CLAIMS

What is claimed is:

1. Use of a hepatic delivery vehicle (HDV) composition comprising insulin and a lipid-based nanoparticle in the preparation of a medicament for ~~the~~ reducing or eliminating occurrence of significant iatrogenic hyperinsulinemia ~~treatment of diabetes mellitus~~ in a subject having diabetes mellitus, wherein the subject has A1c values equal to or greater than 8.5% and has been administered a free insulin formulated in the absence of a HDV, wherein the medicament is to be administered to the subject;

wherein the insulin is dispersed within the lipid-based nanoparticle;

wherein the amount of the insulin in the HDV composition is equal to or lower than the amount of free insulin that would be administered in the absence of a HDV to treat the diabetes mellitus in the subject;

wherein the administration results in ~~approximately~~ equivalent or better blood glucose control as afforded by the amount of free insulin that would be administered in the absence of a HDV to treat the diabetes mellitus in subject and wherein the administration does not cause significant hypoglycemia in the subject;

wherein the lipid-based nanoparticle is enclosed by a bipolar lipid membrane comprising cholesterol, dicetyl phosphate, an amphipathic lipid, and a hepatocyte receptor binding molecule;

wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycerol-[3-phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl), 1,2-dimyristoyl-sn-glycero-3-phosphate, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphate, 1,2-dipalmitoyl-sn-glycero-3-phosphate, and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine;

wherein the at least one hepatocyte receptor binding molecule extends outward from the lipid-based nanoparticle; and

wherein the size of the lipid-based nanoparticle ranges from ~~about~~ 10 nm to ~~about~~ 150 nm.

2. The use of claim 1, wherein the amount of the insulin in the HDV composition causes no significant iatrogenic hyperinsulinemia in the subject.

~~3. The use of claim 2, wherein the amount of free insulin that would be administered to treat the diabetes mellitus in subject causes significant iatrogenic hyperinsulinemia in the subject.~~

~~4.~~3. Use of a hepatic delivery vehicle (HDV) composition comprising insulin and a lipid-based nanoparticle in the preparation of a medicament for treating or ameliorating diabetes mellitus in ~~increasing the volume of distribution of an insulin administered to~~ a subject, wherein the subject has HbA1c values equal to or greater than 8.5% and has been administered a free insulin formulated in the absence of a HDV, wherein the medicament is to be administered to the subject;

wherein the insulin is dispersed within the lipid-based nanoparticle;

wherein the amount of the insulin in the HDV composition is equal to or lower than the amount of free insulin administered in the absence of a HDV to treat the diabetes mellitus in the subject;

wherein the administration results in equivalent or better blood glucose control as afforded by the amount of free insulin administered in the absence of a HDV to treat the diabetes mellitus in subject and wherein the administration does not cause significant hypoglycemia in the subject;

wherein the lipid-based nanoparticle is enclosed by a bipolar lipid membrane comprising cholesterol, dicetyl phosphate, an amphipathic lipid, and a hepatocyte receptor binding molecule;

wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycerol-[3-phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl), 1,2-dimyristoyl-sn-glycero-3-phosphate, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphate, 1,2-dipalmitoyl-sn-glycero-3-phosphate, and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine;

wherein the at least one hepatocyte receptor binding molecule extends outward from the lipid-based nanoparticle; and

wherein the size of the lipid-based nanoparticle ranges from ~~about~~ 10 nm to ~~about~~ 150 nm.

~~5.~~4. Use of a hepatic delivery vehicle (HDV) composition comprising insulin and a lipid-based nanoparticle in the preparation of a medicament for reducing blood glucose levels in a subject suffering from diabetes mellitus, wherein the subject has HbA1c values between 7% and 8% and has been administered a free insulin formulated in the absence of a HDV~~increasing or improving glycemic control in a subject being administered an insulin~~, wherein the medicament is to be administered to the subject;

wherein the insulin is dispersed within the lipid-based nanoparticle;

wherein the amount of the insulin in the HDV composition is equal to the amount of free insulin administered in the absence of a HDV to treat the diabetes mellitus in the subject;

wherein the lipid-based nanoparticle is enclosed by a bipolar lipid membrane comprising cholesterol, dicetyl phosphate, an amphipathic lipid, and a hepatocyte receptor binding molecule;

wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycerol-[3-phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl), 1,2-dimyristoyl-sn-glycero-3-phosphate, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphate, 1,2-dipalmitoyl-sn-glycero-3-phosphate, and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine;

wherein the at least one hepatocyte receptor binding molecule extends outward from the lipid-based nanoparticle; and

wherein the size of the lipid-based nanoparticle ranges from ~~about~~ 10 nm to ~~about~~ 150 nm.

~~6. Use of a composition comprising a lipid-based nanoparticle in the preparation of a medicament for increasing or improving basal glucose control in a subject, wherein the medicament is to be administered to the subject; wherein the insulin is dispersed within the nanoparticle;~~

~~wherein the nanoparticle is enclosed by a bipolar lipid membrane comprising cholesterol, dicetyl phosphate, an amphipathic lipid, and a hepatocyte receptor binding molecule;~~

~~wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycerol-[3-~~

~~phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl), 1,2-dimyristoyl-sn-glycero-3-phosphate, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphate, 1,2-dipalmitoyl-sn-glycero-3-phosphate, and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine;~~

~~wherein the at least one hepatocyte receptor binding molecule extends outward from the nanoparticle; and~~

~~wherein the size of the nanoparticle ranges from about 10 nm to about 150 nm.~~

~~7.~~5. The use of claim ~~6~~1, wherein the insulin comprises bolus insulin.

~~8.~~6. The use of claim ~~7~~5, wherein the subject is to be further administered a basal insulin.

~~9. The use of claim 8, wherein the basal insulin is formulated in a composition comprising a lipid-based nanoparticle, wherein the basal insulin is dispersed within the nanoparticle;~~

~~wherein the nanoparticle is enclosed by a bipolar lipid membrane comprising cholesterol, dicetyl phosphate, an amphipathic lipid, and a hepatocyte receptor binding molecule;~~

~~wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycerol-[3-phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl), 1,2-dimyristoyl-sn-glycero-3-phosphate, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphate, 1,2-dipalmitoyl-sn-glycero-3-phosphate, and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine;~~

~~wherein the at least one hepatocyte receptor binding molecule extends outward from the nanoparticle; and~~

~~wherein the size of the nanoparticle ranges from about 10 nm to about 150 nm.~~

~~10.~~7. Use of a hepatic delivery vehicle (HDV) composition comprising insulin and a lipid-based nanoparticle in the preparation of a medicament for lowering blood glucose levels ~~increasing or improving basal glucose control~~ in a subject suffering from diabetes mellitus~~being administered an insulin~~, wherein the subject has been administered in a

continuous manner a free insulin formulated in the absence of a HDV, wherein the medicament is to be administered in a continuous manner to the subject; wherein the insulin is dispersed within the lipid-based nanoparticle;

wherein the amount of the insulin in the HDV composition is equal to or lower than the amount of free insulin administered in a continuous manner in the absence of a HDV to treat the diabetes mellitus in the subject;

wherein the administration results in approximately equivalent or better blood glucose control as afforded by the amount of free insulin administered in a continuous manner in the absence of a HDV to treat the diabetes mellitus in subject;

wherein the lipid-based nanoparticle is enclosed by a bipolar lipid membrane comprising cholesterol, dicetyl phosphate, an amphipathic lipid, and a hepatocyte receptor binding molecule;

wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycerol-[3-phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl), 1,2-dimyristoyl-sn-glycero-3-phosphate, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphate, 1,2-dipalmitoyl-sn-glycero-3-phosphate, and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine;

wherein the at least one hepatocyte receptor binding molecule extends outward from the lipid-based nanoparticle; and

wherein the size of the lipid-based nanoparticle ranges from ~~about~~ 10 nm to ~~about~~ 150 nm.

~~11.~~8. The use of claim ~~10~~7, wherein the medicament is to be administered in a continuous~~ly~~ manner to the subject over a period of at least 24 hours.

~~12.~~9. The use of any of claims ~~10-11~~7-8, wherein the medicament is to be administered in a continuous~~ly~~ manner to the subject using a pump.

~~13. The use of any of claims 1-12, wherein the subject has a hemoglobin A1c level equal to or greater than 8.5%.~~

~~14. The use of any of claims 1-12, wherein the subject has a hemoglobin A1c level lower~~

~~than 8.5%, optionally wherein the subject has a hemoglobin A1C level equal to or greater than 6.5%.~~

~~15.~~10. The use of any of claims 1-~~9~~14, wherein the membrane further comprises at least one agent selected from the group consisting of a stabilizer and stearoyl lysophosphatidylcholine.

~~16.~~11. The use of claim 10~~15~~, wherein the stabilizer is selected from the group consisting of m-cresol, benzyl alcohol, methyl 4-hydroxybenzoate, thiomersal, and butylated hydroxytoluene (2,6-di-*tert*-butyl-4-methylphenol).

~~17.~~12. The use of any of claims ~~15-16~~10-11, wherein the stabilizer ranges from ~~about~~ 10% to ~~about~~ 25 % (w/w) in the membrane.

~~18.~~13. The use of claim 10~~15~~, wherein the stearoyl lysophosphatidylcholine ranges from ~~about~~ 5% to ~~about~~ 30% (w/w) in the membrane.

~~19.~~14. The use of any of claims 1-~~9~~14, wherein the insulin is covalently bound to the nanoparticle.

~~20.~~15. The use of any of claims 1-~~9~~14, wherein the insulin is not covalently bound to the nanoparticle.

~~21.~~16. The use of any of claims 1-~~9~~14, wherein the insulin is suspended in an aqueous solution comprising a free dissolved insulin that is not dispersed within the nanoparticle.

~~22.~~17. The use of claim 16~~21~~, wherein the nanoparticle-dispersed insulin and the free dissolved insulin are independently selected from the group consisting of insulin lispro, insulin aspart, regular insulin, insulin glargine, insulin zinc, extended human insulin zinc suspension, isophane insulin, human buffered regular insulin, insulin glulisine, recombinant human regular insulin, recombinant human insulin isophane, and any combinations thereof.

~~23.~~18. The use of any of claims 1-~~9~~14, wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-

glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, and 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl).

~~24.~~19. The use of any of claims 1-~~9~~14, wherein the hepatocyte receptor binding molecule comprises biotin.

~~25.~~20. The use of claim 19~~24~~, wherein the biotin-containing hepatocyte receptor binding molecule comprises at least one selected from the group consisting of N-hydroxysuccinimide (NHS) biotin; sulfo-NHS-biotin; N-hydroxysuccinimide long chain biotin; sulfo-N-hydroxysuccinimide long chain biotin; D-biotin; biocytin; sulfo-N-hydroxysuccinimide-S-S-biotin; biotin-BMCC; biotin-HPDP; iodoacetyl-LC-biotin; biotin-hydrazide; biotin-LC-hydrazide; biocytin hydrazide; biotin cadaverine; carboxybiotin; photobiotin; *ρ*-aminobenzoyl biocytin trifluoroacetate; *ρ*-diazobenzoyl biocytin; biotin DHPE (2,3-diacetoxypropyl 2-(5-((3aS,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)ethyl phosphate); biotin-X-DHPE (2,3-diacetoxypropyl 2-(6-(5-((3aS,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)hexanamido) ethyl phosphate); 12-((biotinyl)amino)dodecanoic acid; 12-((biotinyl)amino)dodecanoic acid succinimidyl ester; S-biotinyl homocysteine; biocytin-X; biocytin x-hydrazide; biotinethylenediamine; biotin-XL; biotin-X-ethylenediamine; biotin-XX hydrazide; biotin-XX-SE; biotin-XX, SSE; biotin-X-cadaverine; α-(t-BOC)biocytin; N-(biotinyl)-N'-(iodoacetyl) ethylenediamine; DNP-X-biocytin-X-SE; biotin-X-hydrazide; norbiotinamine hydrochloride; 3-(N-maleimidylpropionyl)biocytin; ARP; biotin-l-sulfoxide; biotin methyl ester; biotin-maleimide; biotin-poly(ethyleneglycol) amine; (+) biotin 4-amidobenzoic acid sodium salt; Biotin 2-N-acetylamino-2-deoxy-β-D-glucopyranoside; Biotin-α-D-N-acetylneuraminide; Biotin-α-L-fucoside; Biotin lacto-N-bioside; Biotin–Lewis-A trisaccharide; Biotin–Lewis-Y tetrasaccharide; Biotin-α-D-mannopyranoside; and biotin 6-O-phospho-α-D-mannopyranoside.

~~26.~~21. The use of claim 19~~24~~, wherein the biotin-containing hepatocyte receptor binding molecule comprises at least one selected from the group consisting of biotin DHPE and biotin-X-DHPE.

~~27.~~22. The use of any of claims 1-~~9~~14, wherein the composition further comprises cellulose acetate phthalate, which is at least partially bound to the therapeutic agent dispersed within

the nanoparticle.

~~28.~~23. The use of any of claims 1-~~9~~14, wherein the composition further comprises at least one charged organic molecule bound to the therapeutic agent dispersed within the nanoparticle, wherein the charged organic molecule is at least one selected from the group consisting of protamines, polylysine, poly (arg-pro-thr)$_n$ in a mole ratio of 1:1:1, poly (DL-Ala-poly-L-lys)$_n$ in a mole ratio of 6:1, histones, sugar polymers comprising a primary amino group, polynucleotides with primary amino groups, proteins comprising amino acid residues with carboxyl (COO^-) or sulfhydral (S^-) functional groups, and acidic polymers.

~~29.~~24. The use of any of claims 1-~~9~~14, wherein the cholesterol ranges from ~~about~~ 5% to ~~about~~ 25% (w/w) in the membrane.

~~30.~~25. The use of any of claims 1-~~9~~14, wherein the dicetyl phosphate ranges from ~~about~~ 10% to ~~about~~ 25% (w/w) in the membrane.

~~31.~~26. The use of any of claims 1-~~9~~14, wherein the DSPC ranges from ~~about~~ 40% to ~~about~~ 75% (w/w) in the membrane.

~~32.~~27. The use of any of claims 1-~~9~~14, wherein the hepatocyte receptor binding molecule ranges from ~~about~~ 0.5% to ~~about~~ 10% (w/w) in the membrane.

~~33.~~28. The use of claim 10~~15~~, wherein the amount of the stearoyl lysophosphatidylcholine in the membrane is ~~about~~ 5%-30% (w/w) of the amount of DSPC in the membrane.

~~34.~~29. The use of claim 10~~15~~, wherein the membrane comprises one of the following:

(a) cholesterol, dicetyl phosphate, DSPC, stearoyl lysophosphatidylcholine, m-cresol, and at least one selected from the group consisting of biotin DHPE and biotin-X-DHPE;

(b) cholesterol, dicetyl phosphate, DSPC, m-cresol, and at least one selected from the group consisting of biotin DHPE and biotin-X-DHPE; and

(c) cholesterol, dicetyl phosphate, DSPC, stearoyl lysophosphatidylcholine, and at least one selected from the group consisting of biotin DHPE and biotin-X-DHPE.

~~35.~~30. The use of claim 10~~15~~, wherein the membrane comprises cholesterol, dicetyl

phosphate, DSPC, stearoyl lysophosphatidylcholine, m-cresol, and biotin DHPE in a % (w/w) ratio selected from the group consisting of:

(a) ~~about~~ 9.4 : 18.1 : 56.8 : 14.1 : 0.0 : 1.5;

(b) ~~about~~ 7.7 : 15.0 : 58.6 : 0.0 : 17.4 : 1.3; and

(c) ~~about~~ 8.4 : 16.2 : 47.5 : 7.6 : 19.0 : 1.3;

~~36. The use of any of claims 4-14, wherein the subject has diabetes mellitus.~~

~~37.~~31. The use of any of claims 1-9~~14~~, wherein the subject has Type 1 diabetes or Type 2 diabetes.