NEW AMPHIPHILIC POLYMERS WITH VARIABLE LENGTH AND NUMBER OF LIPID CHAINS AS ALTERNATIVES TO PEG FOR THE FORMULATION OF LIPID NANOPARTICLES ENCAPSULATING siRNA

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Nowadays, it is well known that blood biomolecules, especially proteins, adhere to the surface of nanovectors such as lipid nanoparticles (LNPs) after systemic administration. This phenomenon is commonly referred to as the protein corona formation. The presence of this layer of blood proteins can alter crucial properties such as physicochemical characteristics, particle half-life, cellular uptake, biodistribution and recognition by the immune system. Consequently, this may result in the rapid clearance of LNPs and, subsequently, therapeutic inefficacy. To prevent this phenomenon, polyethylene glycol (PEG) is incorporated as one of the typical components in LNPs to provide steric stability and extend the particle half-life. Conversely, the use of PEG is related to several issues concerning immunogenicity, cellular uptake and endosomal escape resulting in drug inefficiency.

Therefore, the purpose of this project is to suggest alternatives to the commonly used PEG in LNP formulations, with the aim of improving both the antitumor efficacy and the safety. The objective is to combine two approaches of modifying the length and the number of lipid chains of lipid-PEG to modulate their anchoring in LNPs and thus their biodistribution. The nature of the hydrophilic chain (PEG) will also be replaced to reduce immune effects with new polymers such as PNMVA, PNVP, polyglycerols and polysarcosin. The impact on physicochemical properties, *in vitro* evaluation of LNP-siRNA uptake and efficiency, *in vitro* and *in vivo* toxicity evaluation, *in vivo* biodistribution and immunogenicity evaluation of LNP-siRNA complex will be assessed with the purpose of improving the antitumor efficacy.

This poster presents early results for various lipid-PEG and lipid-polymer formulations, comparing them with DSPE-PEG_{2000} and DMG-PEG_{2000} used as controls. Protein corona formation post-incubation in complete FBS is monitored using Nanosight NS300.