

WHAT IS CLAIMED IS:

1. A recombinant nucleic acid molecule comprising:
 - a negative strand nucleic acid molecule or a pgRNA nucleic acid molecule encoding a chemokine, a cytokine, an apoptosis inducing protein, diphtheria toxin A (or a fragment thereof), or any combination thereof, flanked by a first and second viral transcription recognition signal;
 - a first promoter upstream (5') of the first viral transcription recognition signal;
 - and
 - a second promoter adjacent and 5' to the negative strand nucleic acid molecule or pgRNA nucleic acid molecule encoding a chemokine, a cytokine, an apoptosis inducing protein, diphtheria toxin A (or a fragment thereof), or any combination thereof.
2. The recombinant nucleic acid molecule of claim 1, wherein the negative strand nucleic acid molecule is negative sense RNA, negative sense DNA, single or double strand DNA that expresses a non-coding, negative sense RNA, or any combination thereof.
3. The recombinant nucleic acid molecule of claim 1 or 2, wherein the first and second viral transcription recognition signal is selected from a virus selected from a negative strand virus, an RNA reverse transcribing virus, or a DNA reverse transcribing virus.
4. The recombinant nucleic acid molecule of any one of claims 1-3, further comprising a poly A tail downstream (3') of the negative strand nucleic acid molecule or pgRNA nucleic acid molecule encoding a chemokine, a cytokine, an apoptosis inducing protein, or combination thereof.
5. The recombinant nucleic acid molecule of any one of claims 1-4, wherein the apoptosis inducing protein is selected from the group consisting of BAX, BID, BAK, BAD, caspase 2, caspase 8, caspase 9, caspase 10, caspase 11, caspase 12, cytochrome C, SMAC, and apoptosis-inducing factor, or any combination thereof.

6. The recombinant nucleic acid molecule of any one of claims 1-5, wherein the first promoter comprises a strong ubiquitous promoter or a liver-tissue-specific promoter, selected from the group consisting of TBG (Thyroxine Binding Globulin), albumin promoter and/or enhancing element, AFP (alpha-fetoprotein) promoter, AAT (Alpha-1-antitrypsin) promoter, ApoE (Apolipoprotein E) promoter or PEPCK (Phosphoenolpyruvate carboxykinase) promoter.

7. The recombinant nucleic acid molecule of any one of claims 1-6, wherein the second promoter comprises elongation factor 1_{alpha} binding sequence (EFS).

8. The recombinant nucleic acid molecule of any one of claims 1-7, wherein the chemokine is selected from CCL1, CCL2, CCL3, CCL4, CCL5, CCL6, CCL7, CCL8, CCL9, CCL10, CCL11, CCL12, CCL13, CCL14, CCL15, CCL16, CCL17, CCL18, CCL19, CCL20, CCL21, CCL22, CCL23, CCL24, CCL25, CCL26, CCL27, CCL28, CXCL1, CXCL2, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL14, CXCL15, CXCL16, CXCL17, XCL1, XCL2, and CX3CL1.

9. The recombinant nucleic acid molecule of any one of claims 1-8, wherein the cytokine is selected from the group consisting of IL-15, IL-2, IL-8, IL-10, IL-12, IL-6, IFN- α , IFN- β , IFN- γ , TNF- α , CD40L, Mig, and Crg-2.

10. The recombinant nucleic acid molecule of claim 3, wherein the viral transcription recognition signal comprises epsilon recognition signal as set forth in SEQ ID NO:1 or a corona virus recognition sequence selected from the group consisting of: SEQ ID: 25, SEQ ID: 26, SEQ ID: 28, and SEQ ID: 30.

11. The recombinant nucleic acid molecule of claim 3, wherein the virus is corona virus, Hepatitis B virus, Hepatitis D virus, ebola virus, Marburg virus, human parainfluenza virus 1, measles virus, mumps virus, human respiratory syncytial virus, vesicular stomatitis Indiana virus, rabies virus, bovine ephemeral fever virus, lymphocytic choriomeningitis virus, Bunyamwera virus, Hantaan virus, Nairobi sheep disease virus, sandfly fever Sicilian virus,

influenza virus A, influenza virus C, Thogoto virus, mouse mammary tumor virus, murine leukemia virus, avian leukosis virus, Mason-Pfizer monkey virus, bovine leukemia virus, human immunodeficiency virus 1, human spumavirus, duck hepatitis B virus, coronavirus, and any combination thereof.

~~12. The recombinant nucleic acid molecule of any one of claims 1-11, wherein the nucleic acid molecule does not comprise sequences (coding or noncoding) for viral polymerase, reverse transcriptase, capsid, envelope, a packaging signal, or a translocation motif.~~

~~13.~~12. A vector comprising the recombinant nucleic acid sequence of any one of claims 1-~~12~~11.

~~14.~~13. The vector of claim ~~13~~12, wherein the vector comprises a delivery vector or vehicle for delivery to a mammalian cell.

~~15.~~14. The delivery vector or vehicle of claim ~~14~~13, wherein the vector or vehicle comprises a VLP, an adeno-associated virus (AAV), a liposome, a nanoparticle, a micelle, a polymeric vesicle, or a polymersome.

~~16.~~15. A pharmaceutical composition comprising any one of the recombinant nucleic acid sequences of any one of claims 1-~~12~~11 or ~~any one of the~~ vectors of any one of claims ~~13-15~~12-14.

~~17.~~16. A replication incompetent virus-like particle (VLP) comprising:

an optional translocation motif (TLM) fused to a capsid protein from a hepatitis B viral capsid or a hepatitis D viral capsid or coronavirus fusion protein; and

a negative strand nucleic acid molecule or a pgRNA nucleic acid molecule encoding a chemokine, a cytokine, a apoptosis inducing protein, diphtheria toxin A (or a fragment thereof), or any combination thereof, flanked by a first and second viral transcription recognition signal;

a first promoter upstream (5') of the first viral transcription recognition signal;
and

a second promoter adjacent and 5' to the negative strand nucleic acid molecule or pgRNA nucleic acid molecule encoding a chemokine, a cytokine, a apoptosis inducing protein, diphtheria toxin A (or a fragment thereof), or any combination thereof.

~~18.~~ 17. A replication incompetent virus-like particle (VLP) comprising:

a negative strand nucleic acid molecule or a pgRNA nucleic acid molecule encoding a chemokine, a cytokine, a apoptosis inducing protein, diphtheria toxin A (or a fragment thereof), or any combination thereof, flanked by a first and second target viral transcription recognition signal;

a first promoter upstream (5') of the first viral transcription recognition signal;
and

a second promoter adjacent and 5' to the negative strand nucleic acid molecule or pgRNA nucleic acid molecule encoding a chemokine, a cytokine, a apoptosis inducing protein, diphtheria toxin A (or a fragment thereof), or any combination thereof, wherein the VLP exhibits tropism for the target virally infected cells.

~~19. The replication incompetent virus like particle of claim 17 or 18, wherein the negative strand nucleic acid molecule is negative sense RNA, negative sense DNA, single or double strand DNA that expresses a non coding, negative sense RNA, or any combination thereof.~~

~~20. The replication incompetent virus like particle of any one of claims 17-19, further comprising a poly A tail downstream (3') of the negative strand nucleic acid molecule or pgRNA nucleic acid molecule encoding a chemokine, a cytokine, a apoptosis inducing protein, or combination thereof.~~

~~21. The replication incompetent virus like particle of any one of claims 17-20, wherein the first promoter comprises a strong ubiquitous promoter or a liver tissue specific promoter selected from the group consisting of TBG (Thyroxine Binding Globulin), albumin promoter and/or enhancing element, AFP (alpha fetoprotein) promoter, AAT (Alpha 1 antitrypsin) promoter, ApoE (Apolipoprotein E) promoter or PEPCK (Phosphoenolpyruvate carboxykinase) promoter.~~

22. — ~~The replication incompetent virus like particle of any one of claims 17-21, wherein the second promoter comprises elongation factor 1alpha binding sequence (EFS).~~

23. — ~~The replication incompetent virus like particle of any one of claims 17-22 wherein the viral transcription recognition signal is selected from a virus selected from a negative strand virus, an RNA reverse transcribing virus, or a DNA reverse transcribing virus.~~

24. — ~~The replication incompetent virus like particle of claim 23, wherein the viral transcription recognition signal comprises the epsilon recognition signal (SEQ ID NO:1) or a viral recognition sequence of a coronavirus, such as SEQ ID: 25 or SEQ ID: 26.~~

25. — ~~The replication incompetent virus like particle of any one of claims 17-24, wherein the apoptosis inducing protein is selected from the group consisting of BAX, BID, BAK, BAD, caspase 2, caspase 8, caspase 9, caspase 10, caspase 11, caspase 12, cytochrome C, SMAC, and apoptosis inducing factor.~~

26. — ~~The replication incompetent virus like particle of any one of claims 17-25, wherein the chemokine is selected from CCL1, CCL2, CCL3, CCL4, CCL5, CCL6, CCL7, CCL8, CCL9, CCL10, CCL11, CCL12, CCL13, CCL14, CCL15, CCL16, CCL17, CCL18, CCL19, CCL20, CCL21, CCL22, CCL23, CCL24, CCL25, CCL26, CCL27, CCL28, CXCL1, CXCL2, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL14, CXCL15, CXCL16, CXCL17, XCL1, XCL2, and CX3CL1.~~

27. — ~~The replication incompetent virus like particle of any one of claims 17-26, wherein the cytokine is selected from the group consisting of IL-15, IL-2, IL-8, IL-10, IL-12, IL-6, IFN- α , IFN- β , IFN- γ , TNF- α , CD40L, Mig, and Crg-2.~~

28. — ~~The replication incompetent virus like particle of any one of claims 17-27, wherein the virus is coronavirus, Hepatitis B virus, Hepatitis D virus, ebola virus, Marburg virus, human parainfluenza virus 1, measles virus, mumps virus, human respiratory syncytial virus, vesicular stomatitis Indiana virus, rabies virus, bovine ephemeral fever virus, lymphocytic~~

~~choriomeningitis virus, Bunyamwera virus, Hantaan virus, Nairobi sheep disease virus, sandfly fever Sicilian virus, influenza virus A, influenza virus B, influenza virus C, Thogoto virus, mouse mammary tumor virus, murine leukernia virus, avian leukosis virus, Mason Pfizer monkey virus, bovine leukemia virus, human immunodeficiency virus 1, human spumavirus, duck hepatitis B virus, coronavirus, and any combination thereof.~~

~~29. The replication incompetent virus like particle of any one of claims 17-28, wherein the nucleic acid molecule does not comprise sequences (coding or noncoding) for viral capsid, polymerase, reverse transcriptase, envelope, packaging signal, or translocation motifs.~~

~~30.18. A pharmaceutical composition comprising the replication incompetent virus-like particle of any one of claims 17-29~~16 or 17.

~~31.19. A method of treating a viral infection in a subject in need thereof, the method comprising administering to the subject~~Use of at the recombinant nucleic acid molecule of any one of claims ~~1-12~~11, ~~or the vector of any one of claims 13-15~~12-14, the pharmaceutical compositions of claims 1615 or 3018, or the replication incompetent virus-like particle of ~~any one of claims 17-29~~16 or 17 in the preparation of a medicament for treating a viral infection in a subject in need thereof.

~~32. The method of claim 31,~~ wherein the viral infection comprises:
an infection from a virus classified under Baltimore Classification IV, V, VI, or VII;

~~33. The method of claim 32, wherein the viral infection comprises~~
an infection from a virus selected from the group consisting of coronavirus, Hepatitis B virus, Hepatitis D virus, ebola virus, Marburg virus, human parainfluenza virus 1, measles virus, mumps virus, human respiratory syncytial virus, vesicular stomatitis Indiana virus, rabies virus, bovine ephemeral fever virus, lymphocytic choriomeningitis virus, Bunyamwera virus, Hantaan virus, Nairobi sheep disease virus, sandfly fever Sicilian virus, influenza virus A, influenza virus C, Thogoto virus, mouse mammary tumor virus, murine leukernia virus, avian leukosis virus,

Mason-Pfizer monkey virus, bovine leukemia virus, human immunodeficiency virus 1, human spumavirus, duck hepatitis B virus, and a combination thereof; or

34. ~~The method of claim 32, wherein the viral infection comprises~~
~~_____ an infection from a virus selected from the group consisting of filovirus, paramyxovirus, morbillivirus, rubulavirus, pneumovirus, vesiculovirus, lyssavirus, ephemerovirus, arenavirus, bunyavirus, hantavirus, nairovirus, phlebovirus, Orthohepadnavirus, Avihepadnavirus, Mammalian type B retroviruses, Mammalian type C retroviruses, Avian type C retroviruses, Type D retroviruses, BLV-HTLV retroviruses, Lentivirus, Spumavirus, and a combination thereof.~~

35. ~~The method of claim 31, wherein the nucleic acid molecule, vector, pharmaceutical composition, or replication incompetent virus like particle upon administration enters a liver cell.~~

36. ~~The method of claim 35, wherein the nucleic acid molecule, vector, pharmaceutical composition, or replication incompetent virus like particle upon administration delivers the nucleic acid molecule to a liver cell and the nucleic acid molecule is expressed in the liver cell.~~

37. ~~The method of any one of claims 31-36, wherein the subject has an acute, chronic, or latent viral infection.~~

38. ~~The method of any one of claims 31-37, wherein administration induces an immune response against a cell infected with the virus causing the viral infection.~~

39. ~~The method of any one of claims 31-38, wherein administration induces apoptosis in cells infected with the virus causing the viral infection.~~

40. ~~A method of inducing an immune response against a cell infected with a virus, in a subject in need thereof, the method comprising contacting the subject with the recombinant nucleic acid molecule of any one of claims 1-12, or the vector of any one of claims 13-15, or the~~

pharmaceutical compositions of claims 16 or 30, or the replication incompetent virus-like particle of any one of claims 17-29.

~~41.20. A method of inducing an apoptotic response against a cell infected with a virus, in a subject in need thereof, the method comprising contacting the subject with a pharmaceutical composition comprising~~ Use of the recombinant -nucleic acid molecule of any one of claims 1-1211, or the vector of any one of claims 13-1512-14, or the pharmaceutical compositions of claims 16 or 3015 or 18, or the replication incompetent virus-like particle of any one of claims 17-29 claim 16 or 17 in the preparation of a medicament for inducing an apoptotic response against a cell infected with a virus in a subject in need thereof.

~~42. The method of any one of claims 31-41, wherein the virus is coronavirus, influenza, HBV, HDV, hepatitis A virus (HAV), hepatitis C virus (HCV), or any combination thereof.~~

~~43.21. A method of treating a hepatitis B, influenza, or coronavirus infection in a subject, the method comprising administering to the subject a~~ Use of the recombinant nucleic acid molecule of any one of claims 1-1211, or the vector of any one of claims 13-1512-14, or the pharmaceutical compositions of claims 16 or 3015 or 18, or the replication incompetent virus-like particle of any one of claims 17-29 claim 16 or 17 in the preparation of a medicament for treating a hepatitis B, influenza, or coronavirus infection in a subject in need thereof.

~~44. The method of any one of claims 31-43, further comprising administering at least one antiviral agent, HBV polymerase inhibitor, interferon, TLR modulators such as TLR 7 agonists or TLR 9 agonists, therapeutic vaccines, immune activator of certain cellular viral RNA sensors, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, antiviral compounds of distinct or unknown mechanism, and any combination thereof.~~

~~45. The method of claim 44, further comprising administering at least one antiviral agent 3TC, FTC, L-FMAU, interferon, adefovir dipivoxil, entecavir, telbivudine (L-dT), valtorcitabine (3'-valinyl-L-dC), .beta.-D-dioxolanyl-guanine (DXG), .beta.-D-dioxolanyl-2,6-diaminopurine (DAPD), .beta.-D-dioxolanyl-6-chloropurine (ACP), famciclovir, penciclovir, lobucavir,~~

~~ganciclovir, ribavirin, tenofovir, bictegravir, emtricitabine, Biktarvy, and any combination thereof.~~

~~46. A method of inducing an apoptotic response against a cell infected with an influenza virus, in a subject in need thereof, the method comprising contacting the subject with the recombinant nucleic acid molecule of any one of claims 1-12, or the vector of any one of claims 13-15, or the pharmaceutical compositions of claims 16 or 30, or the replication incompetent virus-like particle of any one of claims 17-29.~~

~~47. The method of any one of claims 31-41, wherein the virus comprises influenza virus is influenza A, influenza B, influenza C, or any combination thereof.~~

~~48. A method of treating influenza in a subject, the method comprising administering to the subject a recombinant nucleic acid molecule of any one of claims 1-12, or the vector of any one of claims 13-15, or the pharmaceutical compositions of claims 16 or 30, or the replication incompetent virus-like particle of any one of claims 17-29.~~

~~49. The method of any one of claims 31-43, further comprising administering at least one antiviral agent 3TC, FTC, L-FMAU, interferon, adefovir dipivoxil, entecavir, telbivudine (L-dT), valtorcitabine (3'-valinyl-L-dC), .beta.-D-dioxolanyl-guanine (DXG), .beta.-D-dioxolanyl-2,6-diaminopurine (DAPD), .beta.-D-dioxolanyl-6-chloropurine (ACP), famciclovir, penciclovir, lobucavir, ganciclovir, ribavirin, tenofovir, bictegravir, emtricitabine, Biktarvy, and any combination thereof.~~

~~50. A method of inducing an apoptotic response against a cell infected with a coronavirus, in a subject in need thereof, the method comprising contacting the subject with the recombinant nucleic acid molecule of any one of claims 1-12, or the vector of any one of claims 13-15, or the pharmaceutical compositions of claims 16 or 30, or the replication incompetent virus-like particle of any one of claims 17-29.~~

51. — ~~A method of treating a coronavirus infection in a subject, the method comprising administering to the subject a recombinant nucleic acid molecule of any one of claims 1-12, or the vector of any one of claims 13-15, or the pharmaceutical compositions of claims 16 or 30, or the replication incompetent virus-like particle of any one of claims 17-29.~~

52. — ~~The method of any one of claims 31-51, wherein the treatment is administered periodically, including once every week, once every 2 weeks, once every 3 weeks, once a month, to once every two months, to once every 3 months, to once every 4 months, to once every 5 months, to once every 6 months, or once every 7 months, or once every 8 months, or once every 9 months, or once every 10 months, or every 11 months, or once annually as a maintenance treatment, or for as long as the patient requires to achieve stable or undetectable disease.~~