

LIPID-PNMVA CONJUGATES FOR SURFACE MODIFICATION OF siRNA-LOADED LIPID NANOPARTICLES

Stefano Pedergrana^a, Manon Berger^b, Géraldine Piel^b, Antoine Debuigne^a.

^a Center for Education and Research on Macromolecules (CERM), CESAM Research Unit, University of Liège, Belgium

^b Laboratory of Pharmaceutical Technology and Biopharmacy, CIRM, University of Liège, Belgium

Polyethylene glycol (PEG) is widely used to functionalize lipid nanocarriers and provide “stealth” properties that prolong blood circulation. However, PEGylation presents important limitations, including the accelerated blood clearance (ABC) effect, hypersensitivity reactions, and the “PEG dilemma,” which can limit cellular uptake and endosomal escape. In this context, poly(N-methyl-N-vinylacetamide) (PNMVA) has recently emerged as a promising PEG alternative, offering non-toxic and less immunogenic coatings for lipid-based delivery systems¹⁻³.

This work aims to broaden the range of lipid-PNMVA conjugates used to formulate LNPs, and to study how the structure of the lipid-polymer affects the nanocarrier morphology, surface properties, and performance. For this purpose, a library of lipid-PNMVA conjugates with different PNMVA molar mass and lipid group was synthesized via reversible addition-fragmentation chain transfer (RAFT) polymerization. Preliminary QCM-D studies were then conducted to evaluate their affinity for lipid bilayers, emphasizing marked impact of the lipid group on the bilayer modification. The same technique also demonstrated the protein repellency of the modified lipid bilayer. All conjugates were then incorporated into siRNA loaded lipid nanoparticle (LNP) formulations at different molar fractions to evaluate their influence on nanoparticle physicochemical properties and encapsulation efficiency. Future work will investigate their biological performance and safety through in vitro (cell transfection and viability) and in vivo studies, aiming to develop effective PEG alternatives for nucleic acid delivery.

¹ Berger M.; Toussaint F.; Djemaa S. Ben; Laloy J.; Pendeville H.; Evrard B.; Jérôme C.; Lechanteur A.; Mottet D.; Debuigne A.; Piel G. J. Control. Release 2023, 361, 87–101. DOI :10.1016/j.jconrel.2023.07.031.

² Berger M.; Toussaint F.; Ben Djemaa S.; Maquoi E.; Pendeville H.; Evrard B.; Jérôme C.; Leblond Chain J.; Lechanteur A.; Mottet D.*; Debuigne A.*, Piel G.* Adv Healthc Mater. 2024, 13(8), 2302712. DOI: 10.1002/adhm.202302712.

³ Debuigne A.; Piel G.; Mottet D.; Toussaint F.; Berger M.; Bendjema S.; Lechanteur A. Polymer Derivatives and their use as lipid nanoparticle modifiers. Patent 2024, WO2024227713A1 & EP4458870A1.

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