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### **Poly(N-Vinyl Amide)-Lipid Conjugates as Poly(Ethylene Glycol) Alternatives for the Modification of Lipid-Based Nanocarriers.**

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Pegylation of drug nanocarriers, and of lipid-based vectors in particular, is a common strategy to grant them stealth properties and promote their prolonged circulation in the blood stream. However, PEG is also associated to the accelerated blood clearance (ABC) effect, leading to the fast elimination of the medicine from the body, and to the PEG *dilemma*, which consists in uptake issues due to the presence of the polymer layer around the carrier. For these reasons, the search for PEG alternatives in drug delivery systems is timely.

This work explores the potential of poly(*N*-vinyl amide)s, including poly(*N*-vinyl pyrrolidone) (PNVP), as PEG alternatives for the development of non-toxic, efficient and less immunogenic lipid-based carriers, in particular siRNA-loaded lipoplexes and lipid nanoparticles dedicated to gene therapy.<sup>1,2</sup> For this purpose, novel poly(*N*-vinyl amide)-lipid conjugates were synthesized by reversible deactivation radical polymerization. This strategy allowed to control the molar mass of the hydrophilic polymer sequence and to functionalize its extremity with lipids, such as 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE), to ensure their anchoring at the surface of the lipid carriers. The surface active properties of these poly(*N*-vinyl amide)-lipid conjugates and their interaction with phospholipid bilayers were studied by Langmuir film balance and quartz crystal microbalance with dissipation monitoring (QCM-D), respectively. The anchoring of the poly(*N*-vinyl amide)-lipid compounds at the surface of siRNA-loaded lipid nanocarriers and their ability to prevent protein adsorption were demonstrated by dynamic light scattering, zeta potential and nanoparticles tracking analyses. *In vitro* and *in vivo* studies demonstrated the non-toxicity, stealth properties and transfection efficiency of the accordingly modified siRNA-loaded lipid nanocarriers. Importantly, compared to their pegylated counterparts, lipid nanocarriers decorated by poly(*N*-vinyl amide)s showed lower immunogenicity in particular after the second injection which constitutes a key step to the development of safer lipid-based carriers.

1. Berger, M.; Toussaint, F.; Djemaa, S. Ben; Laloy, J.; Pendeville, H.; Evrard, B.; Jérôme, C.; Lechanteur, A.; Mottet, D.; Debuigne, A.; Piel, G. Poly(Vinyl Pyrrolidone) Derivatives as PEG Alternatives for Stealth, Non-Toxic and Less Immunogenic siRNA-Containing Lipoplex Delivery. *J. Control. Release* 2023, 361, 87–101. <https://doi.org/10.1016/j.jconrel.2023.07.031>.

2. Patent Application EP23171538.4 “Polymer Derivatives and their use as lipid nanoparticle modifiers”. Inventors : Antoine Debuigne, Géraldine Piel, Denis Mottet, François Toussaint, Manon Berger, Sanaa Bendjema, Anna Lechanteur.

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