Novel alternatives to PEG with improved activity for the decoration of lipid nanoparticles

KEY ACHIEVEMENTS

- Synthesis and in vitro/in vivo characterization of lipids conjugated with PNMVA polymers for the decoration of lipid nanoparticle (LNPs)
- Polymer family patent protected

KEY COMPETITIVE ADVANTAGES

Lipid nanoparticles decorated with PNMVA are less toxic, less immunogenic, and more effective for siRNA-based gene knockdown compared with PEG-decorated counterparts.

ONGOING ACTIVITIES

- Scale up synthesis
- Synthesis of pH-sensitive PNMVA-lipids
- Validation of the stealth, biodistribution, immunological and toxic effects of PNMVA-LNP
- Validation of the efficacy of LNP-PNMVA on a therapeutic target

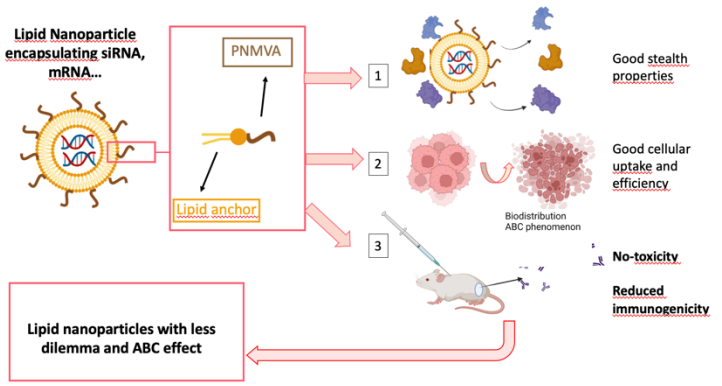
INTELLECTUAL PROPERTY

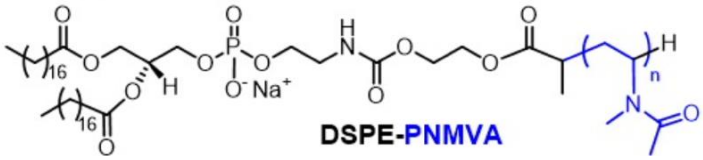
Patent filled: POLYMER DERIVATIVES AND THEIR USE AS LIPID NANOPARTICLE MODIFIERS; EP23171538.4

PARTNERSHIP SOUGHT

Collaboration agreements with industry and/or academia to implement lipid-PNMVA technology in diverse applications.

Lipid-based nanocarriers such as liposomes or LNPs have demonstrated of high interest for delivering genetic material. This has been recently emphasized by the approval of Onpattro® and COVID-19 vaccines. PEGylation is known to provide lipid-based nanocarriers with stealth properties, but it also leads to reduced cellular uptake and endosomal escape, and to the production of anti-PEG antibodies causing accelerated blood clearance (ABC) and hypersensitivity reactions (HSR). Modification of lipids with Poly(N-methyl-N-vinylacetamide) (PNMVA) derivatives is an alternative to PEG for post-insertion into lipoplexes and pre-insertion into LNPs designed for siRNA delivery.





PNMVA compounds with different degrees of polymerization and hydrophobic segments, such as octadecyl and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE), were synthesized. Among them, DSPE-PNMVA efficiently integrated into lipoplex and LNP membranes and prevented protein corona formation around these lipid carriers, exhibiting stealth properties comparable to DSPE-PEG. However, unlike DSPE-PEG, DSPE-PNMVA$_{24}$ showed no adverse impact on lipoplexes cell uptake and endosomal escape. In *in vivo* study with mice, DSPE-PNMVA$_{24}$ lipoplexes demonstrated no liver accumulation, indicating good stealth properties, extended circulation time after a second dose, reduced immunological reaction, and no systemic pro-inflammatory response. Safety of DSPE-PNMVA$_{24}$ was confirmed at the cellular level and in animal models of zebrafish and mice. Overall, **DSPE-PNMVA is an advantageous substitute to DSPE-PEG for siRNA delivery**, offering comparable stealth and toxicity properties while improving efficacy of the lipid-based carriers by minimizing the dilemma effect and reducing immunological reactions, meaning no ABC or HSR effects.

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