Optimization-by-design of hepatotropic lipid nanoparticles targeting the sodium-taurocholate cotransporting polypeptide

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Active targeting and specific drug delivery to parenchymal liver cells is a promising strategy to treat various liver disorders. Here, we modified synthetic lipid-based nanoparticles with targeting peptides derived from the hepatitis B virus large envelope protein (HBVpreS) to specifically target the sodium-taurocholate cotransporting polypeptide (NTCP;; SLC10A1;) on the sinusoidal membrane of hepatocytes. Physicochemical properties of targeted nanoparticles were optimized and NTCP-specific, ligand-dependent binding and internalization was confirmed; in vitro; . The pharmacokinetics and targeting capacity of selected lead formulations was investigated; in vivo; using the emerging zebrafish screening model. Liposomal nanoparticles modified with 0.25 mol% of a short myristoylated HBV derived peptide,; i.e.; MyrHBVpreS2-31, showed an optimal balance between systemic circulation, avoidance of blood clearance, and targeting capacity. Pronounced liver enrichment, active NTCPmediated targeting of hepatocytes and efficient cellular internalization were confirmed in mice by; 111; In gamma scintigraphy and fluorescence microscopy demonstrating the potential use of our hepatotropic, ligand-modified nanoparticles.
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