

REPLACING PEG: LIPID-POLY(*N*-METHYL *N*-VINYLACETAMIDE) CONJUGATES FOR THE SURFACE MODIFICATION OF LIPIDIC NANOVECTORS DEDICATED TO GENE THERAPY

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Surface modification of lipid carriers with polyethylene glycol (PEG) is a well-established strategy to prevent particle aggregation and to provide “stealth” properties, thereby prolonging blood circulation. Nevertheless, PEGylation suffers from important drawbacks, including the accelerated blood clearance (ABC) effect upon repeated dosing, hypersensitivity reactions, and the so-called “PEG dilemma,” which hampers both cellular uptake and endosomal escape. Poly(*N*-methyl *N*-vinylacetamide) (PNMVA) has recently emerged as a promising alternative to PEG, offering non-toxic, efficient, and less immunogenic coatings for lipid-based carriers, especially siRNA-loaded lipid nanoparticles.¹⁻³ In this work, we report the precision synthesis of a library of lipid–PNMVA conjugates via reversible addition–fragmentation chain transfer (RAFT) polymerization. The lipid structure and PNMVA chain length were systematically varied to evaluate their influence on the interaction with lipid bilayers, as well as on the morphology and surface properties of the resulting lipid nanocarriers. These results provide new insights into the design of PEG alternatives for advanced nucleic acid delivery systems.

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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