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I E C B

Smart Lipid Nanoparticles for Nucleic Acids Delivery

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RNA interference provides a targeted approach for silencing gene expression that may prove beneficial in the treatment of diseases such as cancer and genetic disorders. To ensure effective knockdown, siRNA must be entrapped and efficiently conveyed into the cytoplasm of cells. These hydrophilic nucleic acids have to cross the lipid-rich plasmatic and/or endosomal membrane, without being degraded into lysosomes. We have developed new pH-sensitive lipids able to change conformation upon protonation at endosomal pH values, leading to the disruption of the lipid bilayer and thus to the fast release of the nucleic acids into the cytosol. The objective of this work was to design a fast-responding system at pH 5 while remaining stable at blood pH value and during storage. This was achieved by the design and synthesis of a series of switchable lipids, and their incorporation into lipid nanoparticle (LNP) composition. LNP complexed with siRNA exhibited high silencing efficiency, reaching up to 10% on HeLa cells, very similar to a commercial agent, with lower toxicity. Negative controls demonstrated that the improved efficiency was due to the conformational switch of the lipids. In vitro transfection potential was confirmed on various cells lines (HeLa, A549, Huh-7) and siRNA targets (GFP, PCSK9, survivin). In vivo applications are currently focused on liver disease, such as hypercholesterolemia, breast cancer and retinoblastoma.