Hepatocellular carcinoma (HCC) is a global challenge with limited efficient therapies [1]. The stroma-rich tumor microenvironment restricts most nanomedicines from accessing the tumor cells following systemic administration [2]. Combinational therapy based on chemotherapy and gene therapy is a promising strategy for synergistic eradication of the tumor at lower doses. The rational design of nanocarriers dramatically affect their in vivo performance and the fate of treatment [3].

Combo lipid nanoparticles (cLNPs) were designed based on a novel pH-sensitive lipid, a diversity of phospholipids and a Highly-selective targeting peptide. cLNPs were loaded with the cytotoxic drug, sorafenib (SOR), and a small interfering RNA targeting the Midkine gene (MK-siRNA). The lipid composition of cLNPs was tweaked and the physico-chemical properties were manipulated using a novel microfluidic device, iLiNP. The lipid composition and physico-chemical properties of cLNPs significantly-controlled their pharmacokinetics, tumor penetration and gene knockdown efficiency. The optimized cLNPs showed highly-potent gene silencing in the tumor with an siRNA median effective dose of 0.1 mg/Kg following intravenous administration to HCC-bearing mice, compared to minimal effect on the healthy liver. Moreover, the novel combination recruited in this study synergistically-eradicatd HCC in mice at surprisingly-low doses of SOR and MK-siRNA. We believe that our strategy has a promising potential for clinical application in HCC therapy.