Peptide Functionalised Lipid Nanoparticles Targeting Dendritic Cells for Immunotherapy

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Dendritic Cells (DCs) are the most effective immune cells in our biological systems. Regulating both adaptive and innate immune systems and are considered central components of the tumours microenvironment in promoting anti-tumour T-cell response. They survey the local environment with their high expression of membrane and cytosolic receptors for identifying different types of danger signals, including pathogens and tumour cells [1].

With Genetic drug delivery being of worldwide interest with the COVID-19 mRNA vaccine, lipid nanoparticles are emerging as an ideal candidate for immunotherapy, with its enhanced pharmacodynamics and pharmacokinetics and lower side effects compared to other cancer therapies. These properties can be further enhanced with peptide functionalized bioconjugates via thiol-maleimide Michael type addition reaction in mild conditions, at a terminal cysteine group [2]. This allows greater all-round stability, immunogenicity, targeting specificity and intracellular uptake over antibody bioconjugates and small molecules.

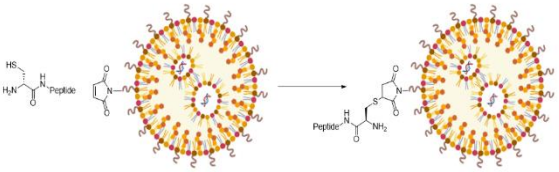

Figure 1 Schematic illustration of bioconjugation of a functionalized peptide to the LNP via thiol-maleimide click reaction. [2]

This study investigates targeting three endosomal receptor types found of DCs; C-type lectin receptor Clec9a, [3] tumour necrosis factor receptor (TNF) CD40 [4] and complement receptor 4 (CR4) CD11c, [1], with functionalised peptides that have been reported to exhibit high binding affinity towards these receptors and bioconjugate them to LNPs for the delivery of mRNA to the DCs for possibly promoting enhanced T cell and anti-tumour cytokine responses for immunotherapy. Cellular uptake of mRNA will be determined with labelled eGFP expressed mRNA encapsulated in the LNP and introduced to mouse DCs. Upon cellular uptake early endosomal release occurs in the cytoplasm disassembling the LNP allowing for observation of eGFP mRNA expression within the DCs.

(1) Liu, Y.; et al. *ACS Applied Bio Materials* **2019**, *2* (3), 1241-1254
(2) Martínez-Jothar, F.;*Journal of Controlled Release* **2018**, *282*, 101-109.
(3) Gou, S.;et al. *Theranostics* **2021**, *11* (15), 7308-7321.
(4) Mamuti, M.; et al. *Adv Mater* **2022**, *34* (24), e2109432.