

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 [embodimentexamples](#), the XDP system comprises nucleic acids encoding components selected from all or a portion of a retroviral gag polypeptide, 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 [embodimentexample](#) 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 [embodimentexample](#), the glycoprotein is VSV-G. In a particular [embodimentexample](#), 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 [embodimentexamples](#) 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 [embodimentexample](#), 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 [embodimentexample](#), 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 [embodimentexamples](#), the CasX comprises a sequence of SEQ ID NOS: 21-233, 343-345, 350-353, 355-367 or 388-397. In some [embodimentexamples](#), 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 [embodimentexamples](#), the scaffold sequence comprises a sequence of SEQ ID NOS: 597-781.

[0008] In some [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexample](#), the therapeutic payload is encapsidated within the XDP upon self-assembly of the XDP. In a particular [embodimentexample](#), 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 [embodimentexample](#), the tropism factor is incorporated on the XDP surface upon self-assembly of the XDP.

[0011] In some [embodimentexamples](#) 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 [embodimentexamples](#) 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 [embodimentexamples](#) 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 [embodimentexamples](#) 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 [embodimentexamples](#) 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 [embodimentexamples](#) 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 [embodimentexamples](#) of the XDP system, the nucleic acids encoding the retroviral components are all or a portion of a *Epsilon*retrovirus 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 [embodimentexamples](#) 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 [embodimentexamples](#) of the XDP system, the nucleic acids encoding the retroviral components are all or a portion of a *Gammaretrovirus* 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 [embodimentexamples](#) 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 [embodimentexamples](#) 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 [embodimentexamples](#) 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 [embodimentexamples](#) 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 [embodimentexamples](#) 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 [embodimentexamples](#) 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), KRKGDEV DGVDEVAKKKSKK (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), PKTRRRPRRSQKRKPPT (SEQ ID NO: 156), RRKKRRPRRKKRR (SEQ ID NO: 159), PKKKSRRKPKKKSRRK (SEQ ID NO: 160), HKKKHPDASVNFSEFSK (SEQ ID NO: 161), QRP GPYDRPQRPGPYDRP (SEQ ID NO: 162), LSPSLSPLLSPSLSP (SEQ ID NO: 163), RGKGGKGLGKGGAKRHRK (SEQ ID NO: 164), PKRGRGRPKRGRGR (SEQ ID NO: 165), MSRRRKANPTKLS ENAKKLAKEVEN (SEQ ID NO: 157), PKKKRKVPPPPAAKRVKLD (SEQ ID NO: 155), and PKKKRKVPPPPKPKRKV (SEQ ID NO: 166), wherein the NLS are located at or near the N-terminus and/or the C-terminus.

[0019] In some [embodimentexamples](#) 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 disclosure 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 disclosure 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 aspects/examples, the present disclosure provides eukaryotic cells comprising the XDP system of any one of the foregoing embodiment/examples, wherein the cell is a packaging cell. In some embodiment/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 [aspectsexamples](#), the present disclosure provides methods of making an XDP comprising a therapeutic payload, the method comprising propagating the packaging cell of any of the [embodimentexamples](#) 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 [embodimentexample](#), the XDP comprises a therapeutic payload of an RNP of a CasX and guide RNA and, optionally, a donor template of any of the [embodimentexamples](#) disclosed herein.

[0022] In other [aspectsexamples](#), 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 [embodimentexamples](#) 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 [embodimentexample](#), the cell is modified *in vitro* or *ex vivo*. In another [embodimentexample](#), the cell is modified *in vivo*. In the foregoing [embodimentexample](#), the XDP is administered to a subject at a therapeutically effective dose, wherein the subject is selected from the group consisting of mouse, rat, pig, non-human primate, and human. In some [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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 [aspectexample](#), 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.

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 one or more retroviral gag polyprotein components;
 - (b) a retroviral gag-transframe region-pol protease polyprotein (gag-TFR-PR);
 - ~~(b)~~(c) a therapeutic payload; and
 - ~~(c)~~(d) a tropism factor.
2. ~~The XDP system of claim 1, 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.~~
3. ~~The XDP system of claim 2, wherein the tropism factor is 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 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.~~
4. ~~The XDP system of claim 2, wherein the tropism factor is 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.~~
5. ~~The XDP system of any one of the preceding claims, wherein the therapeutic payload comprises a protein, a nucleic acid, or comprises both a protein and a nucleic acid.~~
6. ~~The XDP system of claim 5, wherein the protein payload is selected from the group consisting of a cytokine, an interleukin, an enzyme, a receptor, a microprotein, a hormone,~~

~~erythropoietin, ribonuclease (RNase), 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.~~

~~7. The XDP system of claim 6, wherein the CRISPR protein is a Class 1 or Class 2 CRISPR protein.~~

~~8. The XDP system of claim 7, wherein the CRISPR protein is a Class 2 CRISPR protein selected from the group consisting of a Type II, a Type V, or a Type VI protein.~~

~~9. The XDP system of claim 8, wherein the CRISPR protein is a Type V protein selected from the group consisting of Cas12a, Cas12b, Cas12c, Cas12d (CasY), Cas12j and CasX.~~

~~10. The XDP system of claim 9, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21-233, 343-345, 350-353, 355-367 or 388-397, 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.~~

~~11. The XDP system of claim 5, wherein the 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 nucleic acid.~~

~~12. The XDP system of claim 11, 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.~~

~~13. The XDP system of claim 12, 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.~~

~~14. The XDP system of claim 13, wherein the scaffold sequence comprises a sequence of SEQ ID NOS: 597-781.~~

~~15. The XDP system of any one of the preceding claims, wherein the nucleic acids further encode one or more components selected from:~~

- (a) — all or a portion of a retroviral gag polyprotein;
- (b) — one or more protease cleavage sites;
- (c) — a gag transframe region pol protease polyprotein (gag-TFR-PR);
- (d) — a retroviral gag pol polyprotein; and
- (e) — a non-retroviral protease capable of cleaving the protease cleavage sites.

16.2. The XDP system of ~~any one of the preceding claims, claim 1,~~ wherein ~~one or more of the encoded~~ retroviral ~~components are~~ gag polyprotein or the encoded gag-TFR-PR is derived from an *Orthoretrovirinae* virus or a *Spumaretrovirinae* virus.

17.3. The XDP system of claim ~~16,2,~~ wherein the *Orthoretrovirinae* virus is selected from the group consisting of ~~an~~ Lentivirus, Alpharetrovirus, Betaretrovirus, Deltaretrovirus, Epsilonretrovirus, and Gammaretrovirus, ~~and Lentivirus.~~

18.4. The XDP system of claim ~~316,~~ wherein the *Spumaretrovirinae* virus is lentivirus-selected from the group consisting of *Bovispumavirus*, *Equispumavirus*, *Felispumavirus*, *Prosimiispumavirus*, *Simiispumavirus*, or *Spumavirus*.

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.

19. The XDP system of any one of the preceding claims, 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.

20. The XDP system of claim 19, wherein the one or more of the components encoded by the nucleic acids are configured according to any one of FIGS. 36-68.

21. The XDP system of claim 19 or claim 20, wherein the one or more of the retroviral components are encoded by a nucleic acid selected from the group of sequences consisting of SEQ ID NOS: 192, 193, 195, 196, 198-201, 782, and 234-339 as set forth in Table 5.

22. The XDP system of any one of the preceding claims, wherein the components 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.

~~23.~~—The XDP of claim 22, wherein the therapeutic payload is encapsidated within the XDP upon self-assembly of the XDP.

~~24.~~—The XDP system of claim 23, wherein the therapeutic payload comprises a CasX and a guide RNA complexed as a ribonucleoprotein complex (RNP) and, optionally, a donor template.

~~25.~~—The XDP of claim 22, wherein the tropism factor is incorporated on the XDP surface upon self-assembly of the XDP.

~~26.~~—The XDP system of claim 25, wherein the tropism factor confers preferential interaction of the XDP with the cell surface of a target cell and facilitates entry of the XDP into the target cell.

~~27.~~—An XDP system comprising one or more nucleic acids encoding components:

- ~~(a)~~—all or a portion of an *Alpharetrovirus* gag polyprotein;
- ~~(b)~~—a therapeutic payload; and
- ~~(c)~~—a tropism factor.

28.6. The XDP system of claim 274, 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), a P2 peptide, and a nucleocapsid polypeptide (NC), a P1 peptide, and a P6 peptide.

29.7. The XDP system of claim 286, wherein the gag polyproteinvirus comprises an Alpharetrovirus, and wherein the encoded gag polyprotein comprises one or more components selected from the group consisting of~~from N-terminus to C-terminus~~, a matrix polypeptide (MA), a P2A peptide, a P2B peptide, a P10 peptide, a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC).

~~30.~~—The XDP system of any one of claims 27–29, wherein the one or more nucleic acids encode one or more components selected from

- ~~(a)~~—an HIV p1 peptide;
- ~~(b)~~—an HIV p6 peptide;
- ~~(c)~~—a Gag-Pol polyprotein;
- ~~(d)~~—one or more protease cleavage sites;
- ~~(e)~~—a non-retroviral, heterologous protease capable of cleaving the cleavage sites; and
- ~~(f)~~—a gag-transframe region-pol protease polyprotein.

~~31.—The XDP system of any one of claims 27-30, 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.~~

~~32.—The XDP system of claim 31, wherein the tropism factor is 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.~~

~~33.—The XDP system of claim 31, wherein the tropism factor is a glycoprotein having an encoding sequence selected from the group of sequences 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 as set forth in Table 4.~~

~~34.—The XDP system of claim 33, wherein the tropism factor is glycoprotein G from vesicular stomatitis virus (VSV-G), optionally wherein the VSV-G glycoprotein comprises a sequence of SEQ ID NO: 438.~~

~~35.—The XDP system of any one of claims 27-34, wherein the therapeutic payload comprises a protein, a nucleic acid, or comprises both a protein and a nucleic acid.~~

~~36.—The XDP system of claim 35, wherein the protein payload is selected from the group consisting of a cytokine, an interleukin, an enzyme, a receptor, a microprotein, a hormone, erythropoietin, RNase, 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.~~

~~37.—The XDP system of claim 36, wherein the CRISPR protein is a Class 1 or Class 2 CRISPR protein.~~

~~38.~~—The XDP system of claim 37, wherein the CRISPR protein is a Class 2 CRISPR protein selected from the group consisting of Type II, Type V, or Type VI protein.

~~39.~~—The XDP system of claim 38, wherein the CRISPR protein is a Type V protein selected from the group consisting of Cas12a, Cas12b, Cas12c, Cas12d (CasY), Cas12j and CasX.

~~40.~~—The XDP system of claim 39, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21 233, 343 345, 350 353, 355 367 or 388 397, 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.

~~41.~~—The XDP system of claim 39, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21 233, 343 345, 350 353, 355 367 or 388 397.

~~42.~~—The XDP system of any one of claims 39 41, wherein the CasX further comprises one or more NLS selected from the group of sequences consisting of PKKKRKKV (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), KRKGDEV DGVDEVAKKKSKK (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), PKTRRRPRRSQRKRPT (SEQ ID NO: 156), RRKKRRPRRKKRR (SEQ ID NO: 159), PKKKSRKPKKKSrk (SEQ ID NO: 160), HKKKHPDASVNFSEFSK (SEQ ID NO: 161), QRP GPYDRPQRPGPYDRP (SEQ ID NO: 162), LSPSLSPLLSPSLSP (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.

~~43.~~—The XDP system of claim 35, wherein 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.

~~44.~~—The XDP system of claim 43, wherein the CRISPR guide nucleic acid is a single molecule guide RNA comprising a scaffold sequence and a targeting sequence, wherein the targeting sequence is complementary to a target nucleic acid sequence.

~~45.~~—The XDP system of claim 44, wherein the scaffold sequence comprises a sequence of SEQ ID NOS: 597-781, 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.

~~46.~~—The XDP system of claim 45, wherein the scaffold sequence of the guide RNA comprises a sequence of SEQ ID NOS: 597-781.

~~47.~~—The XDP system of any one of claims 44-46, wherein the targeting sequence of the guide RNA consists of 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 consecutive nucleotides.

~~48.~~—The XDP system of any one of claims 27-47, wherein

- ~~(a)~~—the components are encoded on a single nucleic acid;
- ~~(b)~~—the components are encoding on two nucleic acids;
- ~~(c)~~—the components are encoding on three nucleic acids;
- ~~(d)~~—the components are encoding on four nucleic acids; or
- ~~(e)~~—the components are encoding on five nucleic acids.

~~49.~~—The XDP system of claim 48, wherein the one or more of the components encoded by the nucleic acids are configured according to any one of FIGS. 36-68.

~~50.~~—The XDP system of claim 48 or claim 49, wherein the one or more of the components are encoded by nucleic acids selected from the group of sequences consisting of SEQ ID NOS: 192, 193, 195, 196, 198-201, 782, 234-339, 880-933, and 947-1000 as set forth in Tables 5, 24, 27, 30, and 33, or sequences 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.

~~51. The XDP system of any one of claims 27-50, wherein the components 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.~~

~~52. The XDP of claim 51, wherein the therapeutic payload is encapsidated within the XDP upon self-assembly of the XDP.~~

~~53. The XDP system of claim 52, wherein the therapeutic payload comprises a CasX and a guide RNA complexed as a ribonucleoprotein complex (RNP) and, optionally, a donor template.~~

~~54. The XDP of claim 51, wherein the tropism factor is incorporated on the XDP surface upon self-assembly of the XDP.~~

~~55. The XDP system of claim 54, wherein the tropism factor confers preferential interaction with the cell surface of a target cell and facilitates entry of the XDP into the target cell.~~

~~56. An XDP system comprising one or more nucleic acids encoding components:~~

- ~~(a) all or a portion of an *Betaretrovirus* gag polyprotein;~~
- ~~(b) a therapeutic payload; and~~
- ~~(c) a tropism factor.~~

~~57.8. The XDP system of claim 56, wherein the virus comprises a Betaretrovirus, and wherein 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).~~

~~58. The XDP system of claim 56, wherein the gag polyprotein comprises, from N-terminus to C-terminus, a matrix polypeptide (MA), a PP21/24 peptide, a P12/P3/P8 peptide, a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC).~~

~~59. The XDP system of any one of claims 56-58, wherein the nucleic acids further encode one or more components selected from~~

- ~~(a) an HIV p1 peptide;~~
- ~~(b) an HIV p6 peptide;~~
- ~~(c) a Gag-Pol polyprotein;~~
- ~~(d) one or more protease cleavage sites;~~
- ~~(e) a non-retroviral, heterologous protease capable of cleaving the cleavage sites; and~~

(f) — a gag transframe region pol protease polyprotein.

~~60. — The XDP system of any one of claims 56–59, 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.~~

~~61. — The XDP system of claim 60, wherein the tropism factor is 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.~~

~~62. — The XDP system of claim 61, wherein the tropism factor is a glycoprotein having a 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.~~

~~63. — The XDP system of claim 62, wherein the tropism factor is glycoprotein G from vesicular stomatitis virus (VSV-G).~~

~~64. — The XDP system of any one of claims 56–63, wherein the therapeutic payload comprises a protein, a nucleic acid, or comprises both a protein and a nucleic acid.~~

~~65. — The XDP system of claim 64, wherein the protein payload is selected from the group consisting of a cytokine, an interleukin, an enzyme, a receptor, a microprotein, a hormone, erythropoietin, RNase, 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.~~

~~66. — The XDP system of claim 65, wherein the CRISPR protein is a Class 1 or Class 2 CRISPR protein.~~

~~67.~~—The XDP system of claim 66, wherein the CRISPR protein is a Class 2 CRISPR protein selected from the group consisting of Type II, Type V, or Type VI protein.

~~68.~~—The XDP system of claim 67, wherein the CRISPR protein is a Type V protein selected from the group consisting of Cas12a, Cas12b, Cas12c, Cas12d (CasY), Cas12j and CasX.

~~69.~~—The XDP system of claim 68, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21 233, 343 345, 350 353, 355 367 or 388 397, 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.

~~70.~~—The XDP system of claim 68, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21 233, 343 345, 350 353, 355 367 or 388 397.

~~71.~~—The XDP system of any one of claims 68 70, wherein the CasX further comprises one or more NLS selected from the group of sequences consisting of SEQ ID NOS: 130 166, wherein the NLS are located at or near the N-terminus and/or the C-terminus.

~~72.~~—The XDP system of claim 64, wherein 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.

~~73.~~—The XDP system of claim 72, wherein the CRISPR guide nucleic acid is a single-molecule guide RNA comprising a scaffold sequence and a targeting sequence, wherein the targeting sequence is complementary to a target nucleic acid sequence.

~~74.~~—The XDP system of claim 73, wherein the scaffold sequence comprises a sequence of SEQ ID NOS: 597 781, 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.

~~75.~~—The XDP system of claim 73, wherein the scaffold sequence of the guide RNA comprises a sequence of SEQ ID NOS: 597 781.

~~76.~~—The XDP system of any one of claims 73 75, wherein the targeting sequence of the guide RNA consists of 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 consecutive nucleotides.

- ~~77. The XDP system of any one of claims 56-76, wherein~~
- ~~(a) the components are encoded on a single nucleic acid;~~
 - ~~(b) the components are encoding on two nucleic acids;~~
 - ~~(c) the components are encoding on three nucleic acids;~~
 - ~~(d) the components are encoding on four nucleic acids; or~~
 - ~~(e) the components are encoding on five nucleic acids.~~
- ~~78. The XDP system of claim 77, wherein the one or more of the components encoded by the nucleic acids are configured according to any one of FIGS. 36-68.~~
- ~~79. The XDP system of claim 77 or claim 78, wherein the one or more of the components are encoded by nucleic acids selected from the group of sequences consisting of SEQ ID NOS: 192, 193, 195, 196, 198-201, 782, 234-339, 880-933, and 947-1000 as set forth in Tables 5, 24, 27, 30, and 33, or sequences 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.~~
- ~~80. The XDP system of any one of claims 56-79, wherein the components 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.~~
- ~~81. The XDP of claim 80, wherein the therapeutic payload is encapsidated within the XDP upon self-assembly of the XDP.~~
- ~~82. The XDP system of claim 81, wherein the therapeutic payload comprises a CasX and a guide RNA complexed as a ribonucleoprotein complex (RNP) and, optionally, a donor template.~~
- ~~83. The XDP of claim 80, wherein the tropism factor is incorporated on the XDP surface upon self-assembly of the XDP.~~
- ~~84. The XDP system of claim 83, wherein the tropism factor confers preferential interaction with the cell surface of a target cell and facilitates entry of the XDP into the target cell.~~
- ~~85. An XDP system comprising one or more nucleic acid encoding components:~~
- ~~(a) all or a portion of an *Deltaretrovirus* gag polyprotein;~~
 - ~~(b) a therapeutic payload; and~~
 - ~~(c) a tropism factor.~~

86.9. The XDP system of claim ~~853~~, wherein the virus comprises a Deltaretrovirus, and the encoded gag polypeptide comprises one or more components selected from the group consisting of a matrix polypeptide (MA), a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC).

~~87.~~—The XDP system of claim ~~86~~, wherein the ~~gag polypeptide comprises, from N terminus to C terminus, matrix polypeptide (MA), a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC).~~

~~88.~~—The XDP system of any one of claims ~~85–87~~, wherein the ~~nucleic acids encode one or more components selected from~~

~~(a) — an HIV p1 peptide;~~

~~(b) — an HIV p6 peptide;~~

~~(c) — a Gag-Pol polypeptide;~~

~~(d) — one or more protease cleavage sites;~~

~~(e) — a non-retroviral, heterologous protease capable of cleaving the cleavage sites; and~~

~~(f) — a gag-transframe region-pol protease polypeptide.~~

~~89.~~—The XDP system of any one of claims ~~85–88~~, 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.~~

~~90.~~—The XDP system of claim ~~89~~, wherein the tropism factor is 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.~~

~~91.~~—The XDP system of claim ~~89~~, wherein the tropism factor is a glycoprotein having a 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.~~

~~92.—The XDP system of claim 91, wherein the tropism factor is glycoprotein G from vesicular stomatitis virus (VSV-G).~~

~~93.—The XDP system of any one of claims 85-92, wherein the therapeutic payload comprises a protein, a nucleic acid, or comprises both a protein and a nucleic acid.~~

~~94.—The XDP system of claim 93, wherein the protein payload is selected from the group consisting of a cytokine, an interleukin, an enzyme, a receptor, a microprotein, a hormone, erythropoietin, RNase, 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.~~

~~95.—The XDP system of claim 94, wherein the CRISPR protein is a Class 1 or Class 2 CRISPR protein.~~

~~96.—The XDP system of claim 95, wherein the CRISPR protein is a Class 2 CRISPR protein selected from the group consisting of Type II, Type V, or Type VI protein.~~

~~97.—The XDP system of claim 96, wherein the CRISPR protein is a Type V protein selected from the group consisting of Cas12a, Cas12b, Cas12c, Cas12d (CasY), Cas12j and CasX.~~

~~98.—The XDP system of claim 97, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21-233, 343-345, 350-353, 355-367 or 388-397, 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.~~

~~99.—The XDP system of claim 97, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21-233, 343-345, 350-353, 355-367 or 388-397.~~

~~100.—The XDP system of any one of claims 97-99, wherein the CasX further comprises one or more NLS selected from the group of sequences consisting of SEQ ID NOS: 130-166, wherein the NLS are located at or near the N-terminus and/or the C-terminus.~~

~~101.—The XDP system of claim 93, wherein 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.~~

~~102.~~—The XDP system of claim 101, wherein the CRISPR guide nucleic acid is a single-molecule guide RNA comprising a scaffold sequence and a targeting sequence, wherein the targeting sequence is complementary to a target nucleic acid sequence.

~~103.~~—The XDP system of claim 102, wherein the scaffold sequence comprises a sequence of SEQ ID NOS: 597-781, 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.

~~104.~~—The XDP system of claim 102, wherein the scaffold sequence of the guide RNA comprises a sequence of SEQ ID NOS: 597-781.

~~105.~~—The XDP system of any one of claims 102-104, wherein the targeting sequence of the guide RNA consists of 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 consecutive nucleotides.

~~106.~~—The XDP system of any one of claims 85-105, wherein

- ~~(a)~~—the components are encoded on a single nucleic acid;
- ~~(b)~~—the components are encoding on two nucleic acids;
- ~~(c)~~—the components are encoding on three nucleic acids;
- ~~(d)~~—the components are encoding on four nucleic acids; or
- ~~(e)~~—the components are encoding on five nucleic acids.

~~107.~~—The XDP system of claim 106, wherein the one or more of the components encoded by the nucleic acids are configured according to any one of FIGS. 36-68.

~~108.~~—The XDP system of claim 106 or claim 107, wherein the one or more of the components are encoded by nucleic acids selected from the group of sequences consisting of SEQ ID NOS: 192, 193, 195, 196, 198-201, 782, 234-339, 880-933, and 947-1000 as set forth in Tables 5, 24, 27, 30, and 33, or sequences 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.

~~109.~~—The XDP system of any one of claims 85-108, wherein the components 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.

~~110.~~—The XDP of claim 109, wherein the therapeutic payload is encapsidated within the XDP upon self-assembly of the XDP.

~~111.~~—The XDP system of claim 110, wherein the therapeutic payload comprises a CasX and a guide RNA complexed as a ribonucleoprotein complex (RNP) and, optionally, a donor template.

~~112.~~—The XDP of claim 109, wherein the tropism factor is incorporated on the XDP surface upon self-assembly of the XDP.

~~113.~~—The XDP system of claim 112, wherein the tropism factor confers preferential interaction with the cell surface of a target cell and facilitates entry of the XDP into the target cell.

~~114.~~—An XDP system comprising one or more nucleic acid encoding components:

~~(a)~~—all or a portion of an *Epsilonretrovirus* gag polyprotein;

~~(b)~~—a therapeutic payload; and

~~(c)~~—a tropism factor.

~~115.~~10.The XDP system of claim ~~114~~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).

~~116.~~—The XDP system of claim 114, wherein the gag polyprotein comprises, from N-terminus to C-terminus, matrix polypeptide (MA), a p20 peptide, a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC).

~~117.~~—The XDP system of any one of claims 114–116, wherein the nucleic acids encode one or more components selected from

~~(a)~~—an HIV p1 peptide;

~~(b)~~—an HIV p6 peptide;

~~(c)~~—a Gag-Pol polyprotein;

~~(d)~~—one or more protease cleavage sites;

~~(e)~~—a non-retroviral, heterologous protease capable of cleaving the cleavage sites; and

~~(f)~~—a gag-transframe-region-pol-protease polyprotein.

~~118.~~—The XDP system of any one of claims 114–117, 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.

~~119.~~—The XDP system of claim 118, wherein the tropism factor is 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.

~~120.~~—The XDP system of claim 118, wherein the tropism factor is a glycoprotein having a 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.

~~121.~~—The XDP system of claim 120, wherein the tropism factor is glycoprotein G from vesicular stomatitis virus (VSV-G).

~~122.~~—The XDP system of any one of claims 114–121, wherein the therapeutic payload comprises a protein, a nucleic acid, or comprises both a protein and a nucleic acid.

~~123.~~—The XDP system of claim 122, wherein the protein payload is selected from the group consisting of a cytokine, an interleukin, an enzyme, a receptor, a microprotein, a hormone, erythropoietin, RNase, 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.

~~124.~~—The XDP system of claim 123, wherein the CRISPR protein is a Class 1 or Class 2 CRISPR protein.

~~125.~~—The XDP system of claim 124, wherein the CRISPR protein is a Class 2 CRISPR protein selected from the group consisting of Type II, Type V, or Type VI protein.

~~126.~~—The XDP system of claim 125, wherein the CRISPR protein is a Type V protein selected from the group consisting of Cas12a, Cas12b, Cas12c, Cas12d (CasY), Cas12j and CasX.

~~127.~~—The XDP system of claim 126, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21 233, 343 345, 350 353, 355 367 or 388 397, 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.

~~128.~~—The XDP system of claim 126, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21 233, 343 345, 350 353, 355 367 or 388 397.

~~129.~~—The XDP system of any one of claims 126 128, wherein the CasX further comprises one or more NLS selected from the group of sequences consisting of SEQ ID NOS: 130 166, wherein the NLS are located at or near the N terminus and/or the C terminus.

~~130.~~—The XDP system of claim 122, wherein 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.

~~131.~~—The XDP system of claim 130, wherein the CRISPR guide nucleic acid is a single molecule guide RNA comprising a scaffold sequence and a targeting sequence, wherein the targeting sequence is complementary to a target nucleic acid sequence.

~~132.~~—The XDP system of claim 131, wherein the scaffold sequence comprises a sequence of SEQ ID NOS: 597 781 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.

~~133.~~—The XDP system of claim 131, wherein the scaffold sequence of the guide RNA comprises a sequence of SEQ ID NOS: 597 781.

~~134.~~—The XDP system of any one of claims 131 133, wherein the targeting sequence of the guide RNA consists of 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 consecutive nucleotides.

~~135.~~—The XDP system of any one of claims 114 134, wherein

- ~~(a)~~—the components are encoded on a single nucleic acid;
- ~~(b)~~—the components are encoding on two nucleic acids;
- ~~(c)~~—the components are encoding on three nucleic acids;

~~(d) — the components are encoding on four nucleic acids; or~~

~~(e) — the components are encoding on five nucleic acids.~~

~~136. — The XDP system of claim 135, wherein the one or more of the components encoded by the nucleic acids are configured according to any one of FIGS. 36-68.~~

~~137. — The XDP system of claim 135 or claim 136, wherein the one or more of the components are encoded by nucleic acids selected from the group of sequences consisting of SEQ ID NOS: 192, 193, 195, 196, 198-201, 782, 234-339, 880-933, and 947-1000 as set forth in Tables 5, 24, 27, 30, and 33, or sequences 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.~~

~~138. — The XDP system of any one of claims 114-137, wherein the components 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.~~

~~139. — The XDP of claim 138, wherein the therapeutic payload is encapsidated within the XDP upon self-assembly of the XDP.~~

~~140. — The XDP system of claim 139, wherein the therapeutic payload comprises a CasX and a guide RNA complexed as a ribonucleoprotein complex (RNP) and, optionally, a donor template.~~

~~141. — The XDP of claim 139, wherein the tropism factor is incorporated on the XDP surface upon self-assembly of the XDP.~~

~~142. — The XDP system of claim 141, wherein the tropism factor confers preferential interaction with the cell surface of a target cell and facilitates entry of the XDP into the target cell.~~

~~143. — An XDP system comprising one or more nucleic acid encoding components:~~

~~(a) — all or a portion of an *Gammaretrovirus* gag polypeptide;~~

~~(b) — a therapeutic payload; and~~

~~(c) — a tropism factor.~~

~~144.~~11. The XDP system of claim ~~143~~3, wherein the virus comprises a Gammaretrovirus, and wherein the encoded gag polypeptide 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).

~~145.~~—The XDP system of claim 144, wherein the gag polyprotein comprises, from N terminus to C terminus, matrix polypeptide (MA), a p12 peptide, a capsid polypeptide (CA), and a nucleocapsid polypeptide (NC).

~~146.~~12.The XDP system of any one of claims ~~143–145~~1–11, wherein the one or more nucleic acids encode one or more of components selected from

- ~~(a)~~ an HIV p1 peptide;₁
- ~~(b)~~ an HIV p6 peptide;₁
- ~~(c)~~ a Gag-Pol polyprotein;₁
- ~~(d)~~ one or more protease cleavage sites;₁ or
- ~~(e)~~ a non-retroviral, heterologous protease capable of cleaving the cleavage sites;₁ and
- ~~(f)~~ a gag-transframe-region-pol-protease polyprotein.

~~147.~~—The XDP system of any one of claims ~~143–146~~, 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.

~~148.~~—The XDP system of claim 147, wherein the tropism factor is 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.~~

~~149.~~—The XDP system of claim 147, wherein the tropism factor is a glycoprotein having a 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.~~

~~150.~~—The XDP system of claim 149, wherein the tropism factor is glycoprotein G from vesicular stomatitis virus (VSV-G).

~~151.~~—The XDP system of any one of claims 143–150, wherein the therapeutic payload comprises a protein, a nucleic acid, or comprises both a protein and a nucleic acid.

~~152.~~—The XDP system of claim 151, wherein the protein payload is selected from the group consisting of a cytokine, an interleukin, an enzyme, a receptor, a microprotein, a hormone, erythropoietin, RNase, 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.

~~153.~~—The XDP system of claim 152, wherein the CRISPR protein is a Class 1 or Class 2 CRISPR protein.

~~154.~~—The XDP system of claim 153, wherein the CRISPR protein is a Class 2 CRISPR protein selected from the group consisting of Type II, Type V, or Type VI protein.

~~155.~~—The XDP system of claim 154, wherein the CRISPR protein is a Type V protein selected from the group consisting of Cas12a, Cas12b, Cas12c, Cas12d (CasY), Cas12j and CasX.

~~156.~~—The XDP system of claim 155, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21–233, 343–345, 350–353, 355–367 or 388–397, 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.

~~157.~~—The XDP system of claim 155, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21–233, 343–345, 350–353, 355–367 or 388–397.

~~158.~~—The XDP system of any one of claims 155–157, wherein the CasX further comprises one or more NLS selected from the group of sequences consisting of SEQ ID NOS: 130–166, wherein the NLS are located at or near the N terminus and/or the C terminus.

~~159.~~—The XDP system of claim 151, wherein 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.

~~160.~~—The XDP system of claim 159, wherein the CRISPR guide nucleic acid is a single molecule guide RNA comprising a scaffold sequence and a targeting sequence, wherein the targeting sequence is complementary to a target nucleic acid sequence.

~~161.~~—The XDP system of claim 160, wherein the scaffold sequence comprises a sequence of SEQ ID NOS: 597-781, 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.

~~162.~~—The XDP system of claim 160, wherein the scaffold sequence of the guide RNA comprises a sequence of SEQ ID NOS: 597-781.

~~163.~~—The XDP system of any one of claims 160-162, wherein the targeting sequence of the guide RNA consists of 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 consecutive nucleotides.

~~164.~~—The XDP system of any one of claims 143-163, wherein

- ~~(a)~~—the components are encoded on a single nucleic acid;
- ~~(b)~~—the components are encoding on two nucleic acids;
- ~~(c)~~—the components are encoding on three nucleic acids;
- ~~(d)~~—the components are encoding on four nucleic acids; or
- ~~(e)~~—the components are encoding on five nucleic acids.

~~165.~~—The XDP system of claim 164, wherein the one or more of the components encoded by the nucleic acids are configured according to any one of FIGS. 36-68.

~~166.~~—The XDP system of claim 164 or claim 165, wherein the one or more of the components are encoded by nucleic acids selected from the group of sequences consisting of SEQ ID NOS: 192, 193, 195, 196, 198-201, 782, 234-339, 880-933, and 947-1000 as set forth in Tables 5, 24, 27, 30, and 33, or sequences 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.

~~167.~~—The XDP system of any one of claims 164-166, wherein the components 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.

~~168.~~—The XDP of claim 167, wherein the therapeutic payload is encapsidated within the XDP upon self-assembly of the XDP.

~~169.~~—The XDP system of claim 168, wherein the therapeutic payload comprises a CasX and a guide RNA complexed as a ribonucleoprotein complex (RNP) and, optionally, a donor template.

~~170.~~—The XDP of claim 167, wherein the tropism factor is incorporated on the XDP surface upon self-assembly of the XDP.

~~171.~~—The XDP system of claim 170, wherein the tropism factor confers preferential interaction with the cell surface of a target cell and facilitates entry of the XDP into the target cell.

~~172.~~—An XDP system comprising one or more nucleic acid encoding components:

- ~~(a)~~—all or a portion of an *Lentivirus* gag polyprotein;
- ~~(b)~~—a therapeutic payload; and
- ~~(c)~~—a tropism factor.

~~173.~~—The XDP system of claim 172, 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.

~~174.~~—The XDP system of claim 173, wherein the gag polyprotein comprises, from N terminus to C terminus, matrix polypeptide (MA), a capsid polypeptide (CA), a p2-peptide, a nucleocapsid polypeptide (NC), a p1-peptide, and a p6-peptide.

~~175.~~—The XDP system of any one of claims 172-173, wherein the nucleic acids encode one or more components selected from

- ~~(a)~~—a Gag-Pol polyprotein;
- ~~(b)~~—one or more protease cleavage sites;
- ~~(c)~~—a non-retroviral, heterologous protease capable of cleaving the cleavage sites; and
- ~~(d)~~—a gag transframe region pol-protease polyprotein.

~~176.~~—The XDP system of any one of claims 172-175, wherein the lentivirus is selected from the group consisting of human immunodeficiency 1 (HIV-1), human immunodeficiency 2 (HIV-2), simian immunodeficiency virus (SIV), feline immunodeficiency virus (FIV), and bovine immunodeficiency virus (BIV).

~~177.~~—The XDP system of claim 176, wherein the lentivirus is HIV-1

~~178.~~—The XDP system of any one of claims 172-177, 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.

~~179.~~—The XDP system of claim 178, wherein the tropism factor is 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.~~

~~180.~~—The XDP system of claim 178, wherein the tropism factor is a glycoprotein having a 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.

~~181.~~—The XDP system of claim 180, wherein the tropism factor is glycoprotein G from vesicular stomatitis virus (VSV-G).

~~182.~~—The XDP system of any one of claims 172-181, wherein the therapeutic payload comprises a protein, a nucleic acid, or comprises both a protein and a nucleic acid.

~~183.~~—The XDP system of claim 182, wherein the protein payload is selected from the group consisting of a cytokine, an interleukin, an enzyme, a receptor, a microprotein, a hormone, erythropoietin, RNase, 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.

~~184.~~—The XDP system of claim 183, wherein the CRISPR protein is a Class 1 or Class 2 CRISPR protein.

~~185.~~—The XDP system of claim 184, wherein the CRISPR protein is a Class 2 CRISPR protein selected from the group consisting of Type II, Type V, or Type VI protein.

~~186.~~—The XDP system of claim 185, wherein the CRISPR protein is a Type V protein selected from the group consisting of Cas12a, Cas12b, Cas12c, Cas12d (CasY), Cas12j and CasX.

~~187.~~—The XDP system of claim 186, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21 233, 343 345, 350 353, 355 367 or 388 397, 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.

~~188.~~—The XDP system of claim 186, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21 233, 343 345, 350 353, 355 367 or 388 397.

~~189.~~—The XDP system of any one of claims 186 188, wherein the CasX further comprises one or more NLS selected from the group of sequences consisting of SEQ ID NOS: 130 166, wherein the NLS are located at or near the N terminus and/or the C terminus.

~~190.~~—The XDP system of claim 182, wherein 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.

~~191.~~—The XDP system of claim 190, wherein the CRISPR guide nucleic acid is a single molecule guide RNA comprising a scaffold sequence and a targeting sequence, wherein the targeting sequence is complementary to a target nucleic acid sequence.

~~192.~~—The XDP system of claim 191, wherein the scaffold sequence comprises a sequence of SEQ ID NOS: 597 781 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.

~~193.~~—The XDP system of claim 191, wherein the scaffold sequence of the guide RNA comprises a sequence of SEQ ID NOS: 597 781.

~~194.~~—The XDP system of any one of claims 191 193, wherein the targeting sequence of the guide RNA consists of 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 consecutive nucleotides.

~~195.~~—The XDP system of any one of claims 172 194, wherein

- ~~(a)~~—the components are encoded on a single nucleic acid;
- ~~(b)~~—the components are encoding on two nucleic acids;
- ~~(c)~~—the components are encoding on three nucleic acids;
- ~~(d)~~—the components are encoding on four nucleic acids; or
- ~~(e)~~—the components are encoding on five nucleic acids.

~~196.~~—The XDP system of claim 195, wherein the one or more of the components encoded by the nucleic acids are configured according to any one of FIGS. 36–68.

~~197.~~—The XDP system of claim 195 or claim 196, wherein the one or more of the components are encoded by nucleic acids selected from the group of sequences consisting of SEQ ID NOS: 192, 193, 195, 196, 198–201, 782, 234–339, 880–933, and 947–1000 as set forth in Tables 5, 24, 27, 30, and 33, or sequences 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.

~~198.~~—The XDP system of any one of claims 195–197, wherein the components 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.

~~199.~~—The XDP of claim 198, wherein the therapeutic payload is encapsidated within the XDP upon self-assembly of the XDP.

~~200.~~—The XDP system of claim 198, wherein the therapeutic payload comprises a CasX and a guide RNA complexed as a ribonucleoprotein complex (RNP) and, optionally, a donor template.

~~201.~~—The XDP of claim 198, wherein the tropism factor is incorporated on the XDP surface upon self-assembly of the XDP.

~~202.~~—The XDP system of claim 201, wherein the tropism factor confers preferential interaction with the cell surface of a target cell and facilitates entry of the XDP into the target cell.

~~203.~~—An XDP system comprising one or more nucleic acid encoding components:

- ~~(a)~~—all or a portion of an *Spumaretrovirinae* gag polyprotein;
- ~~(b)~~—a therapeutic payload; and
- ~~(c)~~—a tropism factor.

~~204.~~—The XDP system of claim 203, wherein the gag polyprotein comprises one or more components selected from the group consisting of a p68 Gag polypeptide and a p3 Gag polypeptide.

~~205.~~—The XDP system of claim 204, wherein the gag polyprotein comprises, from N terminus to C terminus, p68 Gag polypeptide and a p3 Gag polypeptide.

~~206.~~—The XDP system of any one of claims 203–205, wherein the nucleic acids encode one or more components selected from

- ~~(a)~~—an HIV p1 peptide;

- (b) — an HIV p6 peptide;
- (c) — a Gag-Pol polyprotein;
- (d) — one or more protease cleavage sites;
- (e) — a non-retroviral, heterologous protease capable of cleaving the cleavage sites; and
- (f) — a gag-transframe-region-pol-protease polyprotein.

207. — The XDP system of any one of claims 203–206, 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.

208. — The XDP system of claim 207, wherein the tropism factor is 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.

209. — The XDP system of claim 207, wherein the tropism factor is a glycoprotein having a 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.

210. — The XDP system of claim 209, wherein the tropism factor is glycoprotein G from vesicular stomatitis virus (VSV-G).

211. — The XDP system of any one of claims 203–210, wherein the therapeutic payload comprises a protein, a nucleic acid, or comprises both a protein and a nucleic acid.

212. — The XDP system of claim 211, wherein the protein payload is selected from the group consisting of a cytokine, an interleukin, an enzyme, a receptor, a microprotein, a hormone, erythropoietin, RNase, 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.

~~213.~~—The XDP system of claim 212, wherein the CRISPR protein is a Class 1 or Class 2 CRISPR protein.

~~214.~~—The XDP system of claim 213, wherein the CRISPR protein is a Class 2 CRISPR protein selected from the group consisting of Type II, Type V, or Type VI protein.

~~215.~~—The XDP system of claim 214, wherein the CRISPR protein is a Type V protein selected from the group consisting of Cas12a, Cas12b, Cas12c, Cas12d (CasY), Cas12j and CasX.

~~216.~~—The XDP system of claim 215, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21-233, 343-345, 350-353, 355-367 or 388-397, 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.

~~217.~~—The XDP system of claim 216, wherein the CRISPR protein is a CasX comprising a sequence of SEQ ID NOS: 21-233, 343-345, 350-353, 355-367 or 388-397.

~~218.~~—The XDP system of any one of claims 203-217, wherein the CasX further comprises one or more NLS selected from the group of sequences consisting of SEQ ID NOS: 130-166, wherein the NLS are located at or near the N-terminus and/or the C-terminus.

~~219.~~—The XDP system of claim 211, wherein 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.

~~220.~~—The XDP system of claim 219, wherein the CRISPR guide nucleic acid is a single-molecule guide RNA comprising a scaffold sequence and a targeting sequence, wherein the targeting sequence is complementary to a target nucleic acid sequence.

~~221.~~—The XDP system of claim 220, wherein the scaffold sequence comprises a sequence of SEQ ID NOS: 597-781, 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.

~~222.~~—The XDP system of claim 221, wherein the scaffold sequence of the guide RNA comprises a sequence of SEQ ID NOS: 597-781.

~~223.~~—The XDP system of any one of claims 220-222, wherein the targeting sequence of the guide RNA consists of 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 consecutive nucleotides.

~~224.~~—The XDP system of any one of claims 203-223, wherein

- ~~(a)~~—the components are encoded on a single nucleic acid;
- ~~(b)~~—the components are encoding on two nucleic acids;
- ~~(c)~~—the components are encoding on three nucleic acids;
- ~~(d)~~—the components are encoding on four nucleic acids; or
- ~~(e)~~—the components are encoding on five nucleic acids.

~~225.~~—The XDP system of claim 224, wherein the one or more of the components encoded by the nucleic acids are configured according to any one of FIGS. 36-68.

~~226.~~—The XDP system of claim 224 or claim 225, wherein the one or more of the components are encoded by nucleic acids selected from the group of sequences consisting of SEQ ID NOS: 192, 193, 195, 196, 198-201, 782, 234-339, 880-933, and 947-1000 as set forth in Tables 5, 24, 27, 30, and 33, or sequences 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.

~~227.~~—The XDP system of any one of claims 224-226, wherein the components 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.

~~228.~~—The XDP of claim 227, wherein the therapeutic payload is encapsidated within the XDP upon self-assembly of the XDP.

~~229.~~—The XDP system of claim 228, wherein the therapeutic payload comprises a CasX and a guide RNA complexed as a ribonucleoprotein complex (RNP) and, optionally, a donor template.

~~230.~~—The XDP of claim 227, wherein the tropism factor is incorporated on the XDP surface upon self-assembly of the XDP.

~~231.~~—The XDP system of claim 230, wherein the tropism factor confers preferential interaction with the cell surface of a target cell and facilitates entry of the XDP into the target cell.

~~232.~~—The XDP system of any one of the preceding claims, wherein the gag polyprotein and the therapeutic payload is expressed as a fusion protein.

~~233.~~—The XDP system of claim 232, wherein the fusion protein does not comprise a protease cleavage site between the gag polyprotein and the therapeutic payload.

~~234.~~—The XDP system of claim 232, wherein the fusion protein comprises a protease cleavage site between the gag polyprotein and the therapeutic payload.

~~235.~~—The XDP system of any one of claims 232-234, wherein the fusion protein comprises protease cleavage sites between the components of the gag polyprotein.

~~236.~~—The XDP system of claim 234 and/or claim 235, wherein the cleavage sites are capable of being cleaved by the protease of the Gag-Pol polyprotein, the protease of the gag-transframe region-pol protease polyprotein, or the non-retroviral, heterologous protease.

~~237.~~—The XDP system of claim 236, wherein the cleavage sites are capable of being cleaved by the protease of the gag-transframe region-pol protease polyprotein.

~~238.~~—The XDP system of claim 236, wherein the cleavage sites are capable of being cleaved by the protease of the Gag-Pol polyprotein.

~~239.~~13. The XDP system of claim ~~236~~12, wherein 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.

~~240.~~—The XDP system of claim 239, wherein the ~~non-retroviral, heterologous~~ protease is PreScission (HRV3C protease).

~~241.~~—The XDP system of claim 239, wherein the ~~non-retroviral, heterologous~~ protease is tobacco etch virus protease (TEV).

~~242.~~—The XDP system of any one of claims ~~12-13, 44-47, 73-76, 96-99, 103-106, 132-135, 161-164, 192-195 or 221-224~~, wherein the guide RNA further comprises one or more ribozymes.

~~243.~~—The XDP system of claim 242, wherein the one or more ribozymes are independently fused to a terminus of the guide RNA.

244.—The XDP system of claim 242 or claim 243, wherein at least one of the one or more ribozymes is a hepatitis delta virus (HDV) ribozyme, hammerhead ribozyme, pistol ribozyme, hatchet ribozyme, or tobacco ringspot virus (TRSV) ribozyme.

245.—The XDP system of any one of claims 12-13, 44-47, 73-76, 96-99, 103-106, 132-135, 161-164, 192-195 or 221-224, wherein the guide RNA is chemically modified.

246.—The XDP system of any one of claims 12-13, 44-47, 73-76, 96-99, 103-106, 132-135, 161-164, 192-195 or 221-224, wherein the guide RNA comprises an element selected from the group consisting of a Psi packaging element, kissing loop_a, kissing loop_b1, kissing loop_b2, G quadruplex M3q, G quadruplex telomere basket, sarcin-ricin loop, or pseudoknot, wherein the element has affinity to a protein incorporated into the CasX selected from the group consisting of MS2, PP7, Qbeta, U1A, and phage R-loop.

247.—A eukaryotic cell comprising the XDP system of any one of the preceding claims.

248.—The eukaryotic cell of claim 247, wherein the cell is a packaging cell.

249.—The eukaryotic cell of claim 247 or claim 248, wherein 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.

250.—The eukaryotic cell of claim 248 or claim 249, wherein the packaging cell comprises one or more mutations to reduce expression of a cell surface marker.

251.—The eukaryotic cell of any one of claims 247-250, wherein all or a portion of the nucleic acids encoding the XDP system are integrated into the genome of the eukaryotic cell.

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

- (a) — propagating the packaging cell of any one of claims 248-251 under conditions such that XDPs are produced; and
- (b) — harvesting the XDPs produced by the packaging cell.

253.—An XDP produced by the method of claim 252.

254.—The XDP of claim 253, comprising a therapeutic payload of an RNP of a CasX and guide RNA and, optionally, a donor template.

255.—A method of method of modifying a target nucleic acid sequence in a cell, the method comprising contacting the cell with the XDP of claim 254, wherein said contacting comprises

introducing into the cell the RNP and, optionally, the donor template nucleic acid sequence, wherein the target nucleic acid targeted by the guide RNA is modified by the CasX.

~~256.—The method of claim 255, wherein the modification comprises introducing one or more single stranded breaks in the target nucleic acid sequence.~~

~~257.—The method of claim 255, wherein the modification comprises introducing one or more double stranded breaks in the target nucleic acid sequence.~~

~~258.—The method of any one of claims 255-257, wherein the modification comprises insertion of the donor template into the target nucleic acid sequence.~~

~~259.—The method of any one of claims 255-258, wherein the cell is modified in vitro or ex vivo.~~

~~260.—The method of any one of claims 255-258, wherein the cell is modified in vivo.~~

~~261.—The method of claim 260, wherein the XDP is administered to a subject.~~

~~262.—The method of claim 261, wherein the subject is selected from the group consisting of mouse, rat, pig, non human primate, and human.~~

~~263.—The method of claim 261 or 262, wherein 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.~~

~~264.—The method of any one of claims 261-263, wherein the XDP is administered to the subject using a therapeutically effective dose.~~

~~265.—The method of claim 264, wherein the XDP is administered at a dose of 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.~~

~~266.—The method of any one of claims 261-265, wherein 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.~~

~~267.~~—The method of claim 266, wherein 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.

~~268.~~—A method for introducing a CasX and gNA RNP into a cell having a target nucleic acid, comprising contacting the cell with the XDP of claim 253 or claim 254, such that the RNP enters the cell.

~~269.~~—The method of claim 268, wherein the RNP binds to the target nucleic acid.

~~270.~~—The method of claim 269, wherein the target nucleic acid is cleaved by the CasX.

~~271.~~—The method of any one of claims 268-270, wherein the cell is modified in vitro.

~~272.~~—The method of any one of claims 268-270, wherein the cell is modified in vivo.

~~273.~~—The method of claim 272, wherein the XDP is administered to a subject.

~~274.~~—The method of claim 273, wherein the subject is selected from the group consisting of mouse, rat, pig, non-human primate, and human.

~~275.~~—The method of any one of claims 272-274, wherein the XDP is administered to the subject using a therapeutically effective dose.

~~276.~~—The method of claim 275, wherein the XDP is administered at a dose of 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.

~~277.~~—A XDP particle comprising:

- ~~(a)~~—a retroviral matrix (MA) polypeptide;
- ~~(b)~~—a therapeutic payload encapsidated within the XDP; and
- ~~(c)~~—a tropism factor incorporated on the XDP surface.

~~278.~~—The XDP particle of claim 277, further comprising one or more retroviral components selected from:

- ~~(a)~~—a capsid polypeptide (CA);
- ~~(b)~~—a nucleocapsid polypeptide (NC);
- ~~(c)~~—a P2A peptide, a P2B peptide;

- (d) — a P10 peptide;
- (e) — a p12 peptide
- (f) — a PP21/24 peptide;
- (g) — a P12/P3/P8 peptide;
- (h) — a P20 peptide;
- (i) — a p1 peptide; and
- (j) — a p6 peptide

279.14. The XDP ~~particle system~~ of ~~any one of claims 277 or claim 278~~ 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 or tissue.

15. The XDP system of claim **Error! Reference source not found.**, 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.

280. — The XDP particle of claim 279, wherein the tropism factor is a glycoprotein having an ~~sequence selected from the group 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, 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.~~

~~281.~~—The XDP particle of claim 279, wherein the tropism factor is a glycoprotein having an encoding sequence selected from the group 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.

~~282.16.~~The XDP systemparticle of any one of claims ~~277-281~~1-15, wherein the encoded therapeutic payload comprises a protein, a nucleic acid, or ~~comprises both~~ a protein and a nucleic acid.

~~283.~~—The XDP particle of claim 282, wherein the protein payload is selected from the group consisting of a cytokine, an interleukin, an enzyme, a receptor, a microprotein, a hormone, erythropoietin, RNase, 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.

~~284.17.~~The XDP systemparticle of claim 16-283, wherein the ~~CRISPR~~-protein payload is a Class 1 or Class 2 CRISPR protein.

~~285.~~—The XDP particle of claim 284, wherein the ~~CRISPR~~ protein is a Class 2 CRISPR protein selected from the group consisting of Type II, Type V, or Type VI protein.

~~286.18.~~The XDP systemparticle of claim 17-285, 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.

~~287.19.~~The XDP systemparticle of claim 18-286, wherein the ~~CRISPR protein is a~~ CasX comprises ing 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 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.

20. The XDP system of any one of claims ~~Error! Reference source not found.-Error! Reference source not found.~~, wherein the Class 1 or Class 2 CRISPR protein comprises one or more fusion partner proteins.

~~288.21.~~ The XDP ~~system~~particle of claim ~~282~~16, wherein the encoded therapeutic payload comprises~~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 ribonucleic acid (gRNA).

~~289.~~ The XDP ~~particle~~ of claim ~~288~~, 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.~~

~~290.22.~~ The XDP ~~system~~particle of claim ~~21~~289, wherein the gRNA comprises a scaffold sequence selected from the group consisting ~~comprises a sequence~~ of SEQ ID NOs ~~S~~S: 597-781, or a sequence having at least about 70% ~~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.

23. The XDP system of claim **Error! Reference source not found.**, 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, Q β hairpin, boxB, transactivation response element (TAR), phage GA hairpin, phage Δ N 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 1, 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 1 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 1-1 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 1, 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 135, 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 3635, 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 135 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 1-35 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 and a suitable container.

~~291. The XDP particle of claim 290, wherein the scaffold sequence comprises a sequence of SEQ ID NOS: 597-781.~~

~~292. The XDP particle of any one of claims 286-291, wherein the therapeutic payload comprises a CasX and a guide RNA complexed as a ribonucleoprotein complex (RNP) and, optionally, a donor template.~~

~~293. The XDP particle of any one of claims 277-292, wherein the retroviral components are derived from a *Orthoretrovirinae* virus or a *Spumaretrovirinae* virus.~~

~~294. The XDP particle of claim 293, wherein the *Orthoretrovirinae* virus is selected from the group consisting of *Alpharetrovirus*, *Betaretrovirus*, *Deltaretrovirus*, *Epsilonretrovirus*, *Gammaretrovirus*, and *Lentivirus*.~~

~~295. The XDP particle of claim 293, wherein the *Spumaretrovirinae* virus is selected from the group consisting of *Bovispumavirus*, *Equispumavirus*, *Felispumavirus*, *Prosimiispumavirus*, *Simiispumavirus*, and *Spumavirus*.~~

~~296. The XDP particles, or the XDP systems of any one of the preceding claims, for use as a medicament for the treatment of a subject having a disease.~~