IMMUNOGENIC MRNA DELIVERY VEHICLES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and benefit of U.S. Provisional Patent Application No. 63/307,578, filed February 7, 2022, which is incorporated herein by reference in its entirety.

FIELD

[0002] The present disclosure relates to lipid-based delivery vehicles for mRNA vaccines, which include a lysophosphatidylcholine (LPC) compound for enhancing vaccine immunogenicity. The present disclosure also relates to methods for use of mRNA vaccines.

BACKGROUND

[0003] mRNA vaccines have several advantages over traditional vaccines. For instance, mRNA vaccines can be quickly developed, cheaply produced, and safely administered (Pardi et al., Nat Reg Drug Discov, 17(4):261-279, 2018). However, naked mRNA is unstable and is quickly degraded after administration. Fortunately, advances in mRNA chemistry and delivery systems have enabled the rapid production of several effective mRNA COVID-19 vaccines (Hou et al., Nature Review Materials, 6:1078-1094, 2021).

[0004] Even so, there is room for improvement of lipid-based formulations for delivery of mRNA vaccines. Specifically, more immunogenic and/or less reactogenic formulations are desirable.

BRIEF SUMMARY

[0005] The present disclosure relates to lipid-based delivery vehicles for mRNA vaccines, which include a lysophosphatidylcholine (LPC) compound for enhancing vaccine immunogenicity. The present disclosure also relates to methods for use of mRNA vaccines.

[0005a] In one aspect, the present disclosure relates to use of a composition comprising an mRNA encapsulated in a lipid nanoparticle (LNP), in the manufacture of a medicament for stimulating an immune response in an individual, wherein the mRNA comprises a coding region of an antigen, and the LNP comprises a first phospholipid, and at least one lipid selected from the group consisting of an ionizable lipid, a second phospholipid, a pegylated lipid, a structural lipid, and mixtures thereof, wherein the first phospholipid comprises a lysophosphatidylcholine (LPC) with a single acyl chain, and the acyl chain is a C13-C24 acyl chain.

[0005b] In one aspect, the present disclosure relates to a composition comprising an mRNA and a TLR7/8 agonist encapsulated in a lipid nanoparticle (LNP), wherein the mRNA comprises a coding region of an antigen, and the LNP comprises a first phospholipid, and at least one lipid selected from the group consisting of an ionizable lipid, a second phospholipid, a pegylated lipid, a structural lipid, and mixtures thereof, wherein the first phospholipid comprises a lysophosphatidylcholine (LPC) with a single acyl chain, and the acyl chain is a C13-C24 acyl chain. In another aspect, the present disclosure relates to

a composition comprising an mRNA encapsulated in a lipid nanoparticle (LNP), and a TLR7/8 agonist, wherein the mRNA comprises a coding region of an antigen, and the LNP comprises a first phospholipid, and at least one lipid selected from the group consisting of an ionizable lipid, a second phospholipid, a pegylated lipid, a structural lipid, and mixtures thereof, wherein the first phospholipid comprises a lysophosphatidylcholine (LPC) with a single acyl chain, and the acyl chain is a C13-C24 acyl chain.

[0005c] In one aspect, the present disclosure relates to use of a composition comprising: i) an mRNA complexed with one or more lipids (RNA-Lipoplex); and ii) a lysophosphatidylcholine (LPC) with a single C13-C24 acyl chain, wherein the mRNA comprises a coding region of an antigen, and the one or more lipids comprise a first lipid and a second lipid, in the manufacture of a medicament for stimulating an immune response in an individual. In another aspect, the present disclosure relates to a composition comprising: i) an mRNA complexed with one or more lipids (RNA-Lipoplex); ii) a lysophosphatidylcholine (LPC) with a single C13-C24 acyl chain, and iii) a TLR7/8 agonist, wherein the mRNA comprises a coding region of an antigen, and the one or more lipids comprise a first lipid and a second lipid.

[0005d] In one aspect, the present disclosure relates to a pharmaceutical formulation comprising the composition of as disclosed herein, and a pharmaceutically acceptable excipient.

[0005e] In one aspect, the present disclosure relates to use of the composition as disclosed herein in the manufacture of a medicament for producing hyperactivated dendritic cells, wherein the hyperactivated dendritic cells secrete IL-1beta without undergoing cell death within about 48 hours of exposure, wherein the dendritic cells are to be contacted in vivo with the composition. In another aspect, the present disclosure relates to an ex vivo method for production of hyperactivated dendritic cells, the method comprising contacting the dendritic cells with an effective amount of the composition as disclosed herein to produce hyperactivated dendritic cells, wherein the hyperactivated dendritic cells secrete IL-1beta without undergoing cell death within about 48 hours of exposure.

[0005f] In one aspect, the present disclosure relates to a pharmaceutical formulation comprising at least 10^3, 10^4, 10^5 or 10^6 of the hyperactivated dendritic cells produced by the method disclosed herein, and a pharmaceutically acceptable excipient.

[0005g] In one aspect, the present disclosure relates to use of a pharmaceutical formulation, wherein: a) the pharmaceutical formulation is that as disclosed herein, in the manufacture of a medicament for stimulating an immune response against an antigen in an individual in need thereof; or b) the pharmaceutical formulation is that as disclosed herein, in the manufacture of a medicament for treating cancer in an individual in need thereof ; or c) the pharmaceutical formulation is that as disclosed herein, in the manufacture of a medicament for inhibiting abnormal cell proliferation in an individual in need thereof; or d) the pharmaceutical formulation is that as disclosed herein, in the manufacture of a medicament for treating or preventing an infectious disease in an individual in need thereof; optionally wherein the infectious disease is a viral disease and/or a bacterial disease.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] **FIG. 1A-B** show that lipid nanoparticles (LNPs) loaded with both 22:0 Lyso PC and mRNA remain nanoparticle sized (<125 nm) and are relatively uniform in diameter (PDI < 0.3). **FIG. 1A** shows that LNPs loaded with mRNA are larger than LNPs lacking mRNA, and