[0005] Despite the efforts to date, there is a need for improved oncolytic viruses that, in particular, exhibit tumor-selective replication, viral mediated lysis, and/or therapeutic transgene expression for treating cancers and hyperproliferative disorders in human patients.

SUMMARY

[0006] The present disclosure is based, in part, upon the discovery that, for certain viral promoters, the TATA and/or CAAT box, while necessary to drive transcription in normal, healthy cells, is dispensable for active transcription in cancerous cells.

[0006a] In one aspect, the present disclosure refers to a recombinant virus comprising: (i) a modified TATA box-based promoter operably linked to a gene, wherein the modified TATA box-based promoter lacks a functional TATA box and permits selective expression of the gene in a hyperproliferative cell; and/or (ii) a modified CAAT box-based promoter operably linked to a gene, wherein the modified CAAT box-based promoter lacks a functional CAAT box and permits selective expression of the gene in a hyperproliferative cell.

[0006b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the recombinant virus disclosed herein and at least one pharmaceutically acceptable carrier or diluent.

[0006c] In a further aspect, the present disclosure refers to a method of expressing a therapeutic transgene in a target cell comprising exposing the cell to an effective amount of the recombinant virus disclosed herein to express the target transgene.

[0006d] In another aspect, the present disclosure refers to a use of a recombinant virus disclosed herein in the manufacture of a medicament for treating cancer.

[0006e] In a further aspect, the present disclosure refers to a use of a recombinant virus disclosed herein in the manufacture of a medicament for treating hyperproliferative disease.

[0006f] In another aspect, the present disclosure refers to a method of engineering an oncolytic virus, the method comprising modifying a viral TATA box-based promoter operably linked to a gene such that the modified TATA box-based promoter lacks a functional TATA box and permits selective expression of the gene in a hyperproliferative cell and/or modifying a viral CAAT box-based promoter operably linked to a gene such that the modified CAAT box-

based promoter lacks a functional CAAT box and permits selective expression of the gene in a hyperproliferative cell.

[0006g] In a further aspect, the present disclosure refers to an isolated nucleic acid comprising a nucleotide sequence selected from SEQ ID NO: 3, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22 and SEQ ID NO: 23.

[0006h] In another aspect, the present disclosure refers to a recombinant virus disclosed herein for use in treating cancer or hyperproliferative disease.

[0007] In one example, the present disclosure provides a recombinant virus comprising: (i) a modified TATA box-based promoter operably linked to a gene, wherein the modified TATA box-based promoter lacks a functional TATA box and permits selective expression of the gene in a hyperproliferative and/or non-growth arrested cell; and/or (ii) a modified CAAT box-based promoter operably linked to a gene, wherein the modified CAAT box-based promoter lacks a functional CAAT box and permits selective expression of the gene in a hyperproliferative and/or non-growth arrested cell.

[0008] In another example, the present disclosure provides a recombinant virus comprising a modified TATA box-based promoter operably linked to a gene, wherein the modified TATA box-based promoter lacks a functional TATA box and permits selective expression of the gene in a hyperproliferative and/or non-growth arrested cell.

[0009] In another example, the present disclosure provides a recombinant virus comprising a modified CAAT box-based promoter operably linked to a gene, wherein the modified CAAT box-based promoter lacks a functional CAAT box and permits selective expression of the gene in a hyperproliferative and/or non-growth arrested cell.

[0010] In certain examples of any of the foregoing recombinant viruses, the recombinant virus is selected from a recombinant vaccinia virus, adenovirus, adeno-associated virus (AAV), herpes simplex virus 1 (HSV1), myxoma virus, reovirus, poliovirus, vesicular stomatitis virus (VSV), measles virus (MV), and Newcastle disease virus (NDV). In certain examples, the recombinant virus is an adenovirus, *e.g.*, a type 5 adenovirus (Ad5) or a type 35 adenovirus (Ad35), *e.g.,* a type 5 adenovirus. In certain examples, the modified TATA

box-based promoter and/or the modified CAAT box-based promoter is an early gene promoter, *e.g.*, an E1a promoter, E1b promoter, or E4 promoter, *e.g.,* an E1a promoter.

[0011] In certain examples of any of the foregoing recombinant viruses, the modification included in the modified TATA box-based promoter comprises a deletion of the entire TATA box. In certain examples, the virus comprises a deletion of nucleotides corresponding to -27 to -24, -31 to -24, -44 to +54, or -146 to +54 of the adenovirus type 5 E1a promoter, which correspond, respectively, to nucleotides 471 to 474, 467 to 474, 454 to 551 and 352 to 551 of SEQ ID NO: 2, and to nucleotides 472 to 475, 468 to 475, 455 to 552, and 353 to 552 of SEQ ID NO: 8.

[0012] In certain examples, the virus comprises a deletion of nucleotides corresponding to -29 to -26, -33 to -26, -44 to +52, or -148 to +52 of the adenovirus type 5 E1a promoter. In certain examples, the virus comprises a deletion of nucleotides corresponding to nucleotides 471 to 475, 467 to 475, 446 to 551 and 352 to 551 of SEQ ID NO: 2.

[0013] In another example, the present disclosure provides a recombinant virus, wherein the virus is a type 5 adenovirus, and the virus comprises a deletion of nucleotides corresponding to -27 to -24, -31 to -24, -44 to +54, or -146 to +54 of the adenovirus type 5 E1a promoter, which correspond, respectively, to nucleotides 471 to 474, 467 to 474, 454 to 551 and 352 to 551 of SEQ ID NO: 2, and to nucleotides 472 to 475, 468 to 475, 455 to 552, and 353 to 552 of SEQ ID NO: 8.

[0014] In another example, the present disclosure provides a recombinant virus, wherein the virus is a type 5 adenovirus, and the virus comprises a deletion of nucleotides corresponding to -29 to -26, -33 to -26, -44 to +52, or -148 to +52 of the adenovirus type 5 E1a promoter or a deletion of nucleotides corresponding to nucleotides 471 to 475, 467 to 475, 446 to 551 and 352 to 551 of SEQ ID NO: 2.

[0015] In another example, the present disclosure provides a recombinant virus, wherein the virus is a type 5 adenovirus, and the virus comprises a polynucleotide deletion that results in a recombinant type 5 adenovirus comprising the sequence CTAGGACTG (SEQ ID NO: 7), AGTGCCCG (SEQ ID NO: 12), or TATTCCCG (SEQ ID NO: 13), which result from joining the two polynucleotide sequences that would otherwise flank the deleted polynucleotide sequence.

[0016] In certain examples of any of the foregoing recombinant viruses, the modification included in the modified CAAT box-based promoter comprises a deletion of the entire CAAT box. In certain examples, the virus comprises a deletion of nucleotides corresponding to -76 to -68 of the adenovirus type 5 E1a promoter, which corresponds to nucleotides 422 to 430 of SEQ ID NO: 2, and to nucleotides 423 to 431 of SEQ ID NO: 8.

[0017] In another example, the present disclosure provides a recombinant virus, wherein the virus is a type 5 adenovirus, and the virus comprises a deletion of nucleotides corresponding to -76 to -68 of the adenovirus type 5 E1a promoter, which corresponds to nucleotides 422 to 430 of SEQ ID NO: 2, and to nucleotides 423 to 431 of SEQ ID NO: 8.

[0018] In certain examples of any of the foregoing recombinant viruses, the virus comprises the nucleotide sequence of SEQ ID NO: 3, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, or SEQ ID NO: 23**,** or a sequence having 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 3, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, or SEQ ID NO: 23.

[0019] In another example, the present disclosure provides a recombinant virus, wherein the virus is a type 5 adenovirus, and the virus comprises a polynucleotide deletion that results in a recombinant type 5 adenovirus comprising the sequence TTCCGTGGCG (SEQ ID NO: 14), which results from joining the two polynucleotide sequences that would otherwise flank the deleted polynucleotide sequence.

[0020] In certain examples of any of the foregoing recombinant viruses, the virus comprises a deletion of nucleotides corresponding to 477 to 484 of the Ad35 genome.

[0021] In certain examples, any of the foregoing recombinant viruses may further comprise a nucleotide sequence encoding a therapeutic transgene. The therapeutic transgene may encode a therapeutic polypeptide, *e.g.,* an apoptotic agent, antibody, CTL responsive peptide, cytokine, cytolytic agent, cytotoxic agent, enzyme, heterologous antigen expressed on the surface of a tumor cell to elicit an immune response, immunostimulatory or immunomodulatory agent, interferon, lytic peptide, oncoprotein, polypeptide which catalyzes processes leading to cell death, polypeptide which complements genetic defects in somatic cells, tumor suppressor protein, vaccine antigen, and any combination thereof. The therapeutic transgene may encode a therapeutic nucleic acid, *e.g.,* an antisense RNA or a ribozyme. In

certain examples, the therapeutic transgene is selected from acetylcholine, an anti-PD-1 antibody heavy chain or light chain, an anti-PD-L1 antibody heavy chain or light chain, BORIS/CTCFL, CD19, CD20, CD80, CD86, CD137L, CD154, DKK1/Wnt, ICAM-1, IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-17, IL-23, IL-23A/p19, interferon-gamma, TGF-β, a TGF-β trap, FGF, IL-24, IL-27, IL-35, MAGE, NY-ESO-1, p53, and thymidine kinase. In certain examples, the therapeutic transgene is a TGF-β trap. In certain examples, the recombinant virus comprises an E1b-19K and an E1b-55K start site, and the nucleotide sequence encoding the therapeutic transgene is inserted between the start site of E1b-19K and the start site of E1b-55K.

[0022] In certain examples, any of the foregoing recombinant viruses may comprise a deletion of at least one Pea3 binding site, or a functional portion thereof.

[0023] In certain examples, any of the foregoing recombinant viruses may selectively replicate in a hyperproliferative cell and/or a non-growth arrested cell. In certain examples, any of the foregoing recombinant viruses may selectively express E1a, E1b, and/or a therapeutic transgene in a hyperproliferative cell and/or a non-growth arrested cell. In certain examples, any of the foregoing recombinant viruses may selectively have cytolytic activity in a hyperproliferative cell and/or a non-growth arrested cell.

[0024] The hyperproliferative and/or non-growth arrested cell may be a cancer cell, endothelial cell, epidermal cell, fibroblast, and/or immune cell. The hyperproliferative and/or non-growth arrested cell may be a cancer cell, *e.g.*, an anal cancer, basal cell carcinoma, bladder cancer, bone cancer, brain cancer, breast cancer, carcinoma, cholangiocarcinoma, cervical cancer, colon cancer, colorectal cancer, endometrial cancer, gastroesophageal cancer, gastrointestinal (GI) cancer, gastrointestinal stromal tumor, hepatocellular carcinoma, gynecologic cancer, head and neck cancer, hematologic cancer, kidney cancer, leukemia, liver cancer, lung cancer, lymphoma, melanoma, merkel cell carcinoma, mesothelioma, neuroendocrine cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, pediatric cancer, prostate cancer, renal cell carcinoma, sarcoma, skin cancer, small cell lung cancer, squamous cell carcinoma of the skin, stomach cancer, testicular cancer or thyroid cancer cell.

[0025] In another example, the present disclosure provides a recombinant virus comprising any modified or deleted viral regulatory sequence that permits selective expression of the virus in a hyperproliferative and/or non-growth arrested cell.

[0026] In another example, the present disclosure provides a pharmaceutical composition comprising any one or a combination of the foregoing recombinant viruses and at least one pharmaceutically acceptable carrier or diluent.

[0027] In another example, the present disclosure provides a method of treating a hyperproliferative disease, in a subject. The method comprises administering to the subject an effective amount of a recombinant virus described herein to treat the hyperproliferative disease in the subject. In certain examples, the hyperproliferative disease is selected from cancer, atherosclerosis, rheumatoid arthritis, psoriasis, lupus, idiopathic pulmonary fibrosis, sclerodermapulmonary hypertension, asthma, kidney fibrosis, COPD, cystic fibrosis, DIP, UIP, macular degeneration, restenosis, retinopathies, hyperproliferative fibroblast disorders, scleroderma, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection, glomerulopathies and cirrhosis.

[0028] In certain examples, the hyperproliferative disease is cancer. In certain examples, the cancer is selected from anal cancer, basal cell carcinoma, bladder cancer, bone cancer, brain cancer, breast cancer, carcinoma, cholangiocarcinoma, cervical cancer, colon cancer, colorectal cancer, endometrial cancer, gastroesophageal cancer, gastrointestinal (GI) cancer, gastrointestinal stromal tumor, hepatocellular carcinoma, gynecologic cancer, head and neck cancer, hematologic cancer, kidney cancer, leukemia, liver cancer, lung cancer, lymphoma, melanoma, merkel cell carcinoma, mesothelioma, neuroendocrine cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, pediatric cancer, prostate cancer, renal cell carcinoma, sarcoma, skin cancer, small cell lung cancer, squamous cell carcinoma of the skin, stomach cancer, testicular cancer and thyroid cancer.

[0029] In another example, the present disclosure provides a method of inhibiting tumor growth in a subject. The method comprises administering to the subject an effective amount of a recombinant virus described herein to inhibit proliferation of the tumor cell.

[0030] In another example, the present disclosure provides a method of inhibiting proliferation of a tumor cell. The method comprises exposing the cell to an effective amount of a recombinant viruses described herein to inhibit proliferation of the tumor cell.

[0031] In each of the foregoing methods, the recombinant virus can, *e.g.*, be administered in combination with one or more therapies selected from surgery, radiation, chemotherapy, immunotherapy, hormone therapy, and virotherapy. In each of the foregoing methods, the

effective amount of the recombinant virus can comprise, *e.g.*, 10^2-10^{15} plaque forming units (pfus). In each of the foregoing methods, the subject can, *e.g.,* be a human, *e.g.*, a pediatric human, or an animal.

[0032] In each of the foregoing methods, the effective amount of the recombinant virus may, *e.g.,* be identified by measuring an immune response to an antigen in the subject. In certain examples, the immune response to the antigen is measured by injecting the subject with the antigen at an injection site on the skin of the subject and measuring the size of an induration at the injection site.

[0033] In another example, the present disclosure provides a method of expressing a therapeutic transgene in a target cell. The method comprises exposing the cell to an effective amount of the recombinant virus described herein to express the target transgene.

[0034] In another example, the present disclosure provides a method of engineering an oncolytic virus. The method comprises modifying a viral TATA box-based promoter operably linked to a gene such that the modified TATA box-based promoter lacks a functional TATA box and permits selective expression of the gene in a hyperproliferative and/or non-growth arrested cell.

[0035] In another example, the present disclosure provides a method of engineering an oncolytic virus. The method comprises modifying a viral CAAT box-based promoter operably linked to a gene such that the modified CAAT box-based promoter lacks a functional CAAT box and permits selective expression of the gene in a hyperproliferative and/or non-growth arrested cell.

[0036] In another example, the present disclosure provides a method of engineering an oncolytic virus. The method comprises modifying a viral TATA box-based promoter operably linked to a gene such that the modified TATA box-based promoter lacks a functional TATA box and permits selective expression of the gene in a hyperproliferative and/or non-growth arrested cell and/or modifying a viral CAAT box-based promoter operably linked to a gene such that the modified CAAT box-based promoter lacks a functional CAAT box and permits selective expression of the gene in a hyperproliferative and/or non-growth arrested cell.

[0037] In another example, the present disclosure provides an isolated nucleic acid comprising a nucleotide sequence of SEQ ID NO: 3, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, or SEQ ID NO: 23**,** or a sequence having 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%

sequence identity to SEQ ID NO: 3, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, or SEQ ID NO: 23. In certain examples, the isolated nucleic acid comprises the nucleotide sequence of SEQ ID NO: 4. The present disclosure provides host cells comprising one or more of the foregoing nucleic acids.

[0038] In another example, the present disclosure provides a method of producing a recombinant virus. The method comprises: (a) growing one or more of the foregoing host cells under conditions so that the host cell produces the recombinant virus; and (b) purifying the recombinant virus.

[0039] These and other examples and advantages of the invention are illustrated by the following figures, detailed description and claims.

DESCRIPTION OF THE DRAWINGS

[0040] The invention can be more completely understood with reference to the following drawings.

[0041] **FIG. 1A** depicts the nucleotide sequence of the 5' end of Ad-Δ350 (which includes deletions of both the TATA box and the CAAT box) up to the start codon of the E1a gene. The site of the 200 nucleotide deletion from the wild-type adenoviral sequence is denoted with a hyphen. **FIG. 1B** depicts the nucleotide sequence of the 5' end of Ad-TATA up to the start codon of the E1a gene. The site of the 8 nucleotide deletion from the wild-type adenoviral sequence is denoted with a hyphen. **FIG. 1C** depicts the nucleotide sequence of the 5' end of Ad-CAAT up to the start codon of the E1a gene. The site of the 9 nucleotide deletion from the wild-type adenoviral sequence is denoted with a hyphen. **FIG. 1D** depicts the nucleotide sequence of the 5' end of Ad-CAAT-TATA up to the start codon of the E1a gene. The site of the 9 nucleotide and 8 nucleotide deletions from the wild-type adenoviral sequence are denoted with hyphens. **FIG. 1E** depicts the nucleotide sequence of the 5' end of Ad-CAAT-mTATA up to the start codon of the E1a gene. The site of the 9 nucleotide and 4 nucleotide deletions from the wild-type adenoviral sequence are denoted with hyphens. **FIG. 1F** depicts the nucleotide sequence of the 5' end of wild-type Ad5 up to the start codon of the E1a gene. The CAAT box (GGTCAAAGT) and TATA box (TATTTATA) are indicated with boxes.

[0042] **FIG. 2A** depicts a Western blot showing E1a expression levels in cancerous Panc-1 cells at the indicated hours following infection with Ad-Δ350 or Ad-TAV-255. **FIG. 2B** depicts

What is claimed is:

1. A recombinant virus comprising: (i) a modified TATA box-based promoter operably linked to a gene, wherein the modified TATA box-based promoter lacks a functional TATA box and permits selective expression of the gene in a hyperproliferative cell; and/or (ii) a modified CAAT box-based promoter operably linked to a gene, wherein the modified CAAT box-based promoter lacks a functional CAAT box and permits selective expression of the gene in a hyperproliferative cell.

2. The recombinant virus of claim 1, wherein the recombinant virus is selected from a recombinant vaccinia virus, adenovirus, adeno-associated virus (AAV), herpes simplex virus 1 (HSV1), myxoma virus, reovirus, poliovirus, vesicular stomatitis virus (VSV), measles virus (MV), and Newcastle disease virus (NDV).

3. The recombinant virus of claim 2, wherein the recombinant virus is a recombinant adenovirus.

4. The recombinant virus of claim 3, wherein the recombinant virus is selected from a type 5 adenovirus and a type 35 adenovirus.

5. The recombinant virus of any one of claims 1-4, wherein the modified TATA box-based promoter is an early gene promoter.

6. The recombinant virus of claim 5, wherein the modified TATA box-based promoter is an E1a promoter, E1b promoter, or E4 promoter.

7. The recombinant virus of any one of claims 1-6, wherein the modification included in the modified TATA box-based promoter comprises a deletion of the entire TATA box.

8. The recombinant virus of any one of claims 1-7, wherein the virus comprises a deletion of nucleotides corresponding to -27 to -24 of the E1a promoter.

9 The recombinant virus of claim 8, wherein the virus comprises a deletion of nucleotides corresponding to -31 to -24 of the E1a promoter.

10. The recombinant virus of claim 9, wherein the virus comprises a deletion of nucleotides corresponding to -44 to +54 of the E1a promoter.

11. The recombinant virus of claim 10, wherein the virus comprises a deletion of nucleotides corresponding to -146 to +54 of the E1a promoter.

12. The recombinant virus of any one of claims 1-11, wherein the virus comprises a deletion of nucleotides corresponding to 472 to 475 of the Ad5 genome (SEQ ID NO: 8).

13 The recombinant virus of claim 12, wherein the virus comprises a deletion of nucleotides corresponding to 468 to 475 of the Ad5 genome (SEQ ID NO: 8).

14 The recombinant virus of claim 13, wherein the virus comprises a deletion of nucleotides corresponding to 455 to 552 of the Ad5 genome (SEQ ID NO: 8).

15. The recombinant virus of claim 14, wherein the virus comprises a deletion of nucleotides corresponding to 353 to 552 of the Ad5 genome (SEQ ID NO: 8).

16. The recombinant virus of any one of claims 1-15, wherein the virus comprises a polynucleotide deletion that results in a virus comprising the sequence CTAGGACTG (SEQ ID NO: 7), AGTGCCCG (SEQ ID NO: 12) and/or TATTCCCG (SEQ ID NO: 13).

17. The recombinant virus of any one of claims 1-16, wherein the modified CAAT box-based promoter is an early gene promoter.

18. The recombinant virus of claim 17, wherein the modified CAAT box-based promoter is an E1a promoter, E1b promoter, or E4 promoter.

19. The recombinant virus of any one of claims 1-18, wherein the modification included in the modified CAAT box-based promoter comprises a deletion of the entire CAAT box.

20. The recombinant virus of any one of claims 1-19, wherein the virus comprises a deletion of nucleotides corresponding to -76 to -68 of the E1a promoter.

21. The recombinant virus of any one of claims 1-20, wherein the virus comprises a deletion of nucleotides corresponding to 423 to 431 of the Ad5 genome (SEQ ID NO: 8).

22. The recombinant virus of any one of claims 1-21, wherein the virus comprises a polynucleotide deletion that results in a virus comprising the sequence TTCCGTGGCG (SEQ ID NO: 14).

23. The recombinant virus of any one of claims 1-22, wherein the virus comprises a deletion of nucleotides corresponding to 477 to 484 of the Ad35 genome (SEQ ID NO: 24).

24. The recombinant virus of any one of claims 1-23, wherein the modification included in the modified TATA box-based promoter or CAAT box-based promoter does not comprise an addition of or a substitution with a separate, functional promoter sequence.

25. The recombinant virus of any one of claims 1-24, further comprising a nucleotide sequence encoding a therapeutic transgene.

26. The recombinant virus of claim 25, wherein the adenovirus comprises an E1b-19K and an E1b-55K start site, and wherein the nucleotide sequence encoding the therapeutic transgene is inserted between the start site of E1b-19K and the start site of E1b-55K.

27. The recombinant virus of any one of claims 1-26, wherein the recombinant virus selectively replicates in a hyperproliferative cell.

28. The recombinant virus of any one of claims 1-27, wherein the recombinant virus selectively has cytolytic activity in a hyperproliferative cell.

29. The recombinant virus of any one of claims 1-28, wherein the recombinant virus selectively expresses E1a and/or E1b in a hyperproliferative cell.

30. The recombinant virus of any one of claims 25-29, wherein the recombinant virus selectively expresses the therapeutic transgene in a hyperproliferative cell.

31. The recombinant virus of any one of claims 1-29, wherein the hyperproliferative cell is a cancer cell, endothelial cell, epidermal cell, fibroblast, and/or immune cell.

32. A pharmaceutical composition comprising the recombinant virus of any one of claims 1-31 and at least one pharmaceutically acceptable carrier or diluent.

33. A method of expressing a therapeutic transgene in a target cell comprising exposing the cell to an effective amount of the recombinant virus of any one of claims 25-31 to express the target transgene.

34. Use of a recombinant virus of any one of claims 1-31 in the manufacture of a medicament for treating cancer.

35. Use of a recombinant virus of any one of claims 1-31 in the manufacture of a medicament for treating hyperproliferative disease.

36. A method of engineering an oncolytic virus, the method comprising modifying a viral TATA box-based promoter operably linked to a gene such that the modified TATA box-based promoter lacks a functional TATA box and permits selective expression of the gene in a hyperproliferative cell and/or modifying a viral CAAT box-based promoter operably linked to a gene such that the modified CAAT box-based promoter lacks a functional CAAT box and permits selective expression of the gene in a hyperproliferative cell.

37. An isolated nucleic acid comprising a nucleotide sequence selected from SEQ ID NO: 3, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22 and SEQ ID NO: 23.

38. A recombinant virus of any one of claims 1-31 for use in treating cancer or hyperproliferative disease.