Peptide-enhanced lipid nanoparticles for targeted delivery of therapeutic nucleic acids

Amir Akbari, Pall Thordarson, and Joshua McCarroll**

School of Chemistry,
UNSW SYDNEY 2052
Australia

Presenting author e-mail: amir.akbari@unsw.edu.au
Corresponding author e-mail: p.thordarson@unsw.edu.au

For years, lipid-based nanoparticles (LNPs) have been extensively studied in drug delivery due to their several advantages, including enhanced bioavailability, targeted delivery, and biocompatibility.[1] LNPs, commonly characterized by their spherical shape with lipid bilayers enclosing internal compartments, provide flexible and reliable delivery systems. A notable application of LNPs is in delivering therapeutic nucleic acids, formulated with ionizable cationic lipids that facilitate endosomal escape.[2] However, LNPs primarily accumulate in the liver upon intravenous administration, limiting their utility for targeting other organs. Exploring methods to boost LNP specificity for different organs, like integrating targeting ligands, could reduce off-target drug delivery and improve treatment efficiency. Peptide ligands, offering simplicity and lower immunogenicity compared to antibodies, show promise in enhancing targeting specificity.[3] Multivalency, a crucial factor influencing targeting nanoparticles, enhances specificity and avidity. A multivalent interaction refers to the simultaneous occurrence of multiple instances of weak noncovalent binding between two entities, such as a ligand and a receptor.[4] This becomes particularly critical when integrating phage-derived short peptide ligands into nanoparticle design, as there are cases where the peptide's affinity may diminish after screening, especially in monovalent systems.[5] Additionally, an excess of the targeting unit on the nanoparticle does not necessarily increase specificity.[4] Therefore, careful optimization is essential when designing peptide-coated nanoparticles.

The project's goal is to advance targeted delivery of therapeutic RNA using cell-targeting-peptide-functionalized LNPs, initially focusing on medulloblastoma and subsequently on T cells, with an emphasis on optimizing peptide-coated LNPs for selective delivery. Key results/objectives include peptide synthesis, cytotoxicity assessment, LNP functionalization with peptides, and evaluating delivery effectiveness in target systems.

References:

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