Development of Ionizable Lipids and mRNA-Encoded Adjuvants to Enhance the Potency of mRNA Vaccines and Immunotherapies

by

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mRNA lipid nanoparticles (LNPs) have established themselves as a versatile platform for vaccines and immunotherapies. However, their clinical use has revealed opportunities for improvement. For example, increasing their potency to reduce costs and enhance immunogenicity could improve therapeutic outcomes and global accessibility. In this work two strategies are described to enhance the potency of mRNA vaccines and immunotherapies: 1) optimization of the ionizable lipid component of the LNP to enhance mRNA delivery and 2) utilization of immune-remodeling mRNAs to enhance antigen presenting cell (APC) activation and antigen presentation. In the first approach, we utilized epoxide ring-opening combinatorial chemistry to synthesize a library of over 130 cyclic amino alcohol ionizable lipids. We then screened this library for structures which enhance intramuscular mRNA expression and identified the top-performing lipid, AMG1541. AMG1541-containing LNPs formulated with hemagglutinin-encoding mRNA enhanced humoral and cellular immune responses relative to clinical benchmarks in mouse models, enabling up to a 100-fold reduction in vaccine dosing while maintaining protective immunity. We also identified three key structural features which confer potency to AMG1541: β-hydroxyls proximal to the ionizable nitrogens, tail unsaturation, and the cyclic headgroup structure. In the second approach, we identified two mRNA-encoded adjuvants which could be delivered as mRNAs to APCs to enhance their activation and $CD8^+$ T cell priming. When administered to mice with established colon, bladder, and melanoma tumors, we observed tumor regression or complete elimination. Furthermore, co-delivery of these adjuvants with the model antigens ovalbumin and hemagglutinin significantly increased antigen-specific $CD8^+$ T cell priming up to 15-fold and antibody titers up to 5-fold. Together, these advancements in ionizable lipid design and mRNA-encoded adjuvants provide powerful tools for the development of next-generation vaccines and immunotherapies.

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