treated mice showed increased HBP within the heart, indicating a higher blood retention at 6 to 19 h. Data represents mean ± SEM (n = 3 per treatment/control group). $P < 0.005$(**); $P < 0.0005$ (***). Two-way ANOVA of treatment compared with cells exposed to HBP.

1. Gustafson, H.H, et al. *Nano Today* **2015**, *10*, 487-510.
2. Ethridge, M.L, et al. *Nanomedicine* **2013**, *9*, 1-14.
3. Mills, J.A., et al. *Biomaterials Science* **2022**, *10*, 3029-3053.