APME 2025
CATANIA (ITALY), 4-8 May 2025

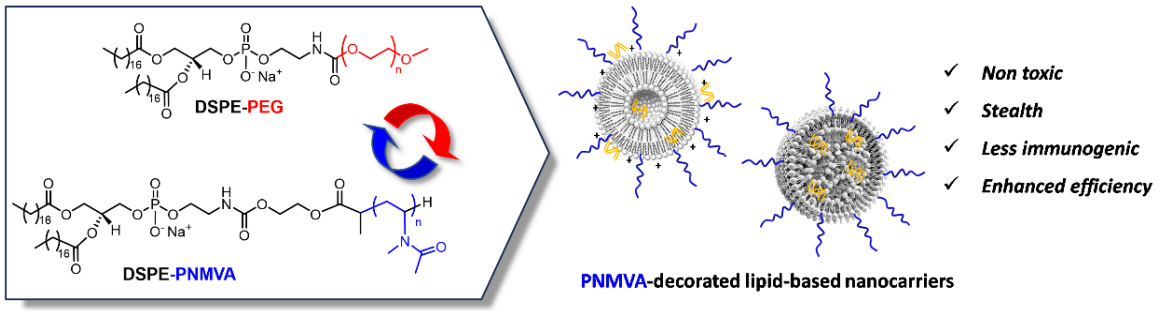
LIPID-POLY(*N*-VINYLAMIDE) CONJUGATES AS PEG ALTERNATIVES TOWARDS SAFER AND EFFICIENT LIPID-BASED siRNA DELIVERY SYSTEMS.

ANTOINE DEBUIGNE,[1] MANON BERGER,[2] FRANÇOIS TOUSSAINT,[1] SANAA BEN DJEMAA,[3] CHRISTINE JEROME,[1] ANNA LECHANTEUR,[2] DENIS MOTTET,[3] GERALDINE PIEL[2].

[1] *Center for Education and Research on Macromolecules (CERM), University of Liège, B6a Allée de la Chimie, Sart Tilman, 4000 Liege, Belgium. email: adebuigne@uliege.be*
[2] *Laboratory of Pharmaceutical Technology and Biopharmacy, University of Liège, Belgium.*
[3] *Gene Expression and Cancer Laboratory (GEC), University of Liège, Belgium.*

Abstract

Pegylation of drug nanocarriers, particularly lipid-based vectors, is commonly used to confer them stealth properties and enhance their circulation time in the bloodstream. However, PEG also promotes the accelerated blood clearance (ABC) effect, which results in rapid drug elimination from the body after repeated administration, and the so-called PEG dilemma, characterized by reduced cellular uptake due to the polymer layer around the carrier. This presentation will explore the potential of poly(*N*-vinylamide)s, including poly(*N*-vinylpyrrolidone) (P*N*VP) and poly(*N*-methyl vinylacetamide) (P*N*MVA), as alternatives to PEG towards non-toxic, efficient, and less immunogenic lipid-based carriers, in particular siRNA-loaded lipoplexes and lipid nanoparticles dedicated to gene therapy.[1,2] Novel lipid-poly(*N*-vinylamide)s conjugates were synthesized by reversible addition-fragmentation chain transfer (RAFT) polymerization, allowing precise control over the molar mass of the hydrophilic polymer sequences and their functionalization with lipids like 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE) to anchor the conjugates at the surface of the lipid carrier. Interactions of these lipid-polymer conjugates with phospholipid bilayers will be discussed based on quartz crystal microbalance analyses. The anchoring of lipid-poly(*N*-vinylamide)s on siRNA-loaded lipid nanocarriers and their ability to inhibit protein adsorption were confirmed through dynamic light scattering, zeta potential measurements, and nanoparticle tracking analysis. *In vitro* and *in vivo* evaluations revealed that the modified siRNA-loaded lipid nanocarriers present low toxicity, effective stealth properties, and high transfection efficiency. Compared to their PEGylated counterparts, P*N*MVA-decorated lipid nanocarriers demonstrate reduced immunogenicity, especially after repeated administration, marking a significant advancement in the development of safer lipid-based delivery systems.[3]



[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.; Jerôme 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.
Acknowledgment: Grant ARC-Lipegalt, Grant GT4Health from Walloon Region and the F.R.S.-FNRS.