the gene encoding PDGF (platelet-derived growth factor), a therapy being considered for use in humans (Lee JA, et al. Lentiviral transfection with the PDGF-B gene improves diabetic wound healing. Plast. Reconstr. Surg. 116 (2): 532 (2005)). However, one major difficulty with use of certain therapeutics, like CRISPR nucleases, in VLP is off-target effects, particularly with long-term expression of the nuclease when traditional expression methods such as via plasmid/viral vectors are used. Accordingly, there remains a need for improved systems for delivery of gene editing systems using particles derived from viral vectors.

SUMMARY

[0005] The present disclosure provides delivery particle (XDP) systems for the delivery of therapeutic payloads, including proteins, nucleic acids, small molecules and the like to target cells and tissues.

[0006] In some examples, the XDP system comprises nucleic acids encoding components selected from all or a portion of a retroviral gag polyprotein, a therapeutic payload, and a tropism factor, wherein the tropism factor is selected from the group consisting of a glycoprotein, an antibody fragment, a receptor, and a ligand to a target cell marker. In one example of the foregoing, the tropism factor is a glycoprotein having a sequence selected from the group of sequences consisting of SEQ ID NOS: 438, 440, 442, 444, 446, 448, 450, 452, 454, 456, 458, 460, 462, 464, 466, 468, 470, 472, 474, 476, 478, 480, 482, 484, 486, 488, 490, 492, 494, 496, 498, 500, 502, 504, 506, 508, 510, 512, 514, 516, 518, 520, 522, 524, 526, 528, 530, 532, 534, 536, 538, 540, 542, 544, 546, 548, 550, 552, 554, 556, 558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594 and 596 as set forth in Table 4, or a sequence having at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity thereto. In a particular example, the glycoprotein is VSV-G. In a particular example, the glycoprotein comprises a sequence of SEQ ID NO: 438.

[0007] The therapeutic payload can be a protein, a nucleic acid, or both a protein and a nucleic acid. In some examples of the XDP system, the protein payload is selected from the group consisting of a cytokine, an interleukin, an enzyme, a receptor, a microprotein, a hormone, erythropoietin, a ribonuclease (RNAse), a deoxyribonuclease (DNAse), a blood clotting factor, an anticoagulant, a bone morphogenetic protein, an engineered protein scaffold, a thrombolytic protein, a CRISPR protein, and an anti-cancer modality. In one example, the therapeutic

payload is a Class 1 or Class 2 CRISPR protein, wherein the Class 2 CRISPR protein selected from the group consisting of a Type II, Type V, or Type VI protein. In one example, the Class 2 CRISPR Type V protein is selected from the group consisting of Cas12a, Cas12b, Cas12c, Cas12d (CasY), Cas12j and CasX, wherein the CasX comprises a sequence of SEQ ID NOS: 21-233, 343-345, 350-353, 355-367 or 388-397 as set forth in Tables 1, 7, 8, 9, or 11, or a sequence having at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity thereto. In some examples, the CasX comprises a sequence of SEQ ID NOS: 21-233, 343-345, 350-353, 355-367 or 388-397. In some examples, the therapeutic payload is a nucleic acid selected from the group consisting of a single-stranded antisense oligonucleotide (ASOs), a double-stranded RNA interference (RNAi) molecule, a DNA aptamer, and a CRISPR guide nucleic acid, wherein the CRISPR guide nucleic acid is a single-molecule guide RNA comprising a scaffold sequence and a targeting sequence, wherein the targeting sequence comprises between 14 and 30 nucleotides and is complementary to a target nucleic acid sequence, and wherein the scaffold sequence comprises a sequence of SEQ ID NOS: 597-781 as set forth in Table 3, or a sequence having at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity thereto. In some examples, the scaffold sequence comprises a sequence of SEQ ID NOS: 597-781.

[0008] In some examples, the XDP system further comprises nucleic acids encoding one or more components selected from one or more protease cleavage sites, a gag-transframe region-pol protease polyprotein (gag-TFR-PR), a retroviral gag-pol polyprotein, and a non-retroviral protease capable of cleaving the protease cleavage sites. In some examples, the retroviral components of the XDP system are derived from a *Orthoretrovirinae* virus or a *Spumaretrovirinae* virus wherein the *Orthoretrovirinae* virus is selected from the group consisting of *Alpharetrovirus, Betaretrovirus, Deltaretrovirus, Epsilonretrovirus, Gammaretrovirus*, and *Lentivirus,* and the *Spumaretrovirinae* virus is selected from the group consisting of *Bovispumavirus, Equispumavirus, Felispumavirus, Prosimiispumavirus, Simiispumavirus,* and *Spumavirus.*

[0009] In some examples, the components of the XDP system are encoded on a single nucleic acid, on two nucleic acids, on three nucleic acids, on four nucleic acids, or on five

nucleic acids, and the nucleic acids are configured according to any one of FIGS. 36-68. In some examples, the components of the XDP system are encoded by nucleic acids selected from the group of sequences of SEQ ID NOS: 192, 193, 195, 196, 198-201, 782, and 234-339 as set forth in Table 5.

[0010] In some examples, the components of the XDP system are capable of self-assembling into an XDP when the one or more nucleic acids are introduced into a eukaryotic host cell and are expressed. In the foregoing example, the therapeutic payload is encapsidated within the XDP upon self-assembly of the XDP. In a particular example, wherein the therapeutic payload comprises a CasX and a guide RNA, the CasX and guide RNA are complexed as a ribonucleoprotein complex (RNP) and, optionally, a donor template is also encapsidated in the XDP. In another particular example, the tropism factor is incorporated on the XDP surface upon self-assembly of the XDP.

[0011] In some examples of the XDP system, the nucleic acids encoding the retroviral components are all or a portion of an *Alpharetrovirus* gag polyprotein, wherein the gag polyprotein comprises one or more components selected from the group consisting of a matrix polypeptide (MA), a P2A peptide, a P2B peptide, a P10 peptide, a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC). In some examples of the XDP system, the nucleic acids further comprise sequences encoding one or more components selected from an HIV p1 peptide, an HIV p6 peptide, a Gag-Pol polyprotein, one or more protease cleavage sites, a non-retroviral, heterologous protease capable of cleaving the cleavage sites, and a gag-transframe region-pol protease polyprotein.

[0012] In some examples of the XDP system, the nucleic acids encoding the retroviral components are all or a portion of an *Betaretrovirus* gag polyprotein, wherein the gag polyprotein comprises one or more components selected from the group consisting of a matrix polypeptide (MA), a PP21/24 peptide, a P12/P3/P8 peptide, a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC). In some examples of the XDP system, the nucleic acids further comprise sequences encoding one or more components selected from an HIV p1 peptide, an HIV p6 peptide, a Gag-Pol polyprotein, one or more protease cleavage sites, a non-retroviral, heterologous protease capable of cleaving the cleavage sites, and a gag-transframe region-pol protease polyprotein.

[0013] In some examples of the XDP system, the nucleic acids encoding the retroviral components are all or a portion of a *Deltaretrovirus* gag polyprotein, wherein the gag

polyprotein comprises one or more components selected from the group consisting of a matrix polypeptide (MA), a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC). In some examples of the XDP system, the nucleic acids further comprise sequences encoding one or more components selected from an HIV p1 peptide, an HIV p6 peptide, a Gag-Pol polyprotein, one or more protease cleavage sites, a non-retroviral, heterologous protease capable of cleaving the cleavage sites, and a gag-transframe region-pol protease polyprotein.

[0014] In some examples of the XDP system, the nucleic acids encoding the retroviral components are all or a portion of a *Epsilonretrovirus* gag polyprotein, wherein the gag polyprotein comprises one or more components selected from the group consisting of a matrix polypeptide (MA), a p20 peptide, a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC). In some examples of the XDP system, the nucleic acids further comprise sequences encoding one or more components selected from an HIV p1 peptide, an HIV p6 peptide, a Gag-Pol polyprotein, one or more protease cleavage sites, a non-retroviral, heterologous protease capable of cleaving the cleavage sites, and a gag-transframe region-pol protease polyprotein.

[0015] In some examples of the XDP system, the nucleic acids encoding the retroviral components are all or a portion of a *Gammanretrovirus* gag polyprotein, wherein the gag polyprotein comprises one or more components selected from the group consisting of a matrix polypeptide (MA), a p12 peptide, a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC). In some examples of the XDP system, the nucleic acids further comprise sequences encoding one or more components selected from an HIV p1 peptide, an HIV p6 peptide, a Gag-Pol polyprotein, one or more protease cleavage sites, a non-retroviral, heterologous protease capable of cleaving the cleavage sites, and a gag-transframe region-pol protease polyprotein.

[0016] In some examples of the XDP system, the nucleic acids encoding the retroviral components are all or a portion of a *Lentivirus* gag polyprotein, wherein the gag polyprotein comprises one or more components selected from the group consisting of a matrix polypeptide (MA), a capsid polypeptide (CA), a p2 peptide, a nucleocapsid polypeptide (NC), a p1 peptide, and a p6 peptide. In some examples of the XDP system, the nucleic acids further comprise sequences encoding one or more components selected from a Gag-Pol polyprotein, one or more protease cleavage sites, a non-retroviral, heterologous protease capable of cleaving the cleavage sites, and a gag-transframe region-pol protease polyprotein.

[0017] In some examples of the XDP system, the nucleic acids encoding the retroviral components are all or a portion of a *Spumaretrovirinae* gag polyprotein, wherein the gag

polyprotein comprises one or more components selected from the group consisting of a p68 Gag polypeptide and a p3 Gag polypeptide. In some examples of the XDP system, the nucleic acids further comprise sequences encoding one or more components selected from an HIV p1 peptide, an HIV p6 peptide, a Gag-Pol polyprotein, one or more protease cleavage sites, a non-retroviral, heterologous protease capable of cleaving the cleavage sites, and a gag-transframe region-pol protease polyprotein.

[0018] In some examples of the CasX system, the CasX further comprises one or more NLS selected from the group of sequences consisting of PKKKRKV (SEQ ID NO: 130), KRPAATKKAGQAKKKK (SEQ ID NO: 131), PAAKRVKLD (SEQ ID NO: 132), RQRRNELKRSP (SEQ ID NO: 133), NQSSNFGPMKGGNFGGRSSGPYGGGGQYFAKPRNQGGY (SEQ ID NO: 134), RMRIZFKNKGKDTAELRRRRVEVSVELRKAKKDEQILKRRNV (SEQ ID NO: 135), VSRKRPRP (SEQ ID NO: 136), PPKKARED (SEQ ID NO: 137), PQPKKKPL (SEQ ID NO: 138), SALIKKKKKMAP (SEQ ID NO: 139), DRLRR (SEQ ID NO: 140), PKQKKRK (SEQ ID NO: 141), RKLKKKIKKL (SEQ ID NO: 142), REKKKFLKRR (SEQ ID NO: 143), KRKGDEVDGVDEVAKKKSKK (SEQ ID NO: 144), RKCLQAGMNLEARKTKK (SEQ ID NO: 145), PRPRKIPR (SEQ ID NO: 146), PPRKKRTVV (SEQ ID NO: 147), NLSKKKKRKREK (SEQ ID NO: 148), RRPSRPFRKP (SEQ ID NO: 149), KRPRSPSS (SEQ ID NO: 150), KRGINDRNFWRGENERKTR (SEQ ID NO: 151), PRPPKMARYDN (SEQ ID NO: 152), KRSFSKAF (SEQ ID NO: 153), KLKIKRPVK (SEQ ID NO: 154), PKTRRRPRRSQRKRPPT (SEQ ID NO: 156), RRKKRRPRRKKRR (SEQ ID NO: 159), PKKKSRKPKKKSRK (SEQ ID NO: 160), HKKKHPDASVNFSEFSK (SEQ ID NO: 161), QRPGPYDRPQRPGPYDRP (SEQ ID NO: 162), LSPSLSPLLSPSLSPL (SEQ ID NO: 163), RGKGGKGLGKGGAKRHRK (SEQ ID NO: 164), PKRGRGRPKRGRGR (SEQ ID NO: 165), MSRRRKANPTKLSENAKKLAKEVEN (SEQ ID NO: 157), PKKKRKVPPPPAAKRVKLD (SEQ ID NO: 155), and PKKKRKVPPPPKKKRKV (SEQ ID NO: 166), wherein the NLS are located at or near the N-terminus and/or the C-terminus.

[0019] In some examples of the XDP system, the non-retroviral, heterologous protease is selected from the group consisting of tobacco etch virus protease (TEV), potyvirus HC protease, potyvirus P1 protease, PreScission (HRV3C protease), b virus NIa protease, B virus RNA-2-encoded protease, aphthovirus L protease, enterovirus 2A protease, rhinovirus 2A protease, picorna 3C protease, comovirus 24K protease, nepovirus 24K protease, RTSV (rice tungro

spherical virus) 3C-like protease, parsnip yellow fleck virus protease, 3C-like protease, heparin, cathepsin, thrombin, factor Xa, metalloproteinase, and enterokinase.

[0019a] In one aspect, the present dislcosure refers to a delivery particle (XDP) system comprising one or more nucleic acids encoding: (a) all or a portion of a retroviral gag polyprotein; (b) a retroviral gag-transframe region-pol protease polyprotein (gag-TFR-PR); (c) a therapeutic payload; and (d) a tropism factor. In another aspect, the present dislocsure provides an eukaryotic packaging cell comprising the XDP system as disclosed herein. In yet another aspect, the present disclosure provides a method of making an XDP comprising a therapeutic payload, the method comprising: (a) propagating the eukaryotic packaging cell as disclosed herein under conditions such that XDPs are produced; and (b) harvesting the XDPs produced by the eukaryotic packaging cell. In another aspect, the present disclosure provides an XDP produced by the method as disclosed herein. In yet another aspect, the present disclosure provides an *in vitro* method of modifying a target nucleic acid sequence in a cell, the method comprising contacting the cell with the XDP as disclosed herein, wherein said contacting comprises introducing into the cell the RNP, and wherein the target nucleic acid is modified by the CRISPR protein. In another aspect, the present disclosure provides the use of the XDP as disclosed herein in the manufacture of a medicament for modifying a target nucleic acid sequence in a cell, wherein the cell is to be contacted with the RNP, wherein said contacting comprises introducing into the cell the RNP, and wherein the target nucleic acid is modified by the CRISPR protein. In another aspect, the present disclosure provides the XDP as disclosed herein for use in therapy in a subject. In yet another aspect, the present disclosure provides a kit comprising the XDP as disclosed herein and a suitable container.

[0020] In other examples, the present disclosure provides eukaryotic cells comprising the XDP system of any one of the foregoing examples, wherein the cell is a packaging cell. In some examples, the eukaryotic cell is selected from the group consisting of HEK293 cells, Lenti-X 293T cells, BHK cells, HepG2, Saos-2, HuH7, NS0 cells, SP2/0 cells, YO myeloma cells, A549 cells, P3X63 mouse myeloma cells, PER cells, PER.C6 cells, hybridoma cells, VERO, NIH3T3 cells, COS, WI38, MRC5, A549, HeLa cells, CHO cells, and HT1080 cells.

[0021] In other examples, the present disclosure provides methods of making an XDP comprising a therapeutic payload, the method comprising propagating the packaging cell of any of the examples under conditions such that XDPs are produced, and harvesting the XDPs produced by the packaging cell. The present disclosure further provides an XDP produced by the foregoing methods. In a particular example, the XDP comprises a therapeutic payload of an RNP of a CasX and guide RNA and, optionally, a donor template of any of the examples disclosed herein.

[0022] In other examples, the present disclosure provides methods of modifying a target nucleic acid sequence in a cell, the methods comprising contacting the cell with the XDP comprising an RNP of any of the examples disclosed herein, wherein said contacting comprises introducing into the cell the RNP comprising the CasX protein, the guide RNA, and, optionally, the donor template nucleic acid sequence, resulting in modification of the target nucleic acid sequence. In some cases, the modification comprises introducing one or more single-stranded breaks in the target nucleic acid sequence. In other cases, the modification comprises introducing one or more double-stranded breaks in the target nucleic acid sequence. In still other cases, the modification comprises insertion of the donor template into the target nucleic acid sequence. In one example, the cell is modified *in vitro* or *ex vivo*. In another example, the cell is modified *in vivo*. In the foregoing example, the XDP is administered to a subject at a therapeutically effective dose, wherein the subject is the subject is selected from the group consisting of mouse, rat, pig, non-human primate, and human. In some examples, the XDP is administered by a route of administration selected from the group consisting of subcutaneous, intradermal, intraneural, intranodal, intramedullary, intramuscular, intravenous, intracerebroventricular, intracisternal, intrathecal, intracranial, intralumbar, intratracheal, intraosseous, inhalatory, intracontralateral striatum, intraocular, intravitreal, intralymphatical, intraperitoneal routes and

sub-retinal routes. In some examples, the therapeutically effective dose is at least about 1×10^5 particles/kg, or at least about 1×10^6 particles/kg, or at least about 1×10^7 particles/kg, or at least about 1×10^8 particles/kg, or at least about 1×10^9 particles/kg, or at least about 1×10^{10} particles/kg, or at least about 1×10^{11} particles/kg, or at least about 1×10^{12} particles/kg, or at least about 1×10^{13} particles/kg, or at least about 1×10^{14} particles/kg, or at least about 1×10^{15} particles/kg, or at least about 1×10^{16} particles/kg. In some examples, the XDP is administered to the subject according to a treatment regimen comprising one or more consecutive doses using a therapeutically effective dose of the XDP. In some examples, the therapeutically effective dose is administered to the subject as two or more doses over a period of at least two weeks, or at least one month, or at least two months, or at least three months, or at least four months, or at least five months, or at least six months, or once a year, or every 2 or 3 years.

[0023] In another example, provided herein are XDP particles, and XDP systems, for use as a medicament for the treatment of a subject having a disease.

INCORPORATION BY REFERENCE

[0024] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. The contents of PCT/US2020/036505, filed on June 5, 2020, and a U.S. provisional application entitled “Engineered CasX Systems”, filed on December 3, 2020, both applications which disclose CasX variants and gNA variants, are hereby incorporated by reference in their entireties.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0026] FIG. 1 shows an SDS-PAGE gel of StX2 purification fractions visualized by colloidal Coomassie staining, as described in Example 1.

[0027] FIG. 2 shows the chromatogram from a size exclusion chromatography assay of the StX2, using of Superdex 200 16/600 pg Gel Filtration, as described in Example 1.

CLAIMS

What is claimed is:

1. A delivery particle (XDP) system comprising one or more nucleic acids encoding:

(a) all or a portion of a retroviral gag polyprotein;

(b) a retroviral gag-transframe region-pol protease polyprotein (gag-TFR-PR);

(c) a therapeutic payload; and

(d) a tropism factor.

2. The XDP system of claim 1, wherein the encoded retroviral gag polyprotein or the encoded gag-TFR-PR is derived from an *Orthoretrovirinae* virus or a *Spumaretrovirinae* virus.

3. The XDP system of claim 2, wherein the *Orthoretrovirinae* virus is selected from the group consisting of Lentivirus, Alpharetrovirus, Betaretrovirus, Deltaretrovirus, Epsilonretrovirus, and Gammaretrovirus.

4. The XDP system of claim 3, wherein the virus is lentivirus.

5. The XDP system of claim 4, wherein the Lentivirus is a human immunodeficiency type 1 (HIV-1) virus or human immunodeficiency type 2 (HIV-2) virus.

6. The XDP system of claim 4, wherein the encoded gag polyprotein comprises one or more components selected from the group consisting of a matrix polypeptide (MA), a capsid polypeptide (CA), a P2 peptide, a nucleocapsid polypeptide (NC), a P1 peptide, and a P6 peptide.

7. The XDP system of claim 6, wherein the virus comprises an Alpharetrovirus, and wherein the encoded gag polyprotein comprises one or more components selected from the group consisting of a matrix polypeptide (MA), a P2A peptide, a P2B peptide, a P10 peptide, a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC).

8. The XDP system of claim 3, wherein the virus comprises a Betaretrovirus, and the encoded gag polyprotein comprises one or more components selected from the group consisting of a matrix polypeptide (MA), a PP21/24 peptide, a P12/P3/P8 peptide, a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC).

9. The XDP system of claim 3, wherein the virus comprises a Deltaretrovirus, and the encoded gag polyprotein comprises one or more components selected from the group consisting of a matrix polypeptide (MA), a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC).

10. The XDP system of claim 3, wherein the virus comprises an Epsilonretrovirus, and wherein the gag polyprotein comprises one or more components selected from the group consisting of a matrix polypeptide (MA), a p20 peptide, a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC).

11. The XDP system of claim 3, wherein the virus comprises a Gammaretrovirus, and wherein the encoded gag polyprotein comprises one or more components selected from the group consisting of a matrix polypeptide (MA), a p12 peptide, a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC).

12. The XDP system of any one of claims 1-11, wherein the one or more nucleic acids encode one or more of

an HIV p1 peptide,

an HIV p6 peptide,

a Gag-Pol polyprotein,

one or more protease cleavage sites, or

a protease capable of cleaving the cleavage sites.

13. The XDP system of claim 12, wherein the protease is selected from the group consisting of tobacco etch virus protease (TEV), potyvirus HC protease, potyvirus P1 protease, PreScission (HRV3C protease), b virus NIa protease, B virus RNA-2-encoded protease, aphthovirus L protease, enterovirus 2A protease, rhinovirus 2A protease, picorna 3C protease, comovirus 24K protease, nepovirus 24K protease, RTSV (rice tungro spherical virus) 3C-like protease, parsnip yellow fleck virus protease, 3C-like protease, heparin, cathepsin, thrombin, factor Xa, metalloproteinase, and enterokinase.

14. The XDP system of any one of claims 1-13, wherein the encoded tropism factor is selected from the group consisting of a glycoprotein, an antibody fragment, a receptor, and a ligand to a target cell marker, wherein the tropism factor has specific binding affinity for a target cell marker on a target cell or tissue.

15. The XDP system of claim 14, wherein the encoded tropism factor comprises a glycoprotein having an encoding sequence selected from the group consisting of SEQ ID NOS: 437, 439, 441, 443, 445, 447, 449, 451, 453, 455, 457, 459, 461, 463, 465, 467, 469, 471, 473, 475, 477, 479, 481, 483, 485, 487, 489, 491, 493, 495, 497, 499, 501,, 503, 505, 507, 509, 511, 513, 515, 517, 519, 521, 523, 525, 527, 529, 531, 533, 535, 537, 539, 541, 543, 545, 547, 549, 551, 553, 555, 557, 559, 561, 563, 565, 567, 569, 571, 573, 575, 577, 579, 581, 583, 585, 587,

589, 591, 593 and 595, or a sequence having at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity thereto.

16. The XDP system of any one of claims 1-15, wherein the encoded therapeutic payload comprises a protein, a nucleic acid, or a protein and a nucleic acid.

17. The XDP system of claim 16, wherein the protein payload is a Class 1 or Class 2 CRISPR protein.

18. The XDP system of claim 17, wherein the Class 2 CRISPR protein is a Type V protein selected from the group consisting of Cas12a, Cas12b, Cas12c, Cas12d (CasY), Cas12j and CasX.

19. The XDP system of claim 18, wherein the CasX comprises a sequence selected from the group consisting of SEQ ID NOs: 21-233, 343-345, 350-353, 355-367 or 388-397, or a sequence having at least about 90% sequence identity thereto.

20. The XDP system of any one of claims 17-19, wherein the Class 1 or Class 2 CRISPR protein comprises one or more fusion partner proteins.

21. The XDP system of claim 16, wherein the encoded therapeutic payload comprises a nucleic acid selected from the group consisting of a single-stranded antisense oligonucleotide (ASOs), a double-stranded RNA interference (RNAi) molecule, a DNA aptamer, and a CRISPR guide ribonucleic acid (gRNA).

22. The XDP system of claim 21, wherein the gRNA comprises a scaffold sequence selected from the group consisting of SEQ ID NOs: 597-781, or a sequence having at least about 70% sequence identity thereto.

23. The XDP system of claim 22, wherein the gRNA comprises a hairpin loop with binding affinity for a protein, thereby facilitating binding of the gRNA to the protein.

24. The XDP system of claim 23, wherein the hairpin loop is selected from the group consisting of MS2 hairpin, PP7 hairpin, Qβ hairpin, boxB, transactivation response element (TAR), phage GA hairpin, phage ΛN hairpin, iron response element (IRE) and U1 hairpin II.

25. The XDP system of any one of claims 1-24, wherein

(a) the components are encoded on a single nucleic acid;

(b) the components are encoded on two nucleic acids;

(c) the components are encoded on three nucleic acids;

(d) the components are encoded on four nucleic acids; or

(e) the components are encoded on five nucleic acids.

26. The XDP system of claim 25, comprising one, two, three, four, or five vectors, wherein each vector comprises a nucleic acid encoding a component of the XDP system and a promoter operably linked to the nucleic acid.

27. The XDP system of claim 26, wherein XDP components are capable of self-assembly when the vectors are introduced into a eukaryotic packaging cell and the cells are cultured under conditions allowing expression of the encoded components.

28. The XDP system of claim 26, wherein upon self-assembly, the encoded therapeutic payload is encapsidated within the XDP and the encoded tropism factor is incorporated on the XDP surface.

29. A eukaryotic packaging cell comprising the XDP system of any one of claims 1-28.

30. The eukaryotic packaging cell of claim 29, wherein the eukaryotic packaging cell is selected from the group consisting of an HEK293 cell, Lenti-X 293T cell, BHK cell, HepG2 cell, Saos-2 cell, HuH7 cell, NS0 cell, SP2/0 cell, YO myeloma cell, A549 cell, P3X63 mouse myeloma cell, PER cell, PER.C6 cell, hybridoma cell, VERO cell, NIH3T3 cell, COS cell, WI38 cell, MRC5 cell, A549 cell, HeLa cell, CHO cell, and HT1080 cell.

31. The eukaryotic packaging cell of claim 29 or 30, wherein the eukaryotic packaging cell comprises one or more mutations to reduce expression of a cell surface marker.

32. A method of making an XDP comprising a therapeutic payload, the method comprising:

(a) propagating the eukaryotic packaging cell of any one of claims 29-31 under conditions such that XDPs are produced; and

(b) harvesting the XDPs produced by the eukaryotic packaging cell.

33. An XDP produced by the method of claim 32.

34. The XDP of claim 33, comprising a therapeutic payload of a ribonucleoprotein (RNP) of a CRISPR protein and a gRNA comprising a targeting sequence complementary to a target nucleic acid sequence.

35. The XDP of claim 34, wherein the targeting sequence comprises between 14 and 30 nucleotides.

36. An *in vitro* method of modifying a target nucleic acid sequence in a cell, the method comprising contacting the cell with the XDP of any one of claims 33-35, wherein said contacting

comprises introducing into the cell the RNP, and wherein the target nucleic acid is modified by the CRISPR protein.

37. The method of claim 36, wherein the modification comprises introducing one or more double-stranded breaks in the target nucleic acid sequence.

38. Use of the XDP of any one of claims 33-35 in the manufacture of a medicament for modifying a target nucleic acid sequence in a cell, wherein the cell is to be contacted with the RNP, wherein said contacting comprises introducing into the cell the RNP, and wherein the target nucleic acid is modified by the CRISPR protein.

39. The use of claim 38, wherein the XDP is to be administered in one or more consecutive doses.

40. The XDP of any one of claims 33-35 for use in therapy in a subject.

41. The XDP for use of claim 40, wherein the subject is selected from the group consisting of mouse, rat, pig, non-human primate, and human.

42. A kit comprising the XDP of any one of claims 33-35 and a suitable container.