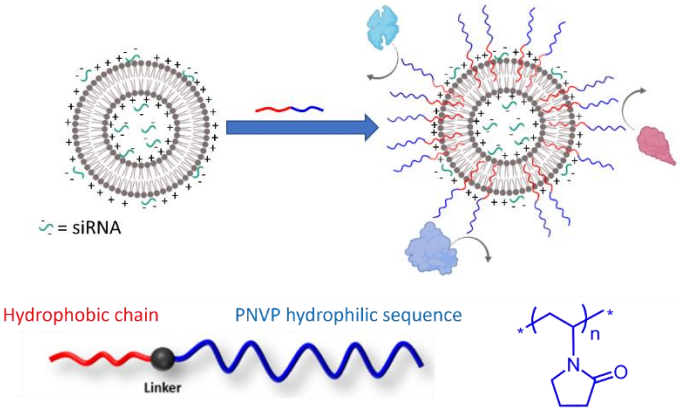
Amphiphilic Poly(*N*-vinylpyrrolidone)-based Lipoplex Modifiers for Drug Delivery Applications.

François Toussaint,[a] *Manon Berger,*[b] *Anna Lechanteur,*[b] *Christine Jérôme,*[a] *Géraldine Piel*[b] *and Antoine Debuigne*[a]

[a] *Center for Education and research on Macromolecules, University of Liège, Sart Tilman B6a, Belgium*

[b]*Laboratory of Pharmaceutical Technology and Biopharmacy, CIRM, University of Liège, Belgium*

SiRNA-loaded lipoplexes, resulting from electrostatic interactions between the polar headgroups of cationic phospholipids and the phosphate groups of siRNA, are promising drug delivery vehicles for cancer therapy.[1] Pegylation of the latter is commonly used to prevent their rapid elimination by macrophages but poly(ethylene glycol) (PEG) may cause immunological responses as well as Accelerated Blood Clearance (ABC effect).[2] As alternative to PEG, we explored the potential of poly(*N*-vinylpyrrolidone) (PNVP) derivatives for the modification of siRNA-loaded lipoplexes. A series of well-defined amphiphilic PNVP-based polymers composed of single or double aliphatic chains was prepared by Reversible Addition Fragmentation chain Transfer (RAFT). The amphiphilicity of these PNVP-based derivatives 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 some PNVP derivatives onto siRNA lipoplexes and their ability to prevent protein adsorption were demonstrated by DLS, zeta potential and Nanoparticle Tracking Analysis (NTA). Overall, this functional PNVP synthesis platform not only allowed to identify the key macromolecular characteristics necessary for the successful modification of lipoplexes but also evidenced the potential of PNVP as PEG alternative for siRNA delivery application.



References:

1 Berger, M.; Lechanteur, A.; Evrard, B.; Piel, G. Innovative Lipoplexes Formulations with Enhanced SiRNA Efficacy for Cancer Treatment: Where Are We Now? *Int. J. Pharm.* **2021**, *605* (June).

2 Zahednezhad, F.; Saadat, M.; Valizadeh, H.; Zakeri-Milani, P.; Baradaran, B. Liposome and Immune System Interplay: Challenges and Potentials. *J. Control. Release* **2019**, *305* (April), 194–209.