Alternative Polymers for More Effective mRNA-LNP Vaccines

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Current mRNA vaccines are relatively safe and effective against COVID-19. However, they contain a widely used polymer – poly(ethylene glycol) (PEG) in their lipid nanoparticle (LNP) formulations, known to induce an antibody response resulting in rapid clearance of PEG-based therapeutic upon subsequent administrations.[1, 2] Therefore, it is highly desirable to find alternative polymers which can replace the PEG component in mRNA vaccines, while still maintaining the vaccines' efficacy. We employed reversible addition-fragmentation chain transfer (RAFT) polymerisation to synthesise five PEG alternative polymers (labelled R1-R5) that could stabilise LNPs encapsulating mRNA molecules. Our synthesis strategy also allowed the introduction of charge along the polymer backbone. The RAFT polymer-LNPs were tested on mice to determine their in vivo gene expression and antigen-specific antibody production.

Based on Figure 1A, the new polymer-LNPs exhibited analogous or higher in vivo transfection of the Luc mRNA cargo in the muscle after 24 h of intramuscular injection, compared to the traditional PEG-based formulation. The variations in structures and properties of the polymers (e.g., branched structure, molecular weight, dispersity) may lead to slight differences in particle size, cellular interactions, and the increased gene expression observed. Additionally, the new polymer-LNP formulation having the highest gene expression in the muscle also displayed higher OVA-specific IgG antibody production compared to the conventional PEG-LNP formulation and naked OVA mRNA (Figure 1B). Therefore, these results show that it is possible to replace PEG with alternative polymers in mRNA vaccines while still maintaining high antibody production efficiency. Together, our work offers a new approach to develop safer and more effective mRNA vaccines by further modifying the properties of RAFT polymers, and expands the potential of these polymers for use in clinical vaccines.

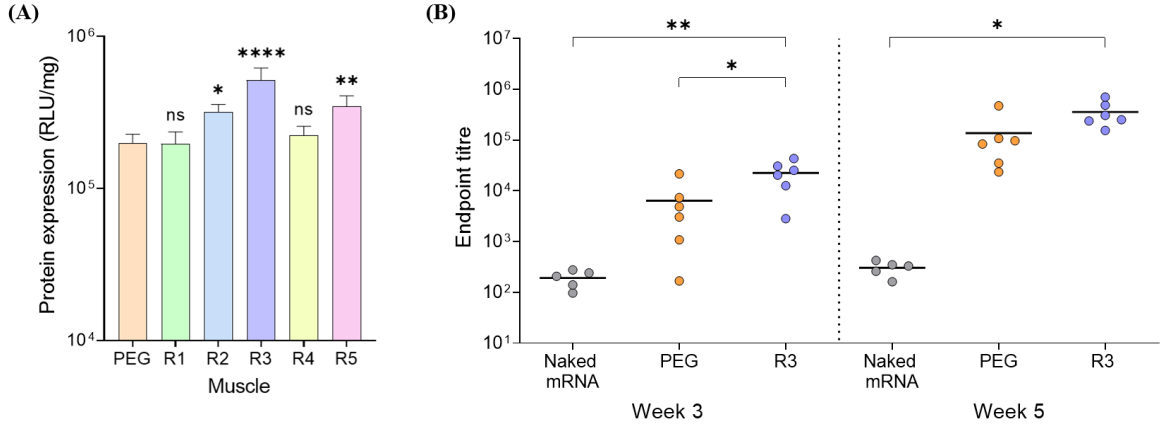

Figure 1: (A) In vivo gene expression of Luc mRNA LNPs. (B) In vivo antibody response of naked OVA mRNA and OVA mRNA LNPs.

References:

[1] Ju, Y.; et al. ACS Nano **2022**, 16, 11769-11780.
[2] Thi, T. T. H.; et al. Polymer **2020**, 12, 298.