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Switchable lipids for pH-sensitive siRNA delivery

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R NA 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 lipidic 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 nano-particle (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. Indeed, liver targeting has been shown in mice by fluorescence imaging. This system has recently been able to reduce the LDL as well as HDL cholesterol blood levels of mice after a single I.V. injection of LNP/siRNA.

Biography

Jeanne Leblond has completed his PhD from Université Paris VI and Post-doctoral studies from faculty of Pharmacy of University of Montréal. She is Assistant Professor at the Faculty of Pharmacy since 2011. She is the Director of the research axis "Drug Formulation and Analysis" and has trained over 20 students in 5 years. She has published 13 research articles, 1 book chapter, most of them in journal with IF higher than 4.5.

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