examples, the endosomolytic agent includes the first targeting ligand. According to some examples, one of the lipid nanoparticle and endosomolytic agent includes the first targeting ligand, and the other of the lipid nanoparticle and endosomolytic agent includes a second targeting ligand. According to some examples, the first and the second targeting ligand recognize and bind to same cell surface molecule. According to some examples, the first and the second targeting ligand are the same or wherein the first and the second targeting ligand are different. According to some examples, the first and the second targeting ligand recognize and bind to same cell surface molecule. According to some examples, the ligand binds to a cell surface molecule selected from the group consisting of a transferrin receptor type 1, transferrin receptor type 2, the EGF receptor, HER2/Neu, a VEGF receptor, a PDGF receptor, an integrin, an NGF receptor, CD2, CD3, CD4, CD8, CD19, CD20, CD22, CD33, CD43, CD38, CD56, CD69, the asialoglycoprotein receptor (ASGPR), GalNAc receptor, prostate-specific membrane antigen (PSMA), a folate receptor, and a sigma receptor. According to some examples, the cell surface molecule is asialoglycoprotein receptor (ASGPR) or GalNAc receptor. According to some examples, the targeting ligand is a monovalent or multivalent D-galactose or N-acetyl-D-galactose. According to some examples, the composition further comprises an additional compound. According to some examples, said additional compound is encompassed in a lipid nanoparticle, and wherein said lipid nanoparticle is different from the nanoparticle comprising the ceDNA. According to some examples, said additional compound is encompassed in the lipid nanoparticle comprising the ceDNA. According to some examples, said additional compound and the endosomolytic agent are comprised in a nanoparticle. According to some examples, said additional compound is a therapeutic agent. According to some examples, said addition compound is an immune modulating agent. According to some examples, the immune modulating agent is an immunosuppressant. According to some examples, the immune modulating agent is selected form the group consisting of like cGAS inhibitors, TLR9 antagonists, Caspase-1 inhibitors, and any combination thereof. According to some examples, said additional compound is a second capsid free, non- viral vector, wherein the first and second capsid free, non-viral vectors are different. According to some examples, the capsid free, non-viral vector is a close-ended DNA (ceDNA) vector comprising at least one heterologous nucleotide sequence between flanking inverted terminal repeats (ITRs), wherein at least one heterologous nucleotide sequence encodes at least one transgene or therapeutic protein of interest. In another aspect, provided herein is a use of the composition the disclosure in the manufacture of a medicament for expressing a desired transgene or therapeutic protein in a cell *in vivo* comprising contacting the cell with the composition of the disclosure. In another aspect, provided herein is a cell containing a composition of the disclosure. According to some examples, the least one heterologous nucleotide sequence that encodes at least one transgene or therapeutic protein is a nucleic acid RNAi agent. In another aspect, the present disclosure provides an *in vitro* method of expressing a desired transgene or therapeutic protein in a cell, comprising contacting the cell with the composition as disclosed herein.

[0027] Other aspects and examples of the disclosure as described herein.

CLAIMS

What is claimed is:

1. A composition comprising:
    a. a capsid free, non-viral vector encapsulated in a lipid nanoparticle (LNP), wherein the LNP lacks fusogenic activity; and
    b. an endosomolytic agent.
2. The composition of claim 1, wherein the capsid free, non-viral vector when digested with a restriction enzyme having a single recognition site on the DNA vector has the presence of characteristic bands of linear and continuous DNA as compared to linear and non-continuous DNA when analyzed on a non-denaturing gel.
3. The composition of claim 1, wherein the endosomolytic agent targets a target cell.
4. The composition of claim 1, wherein the endosomolytic agent is:

(a) a membrane-destabilizing polymer;

(b) a copolymer, a peptide, a membrane-destabilizing toxin ~~or a derivative thereof~~, or a viral fusogenic peptide ~~or derivative thereof~~;

(c) a pH-sensitive polymer;

(d) polyanionic peptide, polycatioinic peptide, amphipathic peptide, hydrophobic peptide or a peptidomimetic; or

(e) a peptide selected from the group consisting of:

AALEALAEALEALAEALEALAEAAAAGGC (SEQ ID NO: 530);

AALAEALAEALAEALAEALAEALAAAAGGC (SEQ ID NO: 531);

ALEALAEALEALAEA (SEQ ID NO: 532);

GLFEAIEGFIENGWEGMIWDYG (SEQ ID NO: 533);

GLFGAIAGFIENGWEGMIDGWYG (SEQ ID NO: 534);

GLFEAIEGFIENGWEGMIDGWYGC (SEQ ID NO: 535);

GLFEAIEGFIENGWEGMIDGWYGC (SEQ ID NO: 536);

GLFEAIEGFIENGWEGMIDGGC (SEQ ID NO: 537);

GLFEAIEGFIENGWEGMIDGGC (SEQ ID NO: 538);

CGLFGEIEELIEEGLENLIDWGNG (SEQ ID NO: 539);

GLFGALAEALAEALAEHLAEALAEALEALAAGGSC (SEQ ID NO: 540);

GLFEAIEGFIENGWEGLAEALAEALEALAAGGSC (SEQ ID NO: 541);

GLFEAIEGFIENGWEGnIDGK (n = norleucine) (SEQ ID NO: 542);

GLFEAIEGFIENGWEGnIDG (n = norleucine) (SEQ ID NO: 543);

GLFEALLELLESLWELLLEA (SEQ ID NO: 544);

GLFKALLKLLKSLWKLLLKA (SEQ ID NO: 545);

GLFRALLRLLRSLWRLLLRA (SEQ ID NO: 546);

WEAKLAKALAKALAKHLAKALAKALKACEA (SEQ ID NO: 547);

GLFFEAIAEFIEGGWEGLIEGC (SEQ ID NO: 548);

GIGAVLKVLTTGLPALISWIKRKRQQ (SEQ ID NO: 549);

H5WYG (SEQ ID NO: 550);

CHK_6HC (SEQ ID NO: 551);

RQIKIWFQNRRMKWKK (SEQ ID NO: 552);

GRKKRRQRRRPPQC (SEQ ID NO: 553);

GALFLGWLGAAGSTM (SEQ ID NO: 554);

GAWSQPKKKRKV (SEQ ID NO: 555);

LLIILRRRIRKQAHAHSK (SEQ ID NO: 556);

GWTLNSAGYLLKINLKALAALAKKIL (SEQ ID NO: 557);

KLALKLALKALKAALKLA (SEQ ID NO: 558);

RRRRRRRRR (SEQ ID NO: 559);

KFFKFFKFFK (SEQ ID NO: 560);

LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES (SEQ ID NO: 561);

SWLSKTAKKLENSAKKRISEGIAIAIQGGPR (SEQ ID NO: 562);

ACYCRIPACIAGERRYGTCIYQGRLWAFCC (SEQ ID NO: 563);

DHYNCVSSGGQCLYSACPIFTKIQGTCYRGKAKCCK ((SEQ ID NO: 564);

RKCRIVVIRVCRRRRPRPPYLPRPRPPPFFPPRLPPRIPPGFPPRFPPRFPGKR (SEQ ID NO: 565);

ILPWKWPWWPWRR (566);

WEAALAEALAEALAEHLAEALAEALEALAA (SEQ ID NO: 567);

CAEALAEALAEALAEALA (SEQ ID NO: 568);

GIGAVLKVLTTGLPALISWIKRKRQQ (SEQ ID NO: 569);

CGIGAVLKVLTTGLPALISWIKRKRQQ (SEQ ID NO: 570);

FIIDIIAFLLMGGFIVYVKNL (SEQ ID NO: 571);

CAAFIIDHAFLLMGGFIVYVKNL (SEQ ID NO: 572);

CARGWEVLKYWWNLLQY (SEQ ID NO: 573);

MVKSKIGSWILVLFVAMWSDVGLCKKRPKP (SEQ ID NO: 574);

KLALKLALKALKAALKLA (SEQ ID NO: 575);

YARAAARQARA (SEQ ID NO: 576);

GDCLPHLKLCKENKDCCSKKCKRRGTNIE (SEQ ID NO: 577);

RRLSYSRRRF (SEQ ID NO: 578);

RGGRLSYSRRRFSTSTGR (SEQ ID NO: 579);

IAWVKAFIRKLRKGPLG (SEQ ID NO: 580);

YTAIAWVKAFIRKLRK (SEQ ID NO: 581);

GLWRALWRLLRSLWRLLWRA (SEQ ID NO: 582);

KWFETWFTEWPKKRK (SEQ ID NO: 583);

KETWWETWWTEWSQPKKKRKV (SEQ ID NO: 584);

AGYLLGK(eNHa)INLKALAALAKKIL (SEQ ID NO: 585);

AGYLLGKINLKALAALAKKIL (SEQ ID NO: 586);

RQIKIVVFQNRRMKWKK (SEQ ID NO: 587);

WEAKLAKALAKALAKHLAKALAKALKACEA (SEQ ID NO: 588);

LLIILRRRIRKQAHAHSK (SEQ ID NO: 589);

YTIVVMPENPRPGTPCDIFTNSRGKRASNG (SEQ ID NO: 590);

AAVALLPAVLLALLAK (SEQ ID NO: 591);

GWTLNSAGYLLGKINLKALAALAKKIL (SEQ ID NO: 592);

GRKKRRQRRPPQ (SEQ ID NO: 593);

KMTRAQRRAAARRNRRWTAR (SEQ ID NO: 594);

KKRKAPKKKRKFA-KFHTFPQTAIGVGAP (SEQ ID NOS: 595 and 600, respectively);

MVTVLFRRLRIRRASGPPRVRV (SEQ ID NO: 596);

LIRLWSHLIHIVVFQNRRLKWKKK (SEQ ID NO: 597);

GALFLGFLGAAGSTMGAWSQPKKKRKV (SEQ ID NO: 598); and

GALFLAFLAAALSLMGLWSQPKKKRKV (SEQ ID NO: 599).

5. The composition of claim 1 wherein the endosomolytic agent is in form of a nanoparticle.

6. The composition of claim 5, wherein the nanoparticle further comprises a cationic lipid, a non-cationic lipid, a sterol ~~or a derivative thereof~~, a conjugated lipid, or any combination thereof.

7. The composition of claim 1, wherein the lipid nanoparticle comprises the endosomolytic agent.

8. The composition of claim 1, wherein the endosomolytic agent is preferentially or specifically taken up by the target cell relative to a non-target cell.

9. The composition of claim 1, wherein the endosomolytic agent comprises a targeting ligand.

10. The composition of claim ~~1~~9, wherein the ligand binds to a cell surface molecule selected from the group consisting of a transferrin receptor type 1, a transferrin receptor type 2, the EGF receptor, HER2/Neu, a VEGF receptor, a PDGF receptor, an integrin, an NGF receptor, CD2, CD3, CD4, CD8, CD19, CD20, CD22, CD33, CD43, CD38, CD56, CD69, the asialoglycoprotein receptor (ASGPR), GalNAc receptor, prostate-specific membrane antigen (PSMA), a folate receptor, and a sigma receptor.

11. The composition of claim 9, wherein the targeting ligand is a monovalent or multivalent D-galactose or N-acetyl-D-galactose.

12. The composition of claim 1, further comprising an additional compound.

13. The composition of any of claims 1-12, wherein the capsid free, non-viral vector is a closed-ended DNA (ceDNA) vector comprising:

at least one ~~heterologous~~ nucleotide sequence between flanking inverted terminal repeats (ITRs), wherein the at least one ~~heterologous~~ nucleotide sequence encodes at least one transgene or therapeutic protein of interest.

14. The composition of claim 13, wherein the ceDNA vector comprise a promoter selected from any of those in Table 7 operatively linked to the least one ~~heterologous~~ nucleotide sequence that encodes at least one transgene or therapeutic protein;
an enhancer selected from any of those in Table 8;
a 5' UTR and/or intron sequence selected from any of those in Table 9A;
a 3' UTR selected from any of those in Table 9B; and/or
at least one poly A sequence selected from any of those in Table 10.

15. The composition of any one of claims 13 to 14, wherein the ceDNA vector comprises at least one promoter ~~operably~~ linked to the at least one ~~heterologous~~ nucleotide sequence.

16. The composition of any one of claims 13 and 14, wherein at least one flanking ITR comprises a functional terminal resolution site and a Rep binding site;
one or both of the flanking ITRs are from a virus selected from the group consisting of : a parvovirus, a dependovirus, and an adeno-associated virus (AAV); one or both of the flanking ITRs are from a virus selected from the group consisting of: a parvovirus, a dependovirus, and an adeno-associated virus (AAV);
the flanking ITRs are symmetric or asymmetric;
the flanking ITRs are symmetrical or substantially symmetrical;
one ~~or both~~ of the ITRs ~~are~~ is a wild type ITR, or wherein both of the flanking ITRs are wild-type ITRs;
the flanking ITRs are from different viral serotypes;
the flanking ITRs are from a pair of viral serotypes shown in Table 2;
one or both of the flanking ITRs comprises a sequence selected from the sequences in Table 3;
at least one of the flanking ITRs is altered from a wild-type AAV ITR sequence by a deletion, an addition, and/or a substitution that affects the overall three-dimensional conformation of the ITR;
one or both of the flanking ITRs are synthetic; and/or
one ~~or both~~ of the flanking ITRs is not a wild-type ITR, or wherein both of the flanking ITRs are not wild-type ITRs.

17. The composition of any one of claims 13, 14 and 16, wherein one or both of the flanking ITRs is modified by a deletion, an insertion, and/or a substitution in at least one of the flanking ITR regions selected from the group consisting of: an A, A', B, B', C, C', D, and D' regions; one or both of the flanking ITRs is modified by a deletion, an insertion, and/or a substitution in at least one of the flanking ITR regions selected from the group consisting of:

an A, A', B, B', C, C', D, and D' regions;

wherein the deletion, insertion, and/or substitution results in the deletion of all or part of a stem-loop structure ~~normally~~ formed by the A, A', B, B' C, or C' regions;

wherein one or both of the flanking ITRs are modified by a deletion, an insertion, and/or a substitution that results in the deletion of all or part of a stem-loop structure ~~normally~~ formed by the B and B' regions;

one or both of the flanking ITRs are modified by a deletion, an insertion, and/or a substitution that results in the deletion of all or part of a stem-loop structure ~~normally~~ formed by the C and C' regions;

one or both of the flanking ITRs are modified by a deletion, an insertion, and/or a substitution that results in the deletion of part of a stem-loop structure ~~normally~~ formed by the B and B' regions and/or part of a stem-loop structure ~~normally~~ formed by the C and C' regions;

one or both of the flanking ITRs comprise a single stem-loop structure in the region that, in a wild-type ITR, would comprise ~~normally comprises~~ a first stem-loop structure formed by the B and B' regions and a second stem-loop structure formed by the C and C' regions;

one or both of the flanking ITRs comprise a single stem and two loops in the region that, in a wild-type ITR, would comprise ~~normally comprises~~ a first stem-loop structure formed by the B and B' regions and a second stem-loop structure formed by the C and C' regions;

one or both of the flanking ITRs comprise a single stem and a single loop in the region that, in a wild-type ITR, would comprise ~~normally comprises~~ a first stem-loop structure formed by the B and B' regions and a second stem-loop structure formed by the C and C' regions; or

both flanking ITRs are altered in a manner that results in an overall three-dimensional symmetry when the flanking ITRs are inverted relative to each other.

18. The composition of any one of claims 13, 14, 16, 17, wherein the ceDNA vector further comprises ~~at least one heterologous nucleotide sequence is under the control of~~ at least one regulatory switch.

19. Use of a capsid free, non-viral vector in the manufacture of a medicament for delivering the capsid free, non-viral vector to the cytosol of a target cell within a subject~~.~~,

wherein the capsid free, non-viral vector is encapsulated in a lipid nanoparticle (LNP), wherein the LNP lacks fusogenic activity; and

wherein the capsid free, non-viral vector and an endosomolytic agent are to be co-administered.

20. The use of claim 19, wherein the capsid free, non-viral vector when digested with a restriction enzyme having a single recognition site on the DNA vector has the presence of characteristic bands of linear and continuous DNA as compared to linear and non-continuous DNA when analyzed on a non-denaturing gel.

21. The use of claim 19, wherein the endosomolytic agent targets the target cell.

22. The use of claim 19, wherein the capsid free, non-viral vector is translocated to nucleus of the cell after administration.

~~23. The use of claim 19, wherein the LNP releases less than 10% of the ceDNA comprised therein at endosomal pH.~~

~~24. The use of claim 19, wherein the LNP does not induce an immune response when administered without the endosomolytic agent.~~

~~25~~23. The use of claim 19, wherein the target cell is a cell that lacks or does not express a functional innate DNA-sensing pathway, has reduced innate DNA-sensing pathway activity or lacks or does not express functional cGAS and/or STING, or which has reduced cGAS and/or STING activity.

~~26~~24. The use of claim 19, wherein the target cell is a hepatocyte.

~~27~~25. The use of claim 19, wherein the endosomolytic agent comprises:

(a) a membrane-destabilizing polymer,

(b) a copolymer, a peptide, a membrane-destabilizing toxin ~~or a derivative thereof~~, or a viral fusogenic peptide ~~or derivative thereof~~;

(c) a pH-sensitive polymer;

(d) a polyanionic peptide, a polycationic peptide, an amphipathic peptide, a hydrophobic peptide or a peptidomimetic; or

(e) a peptide selected from the group consisting of

AALEALAEALEALAEALEALAEAAAAGGC (SEQ ID NO: 530);

AALAEALAEALAEALAEALAEALAAAAGGC (SEQ ID NO: 531);

ALEALAEALEALAEA (SEQ ID NO: 532);

GLFEAIEGFIENGWEGMIWDYG (SEQ ID NO: 533);

GLFGAIAGFIENGWEGMIDGWYG (SEQ ID NO: 534);

GLFEAIEGFIENGWEGMIDGWYGC (SEQ ID NO: 535);

GLFEAIEGFIENGWEGMIDGWYGC (SEQ ID NO: 536);

GLFEAIEGFIENGWEGMIDGGC (SEQ ID NO: 537);

GLFEAIEGFIENGWEGMIDGGC (SEQ ID NO: 538);

CGLFGEIEELIEEGLENLIDWGNG (SEQ ID NO: 539);

GLFGALAEALAEALAEHLAEALAEALEALAAGGSC (SEQ ID NO: 540);

GLFEAIEGFIENGWEGLAEALAEALEALAAGGSC (SEQ ID NO: 541);

GLFEAIEGFIENGWEGnIDGK (n = norleucine) (SEQ ID NO: 542);

GLFEAIEGFIENGWEGnIDG (n = norleucine) (SEQ ID NO: 543);

GLFEALLELLESLWELLLEA (SEQ ID NO: 544);

GLFKALLKLLKSLWKLLLKA (SEQ ID NO: 545);

GLFRALLRLLRSLWRLLLRA (SEQ ID NO: 546);

WEAKLAKALAKALAKHLAKALAKALKACEA (SEQ ID NO: 547);

GLFFEAIAEFIEGGWEGLIEGC (SEQ ID NO: 548);

GIGAVLKVLTTGLPALISWIKRKRQQ (SEQ ID NO: 549);

H5WYG (SEQ ID NO: 550);

CHK_6HC (SEQ ID NO: 551);

RQIKIWFQNRRMKWKK (SEQ ID NO: 552);

GRKKRRQRRRPPQC (SEQ ID NO: 553);

GALFLGWLGAAGSTM (SEQ ID NO: 554);

GAWSQPKKKRKV (SEQ ID NO: 555);

LLIILRRRIRKQAHAHSK (SEQ ID NO: 556);

GWTLNSAGYLLKINLKALAALAKKIL (SEQ ID NO: 557);

KLALKLALKALKAALKLA (SEQ ID NO: 558);

RRRRRRRRR (SEQ ID NO: 559);

KFFKFFKFFK (SEQ ID NO: 560);

LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES (SEQ ID NO: 561);

SWLSKTAKKLENSAKKRISEGIAIAIQGGPR (SEQ ID NO: 562);

ACYCRIPACIAGERRYGTCIYQGRLWAFCC (SEQ ID NO: 563);

DHYNCVSSGGQCLYSACPIFTKIQGTCYRGKAKCCK ((SEQ ID NO: 564);

RKCRIVVIRVCRRRRPRPPYLPRPRPPPFFPPRLPPRIPPGFPPRFPPRFPGKR (SEQ ID NO: 565);

ILPWKWPWWPWRR (566);

WEAALAEALAEALAEHLAEALAEALEALAA (SEQ ID NO: 567);

CAEALAEALAEALAEALA (SEQ ID NO: 568);

GIGAVLKVLTTGLPALISWIKRKRQQ (SEQ ID NO: 569);

CGIGAVLKVLTTGLPALISWIKRKRQQ (SEQ ID NO: 570);

FIIDIIAFLLMGGFIVYVKNL (SEQ ID NO: 571);

CAAFIIDHAFLLMGGFIVYVKNL (SEQ ID NO: 572);

CARGWEVLKYWWNLLQY (SEQ ID NO: 573);

MVKSKIGSWILVLFVAMWSDVGLCKKRPKP (SEQ ID NO: 574);

KLALKLALKALKAALKLA (SEQ ID NO: 575);

YARAAARQARA (SEQ ID NO: 576);

GDCLPHLKLCKENKDCCSKKCKRRGTNIE (SEQ ID NO: 577);

RRLSYSRRRF (SEQ ID NO: 578);

RGGRLSYSRRRFSTSTGR (SEQ ID NO: 579);

IAWVKAFIRKLRKGPLG (SEQ ID NO: 580);

YTAIAWVKAFIRKLRK (SEQ ID NO: 581);

GLWRALWRLLRSLWRLLWRA (SEQ ID NO: 582);

KWFETWFTEWPKKRK (SEQ ID NO: 583);

KETWWETWWTEWSQPKKKRKV (SEQ ID NO: 584);
AGYLLGK(eNHa)INLKALAALAKKIL (SEQ ID NO: 585);
AGYLLGKINLKALAALAKKIL (SEQ ID NO: 586);
RQIKIVVFQNRRMKWKK (SEQ ID NO: 587);
WEAKLAKALAKALAKHLAKALAKALKACEA (SEQ ID NO: 588);
LLIILRRRIRKQAHAHSK (SEQ ID NO: 589);
YTIVVMPENPRPGTPCDIFTNSRGKRASNG (SEQ ID NO: 590);
AAVALLPAVLLALLAK (SEQ ID NO: 591);
GWTLNSAGYLLGKINLKALAALAKKIL (SEQ ID NO: 592);
GRKKRRQRRPPQ (SEQ ID NO: 593);
KMTRAQRRAAARRNRRWTAR (SEQ ID NO: 594);
KKRKAPKKKRKFA-KFHTFPQTAIGVGAP (SEQ ID NOS: 595 and 600, respectively);
MVTVLFRRLRIRRASGPPRVRV (SEQ ID NO: 596);
LIRLWSHLIHIVVFQNRRLKWKKK (SEQ ID NO: 597);
GALFLGFLGAAGSTMGAWSQPKKKRKV (SEQ ID NO: 598); and
GALFLAFLAAALSLMGLWSQPKKKRKV (SEQ ID NO: 599).

~~28~~26. The use of claim 19, wherein the endosomolytic agent is in the form of a nanoparticle; optionally wherein the nanoparticle further comprises a cationic lipid, a non-cationic lipid, a sterol ~~or a derivative thereof~~, a conjugated lipid, or any combination thereof.

~~29~~27. The use of claim 19, wherein the lipid nanoparticle and the endosomolytic agent are formulated into separate compositions for administration to the subject.

~~30~~28. The use of claim ~~29~~27, wherein the separate compositions are to be simultaneously administered are to be sequentially or subsequently administered.

~~31~~29. The use of claim 19, wherein the lipid nanoparticle comprises the endosomolytic agent.

~~32~~30. The use of claim 19, wherein at least one of the endosomolytic agent and the lipid nanoparticle includes a first targeting ligand that binds to a molecule on the surface of the target cell.

~~33~~31. The use of claim ~~32~~30, wherein one of the endosomolytic agent and the lipid nanoparticle includes the first targeting ligand, and the other of the endosomolytic agent and the lipid nanoparticle includes a second targeting ligand.

~~34~~32. The use of claim ~~32~~30, wherein the molecule on surface of the target cell is selected from the group consisting of a transferrin receptor type 1, a transferrin receptor type 2, the EGF receptor, HER2/Neu, a VEGF receptor, a PDGF receptor, an integrin, an NGF receptor, CD2, CD3, CD4, CD8, CD19, CD20, CD22, CD33, CD43, CD38, CD56, CD69, the asialoglycoprotein receptor (ASGPR), GalNAc receptor, prostate-specific membrane antigen (PSMA), a folate receptor, and a sigma receptor.

~~35~~33. The use of claim ~~19~~31, wherein the targeting ligand is a monovalent or multivalent D-galactose or N-acetyl-D-galactose.

~~36~~34. The use of claim 19, further comprising that an additional compound is to be administered to the subject.

~~37~~35. The use of ~~claim36~~claim 34, wherein said additional compound is a therapeutic agent, an immune modulating agent, or a second capsid free, non-viral vector, wherein the first and second capsid free, non-viral vectors are different.

~~38~~36. Use of a capsid free, non-viral vector in the manufacture of a medicament for delivering the capsid free, non-viral vector to the cytosol of a target cell within a subject,

wherein the capsid free, non-viral vector is encapsulated in a lipid nanoparticle (LNP), wherein the LNP lacks fusogenic activity;

wherein the capsid free, non-viral vector and an endosomolytic agent are to be co-administered, and

wherein at least one of the lipid nanoparticle and the endosomolytic agent includes a first targeting ligand that binds to a molecule on the surface of the target cell.

~~39~~37. The use of claim ~~38~~36, wherein the capsid free, non-viral vector when digested with a restriction enzyme having a single recognition site on the DNA vector has the presence of characteristic bands of linear and continuous DNA as compared to linear and non-continuous DNA when analyzed on a non-denaturing gel.

~~40~~38. Use of the composition of any one of claims 13, 14, 16, 17 and 18 in the manufacture of a medicament for expressing a desired transgene or therapeutic protein in a cell *in vivo* comprising contacting the cell with the composition of any one of claims 13, 14, 16, 17 and 18~~-~~.

~~41~~39. A cell containing a composition of any of claims 13, 14, 16, 17 and 18~~-~~.

~~42~~40. The use of any of claims 19-~~39~~37, wherein the capsid free, non-viral vector is a close-ended DNA (ceDNA) vector comprising:

at least one ~~heterologous~~ nucleotide sequence between flanking inverted terminal repeats (ITRs), wherein at least one ~~heterologous~~ nucleotide sequence encodes at least one transgene or therapeutic protein of interest.

41. An *in vitro* method of expressing a desired transgene or therapeutic protein in a cell, comprising contacting the cell with the composition of any one of claims 13, 14, 16, 17 and 18.