CLAIMS:

1. A fusosome comprising:

a) a lipid bilayer comprising a retargeted paramyxoviral fusogen, wherein the fusogen is linked to a targeting moiety that binds a cell surface marker on a liver cell for re-targeted delivery to a liver cell; and

b) a nucleic acid that comprises:

(i) a payload gene encoding an exogenous agent; and

(ii) a positive liver cell-specific regulatory element operatively linked to the payload gene, wherein the positive liver cell-specific regulatory element increases expression of the payload gene in a liver cell relative to an otherwise similar fusosome lacking the positive liver cell- specific regulatory element.

2. The fusosome of claim 1, wherein the nucleic acid further comprises a non-target cell- specific regulatory element (NTCSRE) operatively linked to the payload gene, wherein the NTCSRE decreases expression of the payload gene in a non-liver cell relative to an otherwise similar fusosome lacking the NTCSRE.

3. A fusosome comprising:

a) a lipid bilayer comprising a retargeted paramyxoviral fusogen, wherein the fusogen is linked to a targeting moiety that binds a cell surface marker on a liver cell for re-targeted delivery to a liver cell; and

b) a nucleic acid that comprises:

(i) a payload gene encoding an exogenous agent; and

(ii) a promoter operatively linked to the payload gene, wherein the promoter is chosen from an Apoa2, Cyp3a4, LP1B, MIR122, hemopexin, SERPINA1, or HLP promoter.

~~4. A fusosome comprising:~~

~~a) a lipid bilayer comprising a fusogen; and~~

~~b) a nucleic acid that comprises:~~

~~(i) a payload gene encoding an exogenous agent; and~~

~~(ii) a non-target cell-specific regulatory element (NTCSRE), operatively linked to the payload gene, wherein:~~

~~the NTCSRE is a non-liver cell-specific miRNA recognition sequence, a non-liver cell-specific protease recognition site, a non-liver cell-specific ubiquitin ligase site, a non-liver cell-specific transcriptional repression site, or a non-liver cell-specific epigenetic repression site, and the NTCSRE decreases expression of the payload gene in a non-liver cell or tissue relative to an otherwise similar fusosome lacking the NTCSRE.~~

~~5. The fusosome of claim 4, wherein the nucleic acid further comprises a positive liver~~

~~cell-specific regulatory element operatively linked to the payload gene, wherein the positive liver cell-specific regulatory element increases expression of the payload gene in a liver cell relative to an otherwise similar fusosome lacking the positive liver cell-specific regulatory element.~~

4~~6~~. The fusosome of any of claims 1-3~~5~~, wherein the fusosome further comprises one or both of:

(i) a first exogenous or overexpressed immunosuppressive protein on the lipid bilayer; or

(ii) a first immunostimulatory protein that is absent or present at reduced levels~~, optionally wherein the reduced level is reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% compared to a fusosome generated from an otherwise similar, unmodified source cell~~.

5~~7~~. The fusosome of any of claims 1-4~~6~~, wherein the payload gene is a gene that treats a genetic deficiency.

~~8. A fusosome comprising:~~

~~a) a lipid bilayer comprising a fusogen;~~

~~b) a nucleic acid that comprises a payload gene encoding an exogenous agent for treating a genetic deficiency; and~~

~~c) one or both of:~~

~~(i) a first exogenous or overexpressed immunosuppressive protein on the lipid bilayer; or~~

~~(ii) a first immunostimulatory protein that is absent or present at reduced levels (e.g., reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) compared to a fusosome generated from an otherwise similar, unmodified source cell.~~

6~~9~~. The fusosome of claim 4 or 5~~any of claims 6-8~~, wherein the immunosuppressive protein is a complement regulatory protein or CD47.

7~~10~~. The fusosome of any of claims 4-6~~6-9~~, wherein the immunostimulatory protein is an MHC I or MHC II protein.

8~~11~~. The fusosome of any of claims 1-7~~10~~, wherein the payload gene is selected from among OTC, CPS1, NAGS, BCKDHA, BCKDHB, DBT, DLD, MUT, MMAA, MMAB, MMACHC, MMADHC, MCEE, PCCA, PCCB, UGT1A1, ASS1, PAH, PAL, ATP8B1,

ABCB11, ABCB4, TJP2, IVD, GCDH, ETFA, ETFB, ETFDH, ASL, D2HGDH, HMGCL, MCCC1, MCCC2, ABCD4, HCFC1, LNBRD1, ARG1, SLC25A15, SLC25A13, ALAD, CPOX, HMBS, PPOX, BTD, HLCS, PC, SLC7A7, CPT2, ACADM, ACADS, ACADVL, AGL, G6PC, GBE1, PHKA1, PHKA2, PHKB, PHKG2, SLC37A4, PMM2, CBS, FAH, TAT, GALT, GALK1, GALE, G6PD, SLC3A1, SLC7A9, MTHFR, MTR, MTRR, ATP7B, HPRT1, HJV, HAMP, JAG1, TTR, AGXT, LIPA, SERPING1, HSD17B4, UROD, HFE, LPL,GRHPR, HOGA1, LDLR, ACAD8, ACADSB, ACAT1, ACSF3, ASPA, AUH, DNAJC19, ETHE1, FBP1, FTCD, GSS, HIBCH, IDH2, L2HGDH, MLYCD, OPA3, OPLAH, OXCT1, POLG, PPM1K, SERAC1, SLC25A1, SUCLA2, SUCLG1, TAZ, AGK, CLPB, TMEM70, ALDH18A1, OAT, CA5A, GLUD1, GLUL, UMPS, SLC22A5, CPT1A, HADHA, HADH, SLC52A1, SLC52A2, SLC52A3, HADHB, GYS2, PYGL, SLC2A2, ALG1, ALG2, ALG3, ALG6, ALG8, ALG9, ALG11, ALG12, ALG13, ATP6V0A2, B3GLCT, CHST14, COG1, COG2, COG4, COG5, COG6, COG7, COG8, DOLK, DHDDS, DPAGT1, DPM1, DPM2, DPM3, G6PC3, GFPT1, GMPPA, GMPPB, MAGT1, MAN1B1, MGAT2, MOGS, MPDU1, MPI, NGLY1, PGM1, PGM3, RFT1, SEC23B, SLC35A1, SLC35A2, SLC35C1, SSR4, SRD5A3, TMEM165, TRIP11, TUSC3, ALG14, B4GALT1, DDOST, NUS1, RPN2, SEC23A, SLC35A3, ST3GAL3, STT3A, STT3B, AGA, ARSA, ARSB, ASAH1, ATP13A2, CLN3, CLN5, CLN6, CLN8, CTNS, CTSA, CTSD, CTSF, CTSK, DNAJC5, FUCA1, GAA, GALC, GALNS, GLA, GLB1, GM2A, GNPTAB, GNPTG, GNS, GRN, GUSB, HEXA, HEXB, HGSNAT, HYAL1, IDS, IDUA, KCTD7, LAMP2, MAN2B1, MANBA, MCOLN1, MFSD8, NAGA, NAGLU, NEU1, NPC1, NPC2, SGSH, PPT1, PSAP, SLC17A5, SMPD1, SUMF1, TPP1, AHCY, GNMT, MAT1A, GCH1, PCBD1, PTS, QDPR, SPR, DNAJC12, ALDH4A1, PRODH, HPD, GBA, HGD, AMN, CD320, CUBN, GIF, TCN1, TCN2, PREPL, PHGDH, PSAT1, PSPH, AMT,GCSH, GLDC, LIAS, NFU1, SLC6A9, SLC2A1, ATP7A, AP1S1, CP, SLC33A1, PEX7, PHYH, AGPS, GNPAT, ABCD1, ACOX1, PEX1, PEX2, PEX3, PEX5, PEX6, PEX10, PEX12, PEX13, PEX14, PEX16, PEX19, PEX26, AMACR, ADA, ADSL, AMPD1, GPHN, MOCOS, MOCS1, PNP, XDH, SUOX, OGDH, SLC25A19, DHTKD1, SLC13A5, FH, DLAT, MPC1, PDHA1, PDHB, PDHX, PDP1, ABCC2, SLCO1B1, SLCO1B3, HFE2, ADAMTS13, PYGM , COL1A2, TNFRSF11B, TSC1, TSC2, DHCR7, PGK1, VLDLR, KYNU, F5, C3, COL4A1, CFH, SLC12A2, GK, SFTPC, CRTAP, P3H1, COL7A1, PKLR, TALDO1, TF, EPCAM, VHL, GC, SERPINA1, ABCC6, F8, F9, ApoB, PCSK9, LDLRAP1,ABCG5, ABCG8, LCAT, SPINK5 and GNE.

9~~12~~. The fusosome of any of claims 1-8~~11~~, wherein the payload gene encodes an exogenous agent comprising the sequence set forth in any one of SEQ ID NOS: 161-518, a functional fragment thereof, or a

functional variant thereof comprising an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%, identity to an amino acid sequence set forth in any one of SEQ ID NOS: 161-518.

10~~13~~. The fusosome of any of claims 1-9~~12~~, wherein the payload gene encoding an exogenous agent is chosen from: OTC, CPS1, NAGS, BCKDHA, BCKDHB, DBT, DLD, MUT, MMAA, MMAB, MMACHC, MMADHC, MCEE, PCCA, PCCB, UGT1A1, ASS1, PAH, ATP8B1, ABCB11, ABCB4, TJP2, IVD, GCDH, ETFA, ETFB, ETFDH, ASL, D2HGDH, HMGCL, MCCC1, MCCC2, ABCD4, HCFC1, LMBRD1, ARG1, SLC25A15, SLC25A13, ALAD, CPOX, HMBS, PPOX, BTD, HLCS, PC, SLC7A7, CPT2, ACADM, ACADS, ACADVL, AGL, G6PC, GBE1, PHKA1, PHKA2, PHKB, PHKG2, SLC37A4, PMM2, CBS, FAH, TAT, GALT, GALK1, GALE, G6PD, SLC3A1, SLC7A9, MTHFR, MTR, MTRR, ATP7B, HPRT1, HJV, HAMP, JAG1, TTR, AGXT, LIPA, SERPING1, HSD17B4, UROD, HFE, LPL, GRHPR, HOGA1, or LDLR.

~~14. The fusosome of any of claims 1-13, wherein the fusogen is a viral envelope protein.~~

~~15. The fusosome of any of claims 1-14, wherein the fusogen comprises VSV-G.~~

11~~16~~. The fusosome of any of claims 1-~~15~~10, wherein the retargeted paramyxoviral fusogen comprises paramyxovirus F and G proteins or F and H proteins or F and HN proteins or a derivative thereof, or any combination thereof.

12~~17~~. The fusosome of any of claims 1-11~~14 and 16~~, wherein the retargeted paramyxoviral fusogen comprises a sequence chosen from Nipah virus F and G proteins, measles virus F and H proteins, tupaia paramyxovirus F and H proteins, Hendra virus F and G proteins, Henipavirus F and G proteins, Morbilivirus F and H proteins, respirovirus F and HN protein, a Sendai virus F and HN protein, rubulavirus F and HN proteins, canine distemper virus F and H proteins, or avulavirus F and HN proteins, or a derivative thereof, or any combination thereof.

13. The fusosome of any of claims 1-12, wherein the retargeted paramyxoviral fusogen comprises a sequence of canine distemper virus.

14~~18~~. The fusosome of claim 12~~17~~, wherein the retargeted paramyxoviral fusogen comprises a sequence chosen from a Nipah virus F and G protein or a derivative thereof.

15. The fusosome of claim 14, wherein the retargeted paramyxoviral fusogen comprises a Nipah virus F and G protein.

~~19. The fusosome of any of claims 1-18, wherein the fusogen comprises a targeting moiety that binds a cell surface marker on the liver cell for re-targeted delivery to a liver cell.~~

16~~20~~. The fusosome of any of claims 1-15~~claim 19~~, wherein the targeting moiety is covalently conjugated to the retargeted paramyxoviral fusogen.

17~~21~~. The fusosome of claim 16~~19 or claim 20~~, wherein the targeting moieity is or comprises an antibody or an antigen-binding fragment thereof (e.g.,Fab, Fab', F(ab')2, Fv fragments, scFv antibody fragments, disulfide-linked Fvs (sdFv), a Fd fragment consisting of the VH and CH1 domains, linear antibodies, single domain antibodies such as sdAb (either VL or VH), nanobodies, or camelid VHH domains), an antigen-binding fibronectin type III (Fn3) scaffold such as a fibronectin polypeptide minibody~~an antibody or antigen-binding fragment, a single domain antibody, a DARPin, or an antigen-binding fibronectin type III (Fn3) scaffold~~.

18~~22~~. The fusosome of claim 1~~any claims 1, 2, 5-7, and 9-21~~, wherein the positive liver- specific regulatory element comprises a liver-specific promoter, a liver-specific enhancer, a liver- specific splice site, a liver-specific site extending half-life of an RNA or protein, a liver- specific mRNA nuclear export promoting site, a liver-specific translational enhancing site, or a liver- specific post-translational modification site.

19~~23~~. The fusosome of claim 18~~22~~, wherein the positive liver-specific regulatory element comprises a hepatocyte-specific promoter.

20~~24~~. The fusosome of claim 18 or 19~~22 or 23~~, wherein the positive liver-specific regulatory element comprises a promoter selected from an enhanced transthyretin (ET), Alb, Apoa2, Cyp3a4, LP1B, MIR122, hemopexin, SERPINA1, or HLP promoter.

21~~25~~. The fusosome of claim 20~~24~~, wherein the promoter comprises the sequence set forth in SEQ ID NO:133, or a sequence having at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to the sequence set forth in SEQ ID NO:133.

22~~26~~. The fusosome of claim 20 or 21~~3, claim 24, or claim 25~~, wherein the promoter has the sequence set forth in any of SEQ ID NO: 133-136, or 519-525 or a sequence having at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity thereto.

23~~27~~. The fusosome of claim 18 or 19~~22 or claim 23~~, wherein the positive liver-specific regulatory element comprises a ApoE.HCR-hAAT promoter.

24~~28~~. The fusosome of ~~any of~~ claim 2~~claims 2, 6, 7 and 9-27~~, wherein the NTCSRE comprises a non-liver cell-specific miRNA recognition sequence, non-liver cell-specific protease recognition site, non-liver cell-specific ubiquitin ligase site, non-liver cell-specific transcriptional repression site, or non-liver cell-specific epigenetic repression site.

2529. The fusosome of claim 2428, wherein the NTCSRE comprises a non-liver cell- specific miRNA recognition sequence and the miRNA recognition sequence is able to be bound by one or more of miR-142, mir-181a-2, mir-181b-1, mir-181c, mir-181a-1, mir-181b-2, mir- 181d, miR-223, or miR-126.

2630. The fusosome of any of claims 1-2529, wherein the nucleic acid comprises one or more insulator elements.

2731. The fusosome of claim 2630, wherein the nucleic acid comprises two insulator elements, wherein the two insulator elements comprise a first insulator element upstream of the payload gene and a second insulator element downstream of the payload gene.

2832. The fusosome of any of claims 1-2731, wherein the fusosome is a retroviral vector particle.

2933. The fusosome of any of claims 1-2832, wherein the fusosome is a lentiviral vector.

3034. The fusosome of any of claims 1-2933, wherein the liver cell is chosen from a hepatocyte, liver sinusoidal endothelial cell, cholangiocyte, stellate cell, liver-resident antigen- presenting cell, liver-resident immune lymphocyte, or portal fibroblast.

3135. A pharmaceutical composition comprising the fusosome of any of claims 1-3034, and a pharmaceutically acceptable carrier, diluent, or excipient.

3236. A fusosome of any of claims 1-3034 or pharmaceutical composition of claim 3135 for use in a method of delivering an exogenous agent to a subject, comprising administering to the subject a fusosome of any of the preceding claims, thereby delivering the exogenous agent to the subject.

3337. A fusosome of any of claims 1-3034 or pharmaceutical composition of claim 3135 for use in a method of modulating a function, in a subject, liver, or liver cell, comprising administering to the subject a fusosome of any of the preceding claims, thereby delivering the exogenous agent to the subject.

3438. A fusosome of any of claims 1-3034 or pharmaceutical composition of claim 3135 for use in treating a subject with a genetic deficiency, wherein the fusosome comprises a payload gene encoding an exogenous agent for treating the genetic deficiency.

3539. Use of a fusosome of any of claims 1-3034 or pharmaceutical composition of claim 3135 for manufacture of a medicament for use in treating a subject with a genetic deficiency, wherein the fusosome comprises a payload gene encoding an exogenous agent for treating the genetic deficiency

~~40. The fusosome or pharamaceutical composition for use of claim 38 or the use of claim 39 wherein the fusosome comprises a payload gene encoding an exogenous agent for treating the genetic deficiency.~~

36~~41~~. A method of making the fusosome of any of claims 1-30~~34~~, comprising:

a) providing a cell that comprises the nucleic acid and the targeted paramyxoviral fusogen;

b) culturing the cell under conditions that allow for production of the fusosome, and

c) separating, enriching, or purifying the fusosome from the cell, thereby making the fusosome.