CLAIMS

1. A spherical high-density lipoprotein nanoparticle (HDL-NP) comprising: a core and a shell surrounding and attached to the core, wherein the core comprises a lipid conjugated organic core scaffold, and wherein the spherical HDL-NP is characterized by at least one of the following:

(a) a surface zeta potential of -16 to -30 millivolts (mV);

(b) the organic core scaffold comprising a hydrophobic small molecule-phospholipid conjugate (PL_4); and

(c) the organic core scaffold comprising an amphiphilic DNA-linked small molecule-phospholipid conjugate (DNA- PL_4).

2. The spherical HDL-NP of claim 1, wherein the shell is a lipid shell.

3. The spherical HDL-NP of claim 1 or claim 2, wherein the shell is a lipid bilayer or monolayer.

4. The spherical HDL-NP of any one of claims 1-3, wherein the spherical HDL-NP has a surface zeta potential of about -20 millivolts (mV).

5. The spherical HDL-NP of any one of claims 1-4, wherein the organic core scaffold comprises a hydrophobic small molecule-phospholipid conjugate (PL_4).

6. The spherical HDL-NP of claim 5, wherein the PL_4 comprises a headgroup-modified phospholipid.

7. The spherical HDL-NP of claim 6, wherein the headgroup-modified phospholipid comprises a ring-strained alkyne, 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethan-olamine-N-dibenzocyclooctyl.

8. The spherical HDL-NP of claim 6 or claim 7, wherein the phospholipid is coupled to the small molecule with a plurality of terminal functional groups.

9. The spherical HDL-NP of claim 8, wherein the small molecule is *tetrakis*(4-azidophenyl)methane.

10. The spherical HDL-NP of claim 8 or claim 9, wherein the plurality of functional groups is 2-6 functional groups.

11. The spherical HDL-NP of claim 8 or claim 9, wherein the plurality of functional groups is 4 functional groups.

12. The spherical HDL-NP of any one of claims 8-11, wherein the functional groups are terminal azides (SM-Az).

13. The spherical HDL-NP of any one of claims 1-4, wherein the organic core scaffold comprises an amphiphilic DNA-linked small molecule-phospholipid conjugate (DNA-PL_4).

14. The spherical HDL-NP of claim 13, wherein the DNA is a double stranded oligonucleotide of 5-17 nucleotides in length.

15. The spherical HDL-NP of claim 13, wherein the DNA is a double stranded oligonucleotide of 8-15 nucleotides in length.

16. The spherical HDL-NP of claim 13, wherein the DNA is a double stranded oligonucleotide of 9 nucleotides in length.

17. The spherical HDL-NP of any one of claims 13-16, wherein a first single strand of the double stranded DNA is linked to a phospholipid and forms a ssDNA-phospholipid conjugate (ssDNA-PL).

18. The spherical HDL-NP of claim 17, wherein a second strand of the double stranded DNA, complementary to the first strand of the double stranded DNA is linked to a small molecule.

19. The spherical HDL-NP of claim 18, wherein the small molecule is a tetrahedral small molecule and the small molecule linked to the DNA forms a tetrahedral small molecule-DNA hybrid ($SMDH_4$).

20. The spherical HDL-NP of claim 19, wherein the $SMDH_4$ is linked to the ssDNA-PL through hydrogen bonding between the complementary single strands of DNA.

21. The spherical HDL-NP of any one of claims 1-20, wherein the spherical HDL-NP has a diameter of about 5-30 nm, 5-20 nm, 5-15 nm, 5-10 nm, 8-13 nm, 8-12 nm, or 10 nm.

22. The spherical HDL-NP of any one of claims 1-21, wherein the spherical HDL-NP has a zeta potential closer to human HDL than a synthetic HDL nanoparticle with a gold core.

23. The spherical HDL-NP of claim 22, wherein the zeta potential is -16 to -26 mV.

24. The spherical HDL-NP of any one of claims 1-23, wherein the spherical HDL-NP has a more efficient cholesterol transport capacity than that of apolipoprotein or a synthetic HDL nanoparticle with a gold core.

25. The spherical HDL-NP of any one of claims 1-24, further comprising apolipoprotein.

26. The spherical HDL-NP of any one of claims 1-25, further comprising apolipoprotein A-I (ApoA1).

27. The spherical HDL-NP of any one of claims 1-26, wherein the HDL-NP has a hydrodynamic diameter of greater than 8.7 nm.

28. The spherical HDL-NP of any one of claims 1-27, wherein the HDL-NP has a hydrodynamic diameter of 8.7 nm-~~17-7~~17.7nm.

29. The spherical HDL-NP of any one of claims 1-28, wherein the HDL-NP has a hydrodynamic diameter of 10 nm-15nm.

30. The spherical HDL-NP of any one of claims 1-29, wherein the HDL-NP has a hydrodynamic diameter of 12 nm-14nm.

31. The spherical HDL-NP of any one of claims 1-30, further comprising a therapeutic agent linked to the HDL-NP.

32. The spherical HDL-NP of claim 31, wherein the therapeutic agent is a therapeutic nucleic acid.

33. The spherical HDL-NP of claim 31, wherein the therapeutic agent is an anti-cancer agent.

34. The spherical HDL-NP of claim 33, wherein the anti-cancer agent is a chemotherapeutic agent.

35. The spherical HDL-NP of claim 31, wherein the therapeutic agent is an anti-inflammatory agent.

36. A pharmaceutical composition comprising the spherical HDL-NP of any one of claims 1-35.

37. Use of
a spherical high-density lipoprotein nanoparticle (HDL-NP) according to any one of claims 1-35 ~~comprising: a core and a shell surrounding and attached to the core,~~ in the manufacture of a medicament for the treatment of cancer in a mammalian subject, ~~wherein the core comprises a lipid conjugated organic core scaffold~~ in an effective amount to treat the cancer.

38. Use of
a spherical high-density lipoprotein nanoparticle (HDL-NP) according to any one of claims 1-35 ~~comprising: a core and a shell surrounding and attached to the core,~~ in the manufacture of a medicament for the treatment of an inflammatory disorder in a

mammalian subject ~~wherein the core comprises a lipid conjugated organic core scaffold~~ in an effective amount to treat the inflammatory disorder.

~~39. The use of claim 37 or claim 38, wherein the spherical HDL-NP is a spherical HDL-NP of any one of claims 1-35.~~

~~40. The use of any one of claims 37-39, wherein the subject is a mammal.~~

~~41~~39. The use of claim ~~40~~ 37 or 38, wherein the subject is a human.

~~42~~40. ~~Use of an effective amount of a composition comprising the spherical HDL-NP of any one of claims 1-35 in the manufacture of a medicament~~ The use according to claim 38 for reducing pro-inflammatory NF-kB activity.

~~43~~41. A method for making a spherical high-density lipoprotein nanoparticle (HDL-NP) comprising: preparing a ssDNA-phospholipid conjugate (ssDNA-PL), preparing a tetrahedral small molecule-DNA hybrid ($SMDH_4$), wherein the ssDNA-PL and $SMDH_4$ have complementary DNA sequences, incubating the ssDNA-PL and $SMDH_4$ such that the complementary DNA sequences bases pair with one another to form a DNA-PL core, and adding to the DNA-PL core phospholipid liposomes and apolipoprotein to produce the spherical HDL-NP.

~~44~~42. The method of claim ~~43~~41, wherein the ssDNA-PL comprises an oligonucleotide of at least 9 nucleotides.

~~45~~43. The method of claim ~~44~~42, wherein the oligonucleotide is 9 nucleotides in length.

~~46~~44. The method of claim ~~45~~43, wherein the oligonucleotide comprises SEQ ID NO: 1.

~~47~~45. The method of claim ~~43~~41, wherein the $SMDH_4$ comprises an oligonucleotide of at least 9 nucleotides.

~~48~~46. The method of claim ~~47~~45, wherein the oligonucleotide is 9 nucleotides in length.

~~49~~47. The method of claim ~~48~~46, wherein the oligonucleotide comprises SEQ ID NO: 3.

~~50~~48. The method of any one of claims ~~43~~41-~~49~~47, wherein the apolipoprotein is apolipoprotein A-I.

~~51~~49. An organic core scaffold comprising: 1,2-dipalmitoyl-sn-glycero-3-phosphoethanol- amine-N-dibenzocyclooctyl (DBCO PE) linked to a tetrahedral small molecule core (tetrakis(4-azidophenyl)methane) with four terminal azides.

~~52~~50. The spherical HDL-NP of any one of claims 1-35 for use as a medicament.