with the required substrate (*i.e.*, Man-1-P). However, the delivery and maintenance of such a systemic supply of Man-1-P is problematic, as extracellular enzymes within bodily fluids degrade Man-1-P when delivered exogenously by oral or intravenous administration. Another problem with exogenously delivered Man-1-P is that its high polarity prevents Man-1-P from penetrating into the cell interior (*i.e.*, cytosol) and thus treating the deficiency in PMM production.

[0009] Derivatives of the polar Man-1-P can be synthesized to make Man-1-P more cell-permeable (US Patent Publication No. 2009/0054353). This approach, however, is also problematic, as the cell-permeable Man-1-P derivatives have been shown to be either unstable for clinical use or cytotoxic via the by-products of the Man-1-P derivatives (Eklund et al., *Glycobiology* 2005, 15: 1084-1093; Rutschow et al. *Bioorg Med Chem* 2002, 10: 4043-4049; and Hardre et al., *Bioorg Med Chem Lett* 2007, 17: 152-155).

[0010] Other potential therapies have focused on inhibiting enzymes that catabolize mannose-6-phosphate (Man-6-P), a precursor to Man-1-P, via the inhibition of phosphomannose isomerases (PMI). The approach focuses on forcing the reaction towards optimizing homeostasis, which with the use of PMI inhibitors, would have been skewed toward production of Man-6-P. These approaches, however, are ineffective as clinical treatment options due to their associated toxicity, off-target side effects, and poor selective tissue penetration.

[0011] Another potential solution is to use a delivery vehicle (*e.g.*, lipid particles) to encapsulate and deliver Man-1-P to the cell interior (*see* WO 2015/053910). However, due to the high charge and polarity of phosphorylated carbohydrates in general, the optimal delivery vehicle must overcome challenges of stability, phosphorylated carbohydrates loading rate and concentration, toxicity, and delivery efficiency.

[0012] Accordingly, unmet needs exist for improved compositions and methods for delivering phosphorylated carbohydrates, such as Man-1-P and Man-6-P, to the cell interior in order to treat disorders, such as a congenital disorder of glycosylation (CDG), to subjects (including, for example, humans) in need of such treatment.

BRIEF SUMMARY

[0012a] In an aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

a liposome comprising:

i) 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) or a salt thereof; ~~and~~

ii) ~~(a)~~ one or more phospholipids having a polar head group~~, wherein the polar head group comprises~~ comprising glycerol, choline, phosphate ~~and~~ or serine, and ~~a~~ two unsaturated fatty acid tails, wherein each unsaturated fatty acid tail comprises~~ing~~ a C_{10-28} ~~aliphatic~~ alkenyl chain~~, or~~

~~(b) an acidic cholesterol ester,~~

~~or both (a) and (b)~~; and

iii) polyethylene glycol (PEG) conjugated to at least one phospholipid; and

mannose-1-phosphate or a salt thereof ~~at least one endogenous phosphorylated carbohydrate~~ encapsulated in the liposome.

~~**[0012b]** In another aspect of the present disclosure, there is provided a composition comprising:~~

~~a liposome comprising:~~

~~i) N-dodecanoyl-1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine or a salt thereof; and~~

~~ii) 1,2-dioleoyl-sn-glycero-3-phosphocholine or salt thereof; and~~

~~at least one endogenous phosphorylated carbohydrate encapsulated in the liposome.~~

~~**[0012c]** In a further aspect of the present disclosure, there is provided a composition comprising:~~

~~a liposome comprising:~~

~~i) at least one phospholipid having an ethanolamine head group and at least one unsaturated fatty acid tail, wherein each unsaturated fatty acid tail independently comprises at least one C_{10-28} carbon chain;~~

~~ii) one or more of (a) to (c):~~

~~a) at least one phospholipid having a polar head group and at least one saturated fatty acid tail,~~

~~b) at least one phospholipid having a polar head group and at least one unsaturated fatty acid tail, wherein the polar head group comprises a quaternary ammonium cation, a glycerol group, or a serine group, and~~

~~c) at least one acidic cholesterol ester; and~~

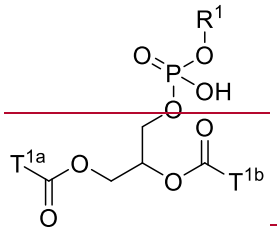
~~iii) polyethylene glycol (PEG), wherein the PEG is conjugated to at least one phospholipid; and~~

~~at least one endogenous phosphorylated carbohydrate encapsulated in the liposome.~~

[0012d] In another aspect of the present disclosure, there is provided a composition comprising:

a liposome comprising:

i) a phospholipid of formula (PL-1):



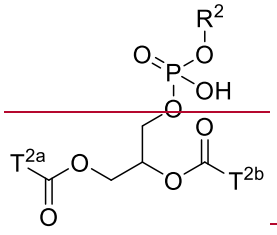
(PL-1),

or a salt thereof, wherein:

at least one of T^{1a} and T^{1b} is an unsaturated carbon chain comprising a C_{10-28} alkenyl or a C_{10-28} alkynyl; and

R^1 is aminoalkyl;

ii) at least one phospholipid of formula (PL-2), at least one phospholipid of formula (PL-3A), or at least one cholesterol ester of formula (CE), or any combination of the foregoing:

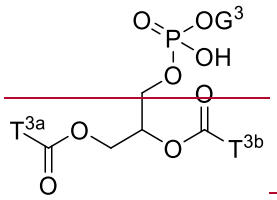


(PL-2),

or a salt thereof, wherein:

each of T^{2a} and T^{2b} is an unsaturated carbon chain comprising a C_{10-28} alkenyl or a C_{10-28} alkynyl; and

R^2 is alkyl substituted with a quaternary ammonium, glycerol, or alkyl substituted with –COOH and $-NH_2$;

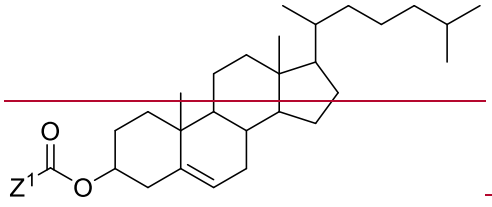


(PL-3A),

or a salt thereof, wherein:

each of T^{3a} and T^{3b} is a carbon chain; and

G^3 is H or alkyl substituted with at least one –OH; and



(CE),

or a salt thereof, wherein:

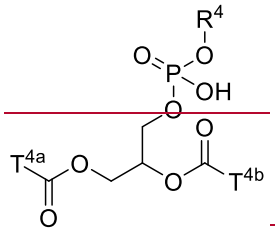
Z^1 is alkyl substituted with –COOH; and

iii) polyethylene glycol (PEG), wherein the PEG is conjugated to at least one phospholipid; and

at least one endogenous phosphorylated carbohydrate encapsulated in the liposome.

[0012e] In a further aspect of the present disclosure, there is provided a composition comprising:

a liposome comprising a phospholipid of formula (PL-4):



(PL-4),

or a salt thereof, wherein:

at least one of T^{1a} and T^{1b} is an unsaturated carbon chain comprising a C_{10-28} alkenyl or a C_{10-28} alkynyl; and

R^4 is an aliphatic chain comprising an amide moiety; and

at least one endogenous phosphorylated carbohydrate encapsulated in the liposome.

[0012f] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the composition disclosed herein, and a pharmaceutically acceptable carrier.

[0012g] In a further aspect of the present disclosure, there is provided a composition disclosed herein for use in a method for delivering a carbohydrate to a human in need thereof.

[0012h] In another aspect of the present disclosure, there is provided a composition disclosed herein for use in a method for delivering a carbohydrate to a cell interior of a subject in need thereof, wherein the composition is to be administered to the subject, and wherein at least a

~~portion of the administered composition traverses the cell plasma membrane to deliver the carbohydrate to the cell interior.~~

~~**[0012i]** In a further aspect of the present disclosure, there is provided a composition disclosed herein for use in treating a congenital disorder of glycosylation (CDG) in a human in need thereof.~~

[0012b] In another aspect of the present disclosure, there is provided a liposomal pharmaceutical composition comprising mannose-1-phosphate or a salt thereof, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), and DSPE-PEG_{2000}, wherein the molar ratio of DOPE, DOPC and DSPE-PEG_{2000} is 30:67:3.

[0012c~~j~~] In ~~another~~ a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a congenital disorder of glycosylation (CDG) in a human in need thereof.

[0012d~~k~~] In ~~a further~~another aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein, for use in therapy~~kit comprising:~~

~~a composition disclosed herein;~~

~~a container; and~~

~~a label or package insert on or associated with the container~~.

[0013] The present disclosure meets the unmet needs described above by providing compositions and kits comprising phosphorylated carbohydrates encapsulated by certain liposomes that address the phosphorylated carbohydrate loading efficiency, cytotoxicity, and

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising:

a liposome comprising:

i) 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) or a salt thereof; ~~and~~

ii) ~~(a)~~ one or more phospholipids having a polar head group comprising glycerol, choline, phosphate or serine, and two unsaturated fatty acid tails, wherein each unsaturated fatty acid tail comprises a C_{10-28} alkenyl chain ~~wherein the polar head group comprises glycerol, choline, phosphate and serine and a fatty acid tail comprising a C_{10-28} aliphatic chain, or~~

~~(b) an acidic cholesterol ester,~~

~~or both (a) and (b)~~; and

iii) polyethylene glycol (PEG) conjugated to at least one phospholipid; and

mannose-1-phosphate or a salt thereof ~~at least one endogenous phosphorylated carbohydrate~~ encapsulated in the liposome.

2. The pharmaceutical composition of claim 1, wherein the phospholipid comprising the polar head group is choline.

~~2.~~3. The pharmaceutical composition of claim 1, wherein the one or more phospholipid having a polar head group is~~comprise~~:

1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC);

~~1,2-dipalmitoyl-phosphatidyl-glycerole;~~

1,2-dioleoyl-sn-glycero-3-phosphoglycerol (DOPG); or

~~1,2-distearoyl-sn-glycero-3-phosphate; or~~

1,2-dioleoyl-sn-glycero-3-phospho-L-serine (DOPS),

or a salt thereof,

or any combination of the foregoing.

~~3.~~4. The pharmaceutical composition of claim 2, wherein the one or more phospholipids having a polar head group comprise 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) or a salt thereof.

~~4. A composition comprising:~~

~~a liposome comprising:~~

~~i) N-dodecanoyl-1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine or a salt thereof; and~~

~~ii) 1,2-dioleoyl-sn-glycero-3-phosphocholine or salt thereof; and~~

~~at least one endogenous phosphorylated carbohydrate encapsulated in the liposome.~~

~~5. The composition of claim 4, wherein the liposome further comprises PEG conjugated to at least one phospholipid.~~

~~6. A composition comprising:~~

~~a liposome comprising:~~

~~i) at least one phospholipid having an ethanolamine head group and at least one unsaturated fatty acid tail, wherein each unsaturated fatty acid tail independently comprises at least one C_{10-28} carbon chain;~~

~~ii) one or more of (a) to (c):~~

~~a) at least one phospholipid having a polar head group and at least one saturated fatty acid tail,~~

~~b) at least one phospholipid having a polar head group and at least one unsaturated fatty acid tail, wherein the polar head group~~

~~comprises a quaternary ammonium cation, a glycerol group, or a serine group, and~~

~~c) at least one acidic cholesterol ester; and~~

~~iii) polyethylene glycol (PEG), wherein the PEG is conjugated to at least one phospholipid; and~~

~~at least one endogenous phosphorylated carbohydrate encapsulated in the liposome.~~

~~7. The composition of claim 6, wherein each unsaturated fatty acid tail of the at least one phospholipid in i) comprises at least one double bond.~~

~~8. The composition of claim 6 or 7, wherein each unsaturated fatty acid tail of the at least one phospholipid in i) comprises one double bond.~~

~~9. The composition of any one of claims 6 to 8, wherein the unsaturated fatty acid tail comprises at least one C_{16-20} carbon chain.~~

~~10. The composition of any one of claims 6 to 9, wherein the phospholipid having an ethanolamine head group and at least one unsaturated fatty acid tail is 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine or salt thereof.~~

~~11. The composition of any one of claims 6 to 10, wherein the saturated fatty acid tail of the at least one phospholipid in a) comprises at least C_{16-20} carbon chain.~~

~~12. The composition of any one of claims 6 to 11, wherein the at least one phospholipid having a polar head group and a saturated fatty acid tail is 1,2-dipalmitoyl-sn-glycero-3-phosphorylglycerol or 1,2-distearoyl-sn-glycero-3-phosphate, or a salt thereof, or a combination of the foregoing.~~

~~13. The composition of any one of claims 6 to 12, wherein the polar head group of the at least one phospholipid in b) is choline.~~

~~14. The composition of any one of claims 6 to 12, wherein the at least one phospholipid having a polar head group with a quaternary ammonium cation and an unsaturated fatty acid tail is 1,2-dioleoyl-sn-glycero-3-phosphocholine or a salt thereof.~~

15. The composition of any one of claims 6 to 12, wherein the polar head group of the at least one phospholipid in b) is serine.

16. The composition of any one of claims 6 to 12, wherein the at least one phospholipid having a polar head group with a serine group and an unsaturated fatty acid tail is 1,2-dioleoyl-sn-glycero-3-phospho-L-serine or a salt thereof.

17. The composition of any one of claims 6 to 12, wherein the polar head group of the at least one phospholipid in b) is glycerol.

18. The composition of any one of claims 6 to 12, wherein the at least one phospholipid having a polar head group with a glycerol group and an unsaturated fatty acid tail is 1,2-dioleoyl-sn-glycero-3-phosphoglycerol or a salt thereof.

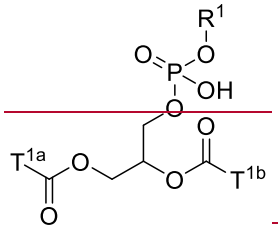
19. The composition of any one of claims 6 to 18, wherein the at least one acidic cholesterol ester is cholesteryl hemisuccinate.

20. The composition of any one of claims 1 to 3 or 5 to 19, wherein the at least one phospholipid conjugated to PEG is 1,2-distearoyl-sn-glycero-3-phosphoethanolamine or a salt thereof.

21. A composition comprising:

a liposome comprising:

i) a phospholipid of formula (PL-1):



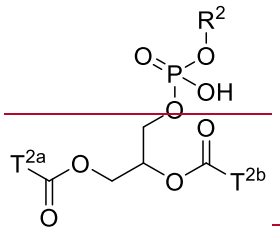
(PL-1),

or a salt thereof, wherein:

at least one of T^{1a} and T^{1b} is an unsaturated carbon chain comprising a C_{10-28} alkenyl or a C_{10-28} alkynyl; and

R^1 is aminoalkyl;

ii) at least one phospholipid of formula (PL-2), at least one phospholipid of formula (PL-3A), or at least one cholesterol ester of formula (CE), or any combination of the foregoing:

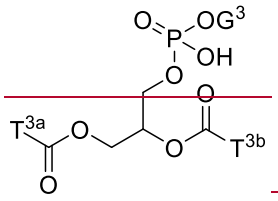


(PL-2),

or a salt thereof, wherein:

each of T^{2a} and T^{2b} is an unsaturated carbon chain comprising a C_{10-28} alkenyl or a C_{10-28} alkynyl; and

R^2 is alkyl substituted with a quaternary ammonium, glycerol, or alkyl substituted with –COOH and $-NH_2$;

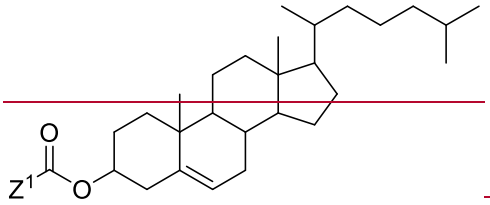


(PL-3A),

or a salt thereof, wherein:

each of T^{3a} and T^{3b} is a carbon chain; and

G^3 is H or alkyl substituted with at least one –OH; and



(CE),

or a salt thereof, wherein:

Z^1 is alkyl substituted with –COOH; and

iii) polyethylene glycol (PEG), wherein the PEG is conjugated to at least one phospholipid; and

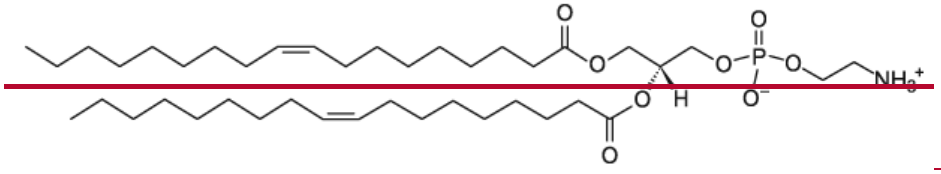
at least one endogenous phosphorylated carbohydrate encapsulated in the liposome.

22. The composition of claim 21, wherein each of T^{1a}, T^{1b}, T^{2a} and T^{2b} is independently an unsaturated carbon chain a comprising one double bond.

23. The composition of claim 22, wherein the unsaturated carbon chain is a *cis*-isomer.

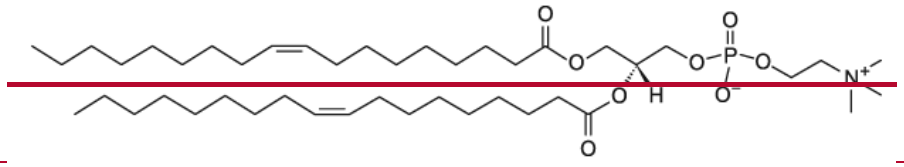
24. The composition of any one of claims 21 to 23, wherein each carbon chain has 10-28 carbon atoms.

25. The composition of claim 24, wherein the at least one phospholipid of formula (PL-1) is

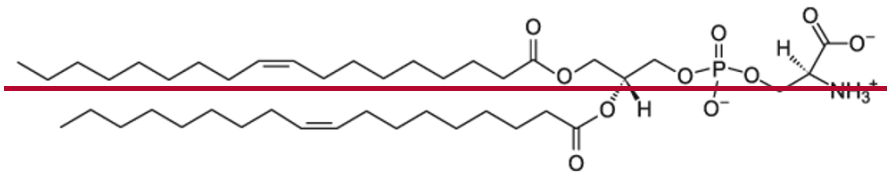


or a salt thereof.

26. The composition of any one of claims 21 to 25, wherein the at least one phospholipid of formula (PL-2) is

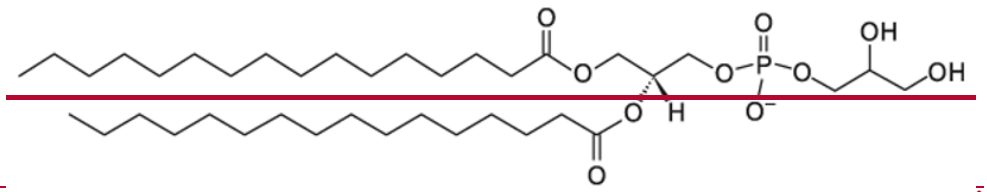


or .

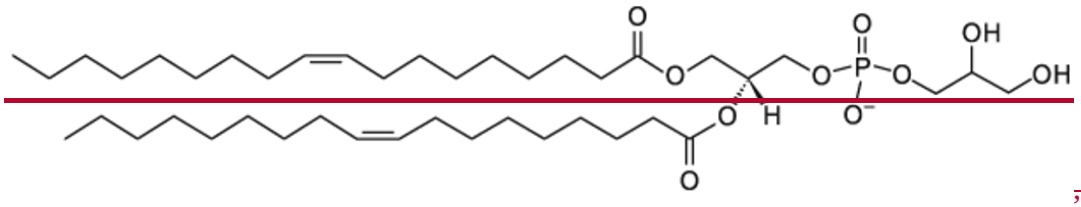


, or a salt thereof.

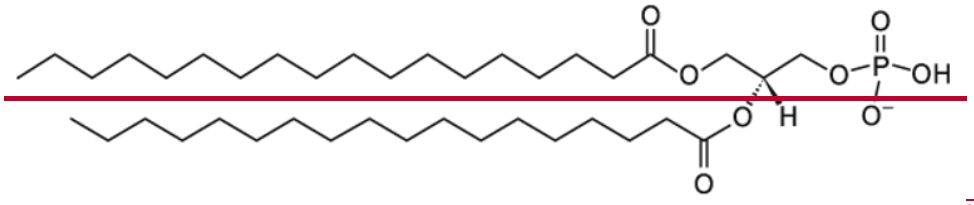
27. The composition of any one of claims 21 to 26, wherein at least one phospholipid of formula (PL-3A) is



;

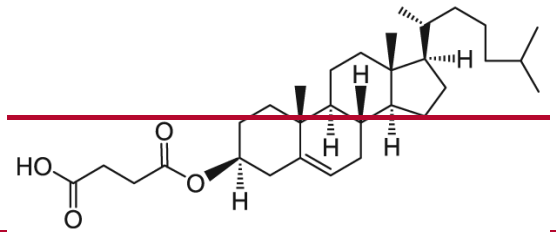


, or



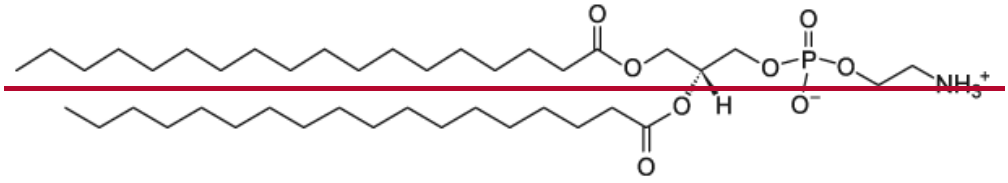
, or a salt thereof.

28. The composition of any one of claims 21 to 27, wherein the at least one cholesterol ester of formula (CE) is



or a salt thereof.

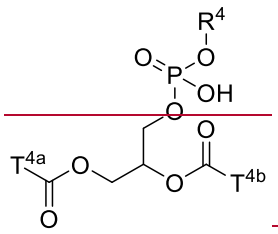
29. The composition of any one of claims 21 to 28, wherein the at least one phospholipid conjugated to PEG is



or a salt thereof.

30. A composition comprising:

a liposome comprising a phospholipid of formula (PL-4):



(PL-4),

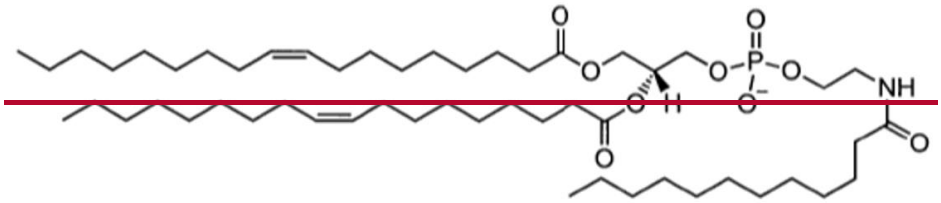
or a salt thereof, wherein:

at least one of T^{1a} and T^{1b} is an unsaturated carbon chain comprising a C_{10-28} alkenyl or a C_{10-28} alkynyl; and

R^4 is an aliphatic chain comprising an amide moiety; and

at least one endogenous phosphorylated carbohydrate encapsulated in the liposome.

31. The composition of claim 30, wherein formula (PL-4) is



or a salt thereof.

32. The composition of any one of claims 1 to 31, wherein the at least one endogenous phosphorylated carbohydrate is a phosphorylated monosaccharide, a phosphorylated disaccharide, a phosphorylated oligosaccharide, a phosphorylated polysaccharide, a phosphorylated mannose, a phosphorylated mannofuranose, a phosphorylated mannopyranos, or a nucleotide sugar, or any combination thereof.

33. The composition of claim 32, wherein the phosphorylated mannose is mannose-1-phosphate.

34. A pharmaceutical composition comprising the composition of any one of the preceding claims, and a pharmaceutically acceptable carrier.

35. A composition of any one of the preceding claims for use in a method for delivering a carbohydrate to a human in need thereof.

36. A composition of any one of claims 1 to 34 for use in a method for delivering a carbohydrate to a cell interior of a subject in need thereof, wherein the composition is to be administered to the subject, and wherein at least a portion of the administered composition traverses the cell plasma membrane to deliver the carbohydrate to the cell interior.

37. A composition of any one of claims 1 to 34 for use in treating a congenital disorder of glycosylation (CDG) in a human in need thereof.

~~38. Use of a composition of any one of claims 1 to 34 in the manufacture of a medicament for treating a congenital disorder of glycosylation (CDG) in a human in need thereof.~~

~~39. The composition for use or use of claim 37 or 38, wherein the congenital disorder of glycosylation (CDG) is CDG-Ia, CDG-Ic, CDG-Ii, CDG-Ik, CDG-Io, CDG-Ip, or DPM2-CDG.~~

~~40. The composition for use or use of claims 37 to 39, wherein the congenital disorder of glycosylation (CDG) is a CDG-Ia disorder.~~

~~41. The composition for use or use of any one of claims 37 to 40, wherein the composition is to be administered to the human, and wherein the administration of the composition induces a 0.05-fold to at least a 3-fold increase in cellular production of higher-order lipid-linked oligosaccharides in the human, as compared to cellular production of higher-order lipid-linked oligosaccharides in the human in the absence of administering the composition to the human.~~

~~42. A kit comprising:~~

~~a composition of any one of claims 1 to 34;~~

~~a container; and~~

~~a label or package insert on or associated with the container.~~

5. The pharmaceutical composition of any one of claims 1-4, wherein the phospholipid conjugated to the PEG is 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE)

6. The pharmaceutical composition of any one of claims 1-4, wherein component (iii) of the liposome is DSPE-PEG_{2000}.

7. The pharmaceutical composition of any one of claims 1-6, wherein the liposome does not comprise cholesterol or a cholesterol ester.

8. The pharmaceutical composition of any one of claims 1-7, wherein the DOPE is present in the composition from about 15 to about 30 molar percent.

9. The pharmaceutical composition of claim 8, wherein the one or more phospholipid having a polar head group is DOPC, wherein the DOPC is present in the composition from about 35 to about 75 molar percent.

10. The pharmaceutical composition of claim 8, wherein the one or more phospholipid having a polar head group is DOPC, wherein the DOPC is present in the composition from about 60 to about 65 molar percent.

11. The pharmaceutical composition of any one of claims 1-7, wherein the DOPE is present in the composition from about 25 to about 30 molar percent.

12. The pharmaceutical composition of claim 11, wherein the one or more phospholipid having a polar head group is DOPC, wherein the DOPC is present in the composition from about 35 to about 75 molar percent.

13. The pharmaceutical composition of claim 11, wherein the one or more phospholipid having a polar head group is DOPC, wherein the DOPC is present in the composition from about 60 to about 65 molar percent.

14. The pharmaceutical composition of any one of claims 1-7, wherein the DOPE is present in the composition from about 30 to about 60 molar percent.

15. The pharmaceutical composition of claim 14, wherein the one or more phospholipid having a polar head group is DOPC, wherein the DOPC is present in the composition from about 35 to about 75 molar percent.

16. The pharmaceutical composition of claim 14, wherein the one or more phospholipid having a polar head group is DOPC, wherein the DOPC is present in the composition from about 60 to about 65 molar percent.

17. The pharmaceutical composition of any one of claims 1-16, wherein the concentration of mannose-1-phosphate in the liposome is from about 2.5 mM to about 5 mM.

18. The pharmaceutical composition of any one of claims 1-16, wherein the concentration of mannose-1-phosphate in the liposome is from about 5 mM to about 10 mM.

19. The pharmaceutical composition of any one of claims 1-18, wherein the average particle size of the liposomes in the composition is about 0.1 microns.

20. A liposomal pharmaceutical composition comprising mannose-1-phosphate or a salt thereof, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), and DSPE-PEG_{2000}, wherein the molar ratio of DOPE, DOPC and DSPE-PEG_{2000} is 30:67:3.

21. Use of a pharmaceutical composition of any one of claims 1 to 20, in the manufacture of a medicament for treating a congenital disorder of glycosylation (CDG) in a human in need thereof.

22. The use of claim 21, wherein the CDG is CDG-Ia, CDG-Ie, CDG-Ii, CDG-Ik, CDG-Io, GDG-Ip, or DPM2-CDG.

23. A pharmaceutical composition of any one of claims 1 to 20, for use in therapy.