

CLAIMS

1. A chimeric protein construct comprising an endoplasmic reticulum-associated
5 degradation (ER-associated degradation, ERAD) mechanism protein binding domain and a targeting domain.
2. The chimeric protein construct of claim 1, wherein the ERAD mechanism protein binding domain comprises: a transmembrane domain of a viral endoplasmic reticulum resident protein or a functional variant thereof, and,
10 an endoplasmic reticulum resident domain or a functional variant thereof.
3. The chimeric protein construct of claim 1 ~~or 2~~, wherein the viral endoplasmic reticulum resident protein is adenovirus E3-19K.
4. The chimeric protein construct of claim 1 ~~or 2~~, wherein the viral endoplasmic reticulum resident protein is not adenovirus E3-19K.
- 15 5. The chimeric protein construct of claim 4, wherein the viral endoplasmic reticulum resident protein is selected from at least one of the group consisting of: HCMV glycoprotein US2, US11, US3, US10, US6, HSV ICP47, CPXV12, BHV UL49.5, EBV BNFL2a, HCMV UL16, UL141, UL142, HIV Nef, HIV Vpu, HHV-7 U21, HHV-8 KK3, HHV-8 KK5, MHV-68 MK3, HTLV-1 p12, Cowpox
20 Virus protein CPXV203.
6. The chimeric protein construct of ~~any one of the preceding claims~~ 1, further

comprising a protein degradation pathway member (e.g. E3 ubiquitin ligase, proteasome, lysosome) binding domain, and optionally, the protein degradation pathway member binding domain being linked to the ERAD mechanism protein binding domain.

5 7. The chimeric protein construct of ~~any one of the preceding claims~~ 1, wherein the targeting domain comprises an antibody specifically targeting a target protein or a functional fragment thereof (e.g., Fd, Fv, Fab, Fab', F(ab')₂, Fv(scFv), single chain antibody (scFv), nanobody, diabody, triabody or tetrabody).

8. The chimeric protein construct of claim 7, wherein the target protein is a
10 pathogenic protein, optionally, being a tumor-associated protein, a virus-associated protein, an immune function-related protein (including immunosuppressive and immune stimulatory proteins), an autoantigen protein, or a protein associated with neurodegenerative diseases.

~~9. The chimeric protein construct of claim 8, wherein the autoantigen protein is
15 selected from the group consisting of:~~

~~an autoantigen associated with type 1 diabete, e.g., an islet cell antigen (ICA), an insulin (IAA), a glutamine acid decarboxylase 65 (GAD65), an insulinoma antigen 2 (IA-2);~~

~~an autoantigen associated with rheumatoid arthritis (RA), e.g., a citrullinated
20 protein/peptide antibody, a heteroribonucleoprotein (heterogeneous nuclear ribonucleoprotein A2/B1), an aldolase, an alpha-enolase, a calreticulin, a heat-~~

~~activated protein (HSP60), BiP, PGK1, a stress-induced phosphoprotein 1, FUSE-BP1/2;—~~

~~an autoantigen associated with systemic lupus erythematosus (SLE), e.g., a deoxyribonucleoprotein, SmD1, SmD3, Clq, a sore anticoagulant (LA), cardiolipin (CL), β 2-glycoprotein I (β 2-GPI), a prothrombin (PT) and phosphatidylserine (PS);—~~

~~an autoantigen associated with systemic sclerosis (SSc)/scleroderma (SD), e.g., Scl-70, SSA, Ro52;—~~

~~an antigen associated with autoimmune liver diseases, e.g., mitochondrial antigen, Spl00, PML, gp210, p62;—~~

~~an autoantigen associated with myasthenia gravis, e.g., an acetylcholine receptor;—~~

~~an autoantigen associated with central nervous system autoimmune disease (limbic encephalitis, encephalomyelitis, cerebellar ataxia), e.g., voltage-gated potassium channels (VGKC) complex, voltage-gated calcium channel receptor, α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor, γ -aminobutyric Acid-B (GABAB) receptors, glycine receptors;—~~

~~an autoantigen associated with multiple sclerosis, e.g., a myelin basic protein (MBP), a myelin-oligodendrocyte glycoprotein (MOG);—~~

~~an autoantigen associated with polymyositis (PM) and dermatomyositis (DM), e.g., Jo-1, Mi-2, PM-Scl, Ro-52;—~~

~~an autoantigen associated with gluten-sensitive enteropathy, e.g., endomysial~~

~~antibody (EMA), tissue transglutaminase (tTG);—~~

~~an autoantigen associated with anti-NMDAR antibody encephalitis, e.g., N-methyl-D-aspartate receptor;—~~

~~an autoantigen associated with neuromyelitis optica (NMO), e.g., aquaporin 4 (AQP4); and,~~

~~an autoantigen associated with reproduction, e.g., ovarian antigen, sperm antigen.~~

~~10. The chimeric protein construct of claim 9, wherein the tumor-associated protein is encoded by an oncogene selected from the group consisting of: BCL-~~

~~2, c-MYC, Ras, HER2, BCR/ABL, ABL1/BCR, TGFB1, TLX1, P53, WNT1,~~

~~10 WNT2, WT1, α v β 3, PKCa, ABL, BCL1, CD24, CDK4, EGFR/ERBB-1,~~

~~HSTF1, INT1/WNT1, INT2, MDM2, MET, MYB, MYC, MYCN, MYCL1,~~

~~RAFI, NRAS, REL, AKT2, APC, BCL2-ALPHA, BCL2-BETA, BCL3, BCR,~~

~~BRCA1, BRCA2, CBL, CCND1, CDKN1A, CDKN1C, CDKN2A, CDKN2B,~~

~~CRK, CRK-II, CSF1R/FMS, DBL, DDOST, PMS-2, PRAD-1, RAF, RHOM-1,~~

~~15 RHOM-2, SIS, TAL2, TANI, TIAM1, TSC2, TRK, TSC1, STK11, PTCH,~~

~~MEN1, MEN2, P57/KIP2, PTEN, HPC1, ATM, XPA/XPG, BCL6, DEK,~~

~~AKAP13, CDH1, BLM, EWSR1/FLI1, FES, FGF3, FER, FGR, FLI1/ERGB2,~~

~~FOS, FPS/FES, FRA1, FRA2, FYN, HCK, HEK, HER3/ERBB-2, ERBB-3,~~

~~HER4/ERBB-4, HST2, INK4A, INK4B, JUN, JUNB, JUND, KIP2, KIT,~~

~~20 KRAS2A, KRAS2B, LCK, LYN, MAS, MAX, MCC, MLH1, MOS, MSH2,~~

~~MYBA, MYBB, NF1, NF2, P53, PDGFB, PIM1, PTC, RBI, RET, ROS1, SKI,~~

~~SRC1, TALI, TGFBR2, THRA1, THRB, TIAM1, TRK, VAV, VHL, WAF1, WNT2, WT1, YES1, ALK/NPM1, AMH1, AXL, FMS, GIP, GLI, GSP, HOX11, HST, IL3, INT2, KS3, K-SAM, LBC, DCC, DPC4/SMAD4, E-CAD, E2F1/RBAP, ELK1, ELK3, EPH, EPHA1, E2F1, EPHA3, ERG, ETS1, ETS2, LMO-1, LMO-2, L-MYC, LYL1, LYT-10, MDM-2, MLH1, MLL, MLM, N-MYC, OST, PAX-5, PMS-1, FGF4, FGF6, FANCA, FLI1/ERGB2, FOSL1, FOSL2, GLI, HRAS1, HRX/MLLT1, HRX/MLLT2, KRAS2, MADH4, MASI, MCF2, MLLT1/MLL, MLLT2/HRX, MTG8/RUNX1, MYCLK1, MYH11/CBFB, NFKB2, NOTCH1, NPM1/ALK, NRG/REL, NTRK1, PBX1/TCF3, PML/RARA, PRCA1, RUNX1, RUNX1/CBFA2T1, SET, SHP2, TCF3/PBX1, TNF α , Clusterin, Survivin, TOE β , c-fos, c-SRC, Estrogen receptor gene (estrogen receptor ER- α), androgen receptor gene (Androgen receptor, AR) and INT-1, optionally, the tumor associated protein is selected from the group consisting of: Bel-2 family members (such as: Bel-2, Bel-xL and Bel-w), VEGF/VEGFR, PDGFR β , EGFR, EGFR mutants, IGF-1R, HDACs, HER2, MYC, KRAS, AFP, CEA, CA199, estrogen receptor (estrogen receptor ER- α), androgen receptor (androgen receptor, AR), tyrosine kinases (c-ABL, BCR-ABL, BTK, FAK, PTK6, Wee1, TRK transmembrane receptors), serine/threonine kinase receptors (IRAK4, LRRK2, B-Raf, RIPK2, CDK4/6, CDK7, CDK8, CDK8/19, CDK9, TBK1), protein kinase II (CK2), epigenetic related proteins (BRD2, BRD3, BRD4, BRDT, TRIM24, BRD9, PBRM1, SMARCA2,~~

SMARCA4, EP300, EZH2, WDR5), adrenomedullin (ADM), DPP3.

~~11. The chimeric protein construct of claim 8, wherein the pathogenic protein is a virus-associated protein selected from the group consisting of: HBV surface antigen, HBV capsid glycoprotein, HBeAg, HBV DNA polymerase, HBV encoded X protein (HBx), HIV Gag protein, HIV Env protein, HIV gp120, HIV reverse transcriptase, HIV gp120, HCV NS3-4A protease, HCV RNA polymerase, HCV envelope protein, EBV DNA polymerase, EBV EBNA1, coronavirus RNA synthetase, coronavirus spike protein, coronavirus envelope protein, coronavirus membrane protein, coronavirus nucleocapsid protein, RNA-dependent RNA polymerase (RdRp), such as the novel coronavirus RNA dependent RNA polymerase, Herpesviruses DNA and RNA polymerase, Herpesvirus capsid glycoprotein, CMV DNA polymerase, CMV capsid glycoprotein, RSV envelope protein, RSV capsid protein, RSV RNA polymerase, influenza virus RNA polymerase, influenza virus envelope protein, HPV DNA polymerase, and HPV capsid protein.~~

~~12~~⁹. The chimeric protein construct of claim 7, wherein the target protein is an immune function-related protein selected from the group consisting of: an antigen-presenting molecule (e.g., a MHC class I molecule, a MHC class II molecule, a MICA/B molecule, etc.), an antigen recognition molecule (e.g., TCR, CD123, NKG2D, etc.), an immune checkpoint molecule (e.g., PD-1, PD-L1, CTLA4, TIM3, TIGIT, LAG3, A2AR, BTLA, IDO1, IDO2, TDO, KIR, NOX2,

VISTA, SIGLEC7, PVR, etc.), an immune stimulatory/co-stimulatory molecule (e.g., CD3, CD80/86, CD28, etc.).

~~13. The chimeric protein construct of claim 7, wherein the target protein is a target protein related to nervous system diseases, and is selected from the group consisting of: Tau, β amyloid protein (amyloid β ($A\beta$)), α synuclein, mutant huntingtin (mHTT), α synuclein, TAR RNA binding protein (TARDBP) and FUS RNA binding protein (FUS).~~

~~14~~10. The chimeric protein construct of claim 2, ~~4 or 5~~, wherein the targeting domain does not specifically binding TCR.

~~15~~11. The chimeric protein construct of claim ~~14~~10, wherein the targeting domain specifically binds MHC I, MHC II, MICA, MICB, ULBP1, ULBP2, ULBP3, ULBP4, ULBP5 and/or ULBP6; and wherein preferably, MHC I is HLA I; and wherein, preferably, MHC II is HLA II.

~~16~~12. The chimeric protein construct of claim 4, wherein the targeting domain specifically binds a TCR.

~~17~~13. The chimeric protein construct of claim ~~16~~12, wherein the virus endoplasmic reticulum resident protein is selected from at least one of the group consisting of: HCMV glycoprotein US2, US11, US3, US10, US6, HSV ICP47, CPXV12, BHV UL49.5, EBV BNFL2a, HCMV UL16, UL141, UL142, HIV Nef, HIV Vpu, HHV-7 U21, HHV-8 KK3, HHV-8 KK5, MHV-68 MK3, HTLV-1 p12, and Cowpox Virus protein CPXV203.

~~18~~14. The chimeric protein construct of ~~any one of the preceding~~ claims 1, which is linked to at least one co-expression moiety.

~~19~~15. The chimeric protein construct of claim ~~18~~14, wherein the at least one co-expression moiety is independently selected from the group consisting of: an
 5 intact viral ER resident glycoprotein (e.g., HCMV US2, US3, US11, US10, adenovirus E3-K1 9, HCMV US6, HSV ICP47), a chimeric antigen receptor (CAR), a functional T cell receptor (TCR), a chemokine receptor, or a NK-cell-activating receptor.

~~20~~16. The chimeric protein construct of claim ~~19~~15, wherein the chemokine
 10 receptor is selected from the group consisting of: CCR4, CCR5, CCR6, CCR7, CCR9, CCR2b, CXCR1, CXCR2, and CXCR4.

~~24~~17. The chimeric protein construct of claim ~~20~~16, wherein the NK-cell-activating receptor comprises: (a) an extracellular domain (ED) of the NK-cell-activating receptor or a functional variant thereof, (b) a transmembrane domain
 15 (TMD) of the NK-cell-activating receptor or a functional variant thereof, and (c) an intracellular domain (ICD) of the NK-cell-activating receptor or a functional variant thereof; and wherein, optionally, a hinge or linker is included among the extracellular domain of the NK-cell-activating receptor or a functional variant thereof, the transmembrane domain of NK-cell-activating receptor or a
 20 functional variant thereof, and/or the intracellular domain of the NK-cell-activating receptor or a functional variant thereof.

~~22~~18. The chimeric protein construct of claim ~~21~~17, wherein the NK-cell-activating receptor is selected from the group consisting of NKG2D, NKG2C, NKG2E, NKG2F, NKG2H, CD94, KIR2DL4, KIR2DS1, KIR2DS2, KIR2DS4, KIR3DS1, a natural cytotoxic receptor, TRAIL, DNAM-1, CD16a, 2B4, NTB-A, CRACC, and NKp80.

~~23~~19. The chimeric protein construct of claim ~~21 or 22~~17, wherein the NK-cell-activating receptor is complexed with a CNK signal transduction module.

~~24~~20. The chimeric protein construct of ~~any one of claims 18-23~~14, wherein the at least one co-expression moiety is linked to the chimeric protein construct by a cleavable linker.

~~25~~21. A nucleic acid molecule encoding the chimeric protein construct of ~~any one of claims 1-24~~.

~~26. The nucleic acid molecule of claim 25, wherein the nucleic acid molecule is deoxyribonucleic acid (DNA), ribonucleic acid (RNA) (for example, mRNA, circular RNA, ccRNA), threose nucleic acid (TNA), glycol nucleic acid (GNA), peptide nucleic acid (PNA), locked nucleic acid (LNA, including LNA with β -D-ribose configuration, α -LNA with α -L-ribose configuration (diastereoisomers of LNA), 2' amino-LNA with 2' amino-functionalization and 2' amino- α -LNA with 2' amino-functionalization), ethylene nucleic acid (ENA), cyclohexenyl nucleic acid (CeNA), and/or chimeras and/or combinations thereof.~~

~~27~~22. A vector comprising the nucleic acid molecule of claim ~~25 or 26~~21, wherein

the nucleic acid molecule is operably linked to at least one polynucleotide regulatory element to express a chimeric protein construct encoded by the nucleic acid molecule.

~~28. The vector of claim 27, wherein the vector is selected from the group consisting of: a plasmid, a nanoplasmid, a cosmid, a viral vector (e.g., an oncolytic viral vector), a minicircle, a RNA vector, or a linear or circular DNA (e.g., a transposon DNA) or RNA molecule.~~

~~29. The vector of claim 28, wherein the vector is a viral vector selected from the group consisting of retrovirus, lentiviral vector, adenovirus, parvovirus (e.g., adeno-associated virus), adeno-associated virus (AAV) vector, coronavirus, negative-strand RNA virus such as orthomyxovirus (e.g., influenza virus), rhabdovirus (e.g., rabies and vesicular stomatitis viruses), paramyxovirus (e.g., Machi and Sendai), positive-strand RNA Virus such as picornavirus and alphavirus, and double-stranded DNA virus, wherein the double-stranded DNA virus comprises adenovirus, herpesvirus (e.g., herpes simplex viruses I and II, Epstein Barr virus, cytomegalovirus) and pox virus (e.g., vaccinia, fowlpox, and canarypox), Norwalk, togavirus, flavivirus, reovirus, papovavirus, hepadnavirus, baculovirus, and hepatitis virus, virus-like particle (VLP).~~

~~30. The vector of claim 29, wherein the viral vector is a retroviral vector.~~

~~31. The vector of claim 30, wherein the retroviral vector is selected from the group consisting of: avian leukoproliferative sarcoma, mammalian C-type, B-~~

~~type virus, D-type virus, HTLV-BLV collection, lentivirus, bubble virus.~~

~~32. The vector of claim 29, wherein the viral vector is a lentiviral vector.~~

~~33. The vector of claim 32, wherein the lentiviral vector is selected from the group consisting of HIV-1, HIV-2, SIV, FIV, BIV, EIAV, CAEV or ovine demyelinating leukoencephalitis lentivirus.~~

~~34. The vector of any one of claims 27-33, wherein the vector is further combined with other vectors comprising other nucleic acid molecules encoding at least one co-expression moiety.~~

~~35~~23. An engineered cell expressing the chimeric protein construct of ~~any one of~~ claims ~~1-25~~, or comprising the nucleic acid molecule of claim ~~26~~21, or comprising the vector of ~~any one of~~ claims ~~27-33~~22.

~~36. The engineered cell of claim 35 expressing the chimeric protein construct of any one of claims 1-18, and a co-expression moiety.~~

~~37~~24. The engineered cell of claim ~~35 or 36~~23, wherein the cell is an immune cell selected from the group consisting of: a T cell, a natural killer (NK) cell, a B cell, a macrophage, a monocyte, a dendrites cell, a neutrophil, or a $\gamma\delta$ T cell.

~~38. The engineered cell of claim 37, wherein the T cell is selected from the group consisting of: CD8+ T cell, CD4+ T cell, cytotoxic T cell, terminal effector T cell, memory T cell, naive T cell, cell group composed of regulatory T cell, natural killer T cell, gamma delta T cell, cytokine induced killer (CIK) T cell, and tumor infiltrating lymphocyte.~~

~~39. A method for producing the engineered cell of any one of claims 35-38, comprising introducing the vector of any one of claims 27 to 34 into a starting cell, under a condition suitable for expressing the nucleic acid molecule of claim 25 or 26.~~

5 ~~40. The method of claim 39, wherein the starting cell is a stem cell or a cell differentiated from a stem cell.~~

~~41. The method of claim 38, wherein the stem cell is a hematopoietic progenitor cell (e.g. T cell progenitor, NK cell progenitor, macrophage progenitor), a hematopoietic stem cell (HSC), a CD34⁺ cell, an embryonic cell line, a~~
10 ~~mesenchymal stem cell or an iPSC cell.~~

~~42. The method of claim 37, wherein the cell is an immune cell.~~

~~43. The method of claim 40, wherein the immune cell is a T cell, a natural killer (NK) cell, a B cell, a macrophage, a monocyte, or a dendritic cell.~~

~~44. The method of claim 41, wherein the cell is a T cell selected from the group consisting of: a CD4⁺ T cell, a CD8⁺ T cell, a cytotoxic T cell, a terminal effector T cell, a memory T cell, a naive T cell, cells composed of regulatory T cells, a~~
15 ~~natural killer T cell, a gamma-delta T cell, a cytokine-induced killer (CIK) T cell, and a tumor-infiltrating lymphocyte.~~

~~45. A cell population produced ex vivo by the method of any one of claims 39-44.~~

20 ~~46~~25. A pharmaceutical composition or kit, comprising:

(i) the chimeric protein construct of ~~any one of claims 1-24~~, or the nucleic acid molecule of claim ~~25 or 26~~21, or the vector of ~~any one of claim s 27-34~~22, or the engineered cell of ~~any one of claims 35-38~~23 ~~or the cell population of claim 45~~, and

(ii) pharmaceutically acceptable medium.

5 ~~47. A method for degrading a target protein, comprising delivery of the vector of any one of claims 27-34 into a cell expressing the target protein.~~

~~48. The method of claim 47, wherein the cell is selected from the group consisting of: a tumor cell, a virus-infected cell, a neural cell, a transplanted cell, and an immune cell.~~

10 ~~49. The method of claim 47 or 48, wherein the delivery comprises delivery by a viral vector (e.g., an oncolytic virus).~~

~~50. The method of claim 49, wherein the vector expresses the chimeric protein construct of any one of claims 1-24 in the cell.~~

15 ~~51. The method of claim 50, wherein the chimeric protein construct is capable of simultaneously binding a target protein and an ERAD mechanism protein, thereby degrading the target protein.~~

~~52. A method of treating a condition or disease in a subject in need thereof, comprising:~~

~~administering a therapeutically effective amount of the pharmaceutical composition of claim 46 to the subject.~~

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~~53. The method of claim 52, wherein the disease comprises various solid tumors~~

- and hematological tumors, viral infectious diseases, autoimmune diseases, and neurological and degenerative diseases (e.g., Alzheimer's disease), metabolic diseases (e.g., diabetes (e.g., type II diabete), lipid metabolism-related diseases (e.g., tumor lipid metabolism, non-alcoholic fatty liver), atherosclerosis (AS),
- 5 tumor glucose metabolism);
- preferably, the solid tumor is selected from the group consisting of nervous system tumors, head and neck tumors, chest tumors, digestive system tumors, genitourinary system tumors, soft tissue and skin tumors, bone tumors, etc.;
- preferably, the nervous system tumors comprise diffuse glioma, diffuse
- 10 astrocytoma and anaplastic astrocytoma, glioblastoma, oligodendroglioma, oligoastrocytoma, diffuse Gliomas, other astrocytomas, ependymomas, neuronal and mixed neuronal glial tumors, medulloblastoma, other embryonal tumors, schwannomas, meningiomas, solitary fibrous tumors and hemangiopericytoma, etc.;
- 15 preferably, the head and neck tumors comprise malignant tumors of the nasal cavity and sinuses, nasopharyngeal cancer, oral cancer, laryngeal cancer, salivary gland tumors, intracranial tumors, thyroid cancer, tongue cancer, etc.;
- preferably, the thoracic tumors comprise lung cancer, esophageal cancer, cardia cancer, breast cancer, mediastinal tumors, etc.;
- 20 preferably, the digestive system tumors comprise gastric cancer, colorectal cancer, sigmoid colon and rectal cancer, liver cancer, pancreatic cancer and

~~periampullary cancer, biliary tract cancer, malignant tumors of the small intestine, etc.;~~

~~preferably, the genitourinary system tumors comprise kidney cancer, prostate cancer, bladder cancer, testicular cancer, penile cancer, cervical cancer, endometrial cancer, ovarian cancer, etc.;~~

~~preferably, the soft tissue and skin tumors comprise malignant fibrous histiocytoma, rhabdomyosarcoma, synovial sarcoma, malignant melanoma of the skin, etc.;~~

~~preferably, the bone tumors comprise osteosarcoma, Ewing's sarcoma, etc.;~~

~~preferably, the colon cancer is colon adenoma;~~

~~preferably, the breast cancer is a triple-negative breast cancer cell;~~

~~preferably, the liver cancer is hepatocellular carcinoma;~~

~~preferably, the disease is a hematological tumor selected from the group consisting of leukemia, lymphoma (HL), multiple myeloma (MM), myelodysplastic syndrome (MDS), etc.;~~

~~preferably, the leukemia is B-cell acute lymphoblastic leukemia, T-cell acute lymphoblastic leukemia, acute myeloid leukemia, etc.;~~

~~preferably, viral infectious diseases comprise: respiratory viral diseases, gastrointestinal viral diseases, liver viral diseases, skin and mucous membrane viral diseases, ocular viral diseases, central nervous system viral diseases, lymphocytic viral diseases, insect-borne viral diseases, lentivirus infection~~

diseases, etc.;

preferably, the respiratory viral diseases comprise infections of rhinovirus, adenovirus, respiratory syncytial virus, parainfluenza virus, and coronavirus; influenza; mumps, etc.;

5 preferably, the gastrointestinal viral diseases comprise polio; coxsackie virus infection; ECHO virus infection; and viral gastroenteritis including rotavirus gastroenteritis, Norwalk virus gastroenteritis, adenovirus gastroenteritis, astrovirus gastroenteritis, coronavirus gastroenteritis and calicivirus gastroenteritis, etc.;

10 preferably, the liver viral diseases comprise viral hepatitis A, viral hepatitis B, viral hepatitis C, viral hepatitis D, viral hepatitis E, Epstein-Barr viral hepatitis, and cytomegalovirus hepatitis, etc.;

preferably, the skin and mucous membrane viral diseases comprise measles, rubella, infantile acute rash, chickenpox and herpes zoster, smallpox, herpes

15 simplex virus infection, rabies and foot-and-mouth disease, etc.;

preferably, the ocular viral diseases comprise epidemic keratoconjunctivitis, follicular conjunctivitis and herpetic keratoconjunctivitis, etc.;

preferably, the central nervous system viral diseases comprise Japanese encephalitis, western equine encephalitis, eastern equine encephalitis, St. Louis

20 encephalitis, Venezuelan equine encephalitis, Murray Valley encephalitis, Californian encephalitis, forest encephalitis and lymphocytic choroid plexus

~~meningitis, etc.;~~

~~preferably, the lymphocytic viral diseases comprise infectious mononucleosis,~~

~~cytomegalovirus infection and acquired immunodeficiency syndrome, etc.;~~

~~preferably, the insect-borne viral diseases comprise viral hemorrhagic fevers~~

5 ~~including epidemic hemorrhagic fever, yellow fever, Crimean-Congo~~

~~hemorrhagic fever, Rift Valley fever, Argentine hemorrhagic fever, Bolivian~~

~~hemorrhagic fever, Lassa fever, Omu-Scrubs hemorrhagic fever, Marburg disease~~

~~and Ebola hemorrhagic fever, etc.; dengue fever and dengue hemorrhagic fever;~~

~~West Nile fever; Colorado tick heat transfer; and sandfly fever, etc.;~~

10 ~~preferably, the lentiviral infection diseases comprise subacute sclerosing~~

~~panencephalitis, Kuru disease, progressive multifocal leukoencephalopathy and~~

~~subacute spongiform encephalopathy (corticostriatal spinal-cord degeneration);~~

~~etc.;~~

~~preferably, the autoimmune diseases comprise organ-specific autoimmune~~

15 ~~diseases and systemic autoimmune diseases;~~

~~preferably, the organ-specific autoimmune diseases comprise chronic~~

~~lymphocytic thyroiditis, hyperthyroidism, insulin-dependent diabetes mellitus,~~

~~myasthenia gravis, ulcerative colitis, pernicious anemia with chronic atrophic~~

~~gastritis, pulmonary hemorrhage nephritic syndrome, vulgaris Pemphigus,~~

20 ~~pemphigoid, primary biliary cirrhosis, multiple sclerosis, acute idiopathic~~

~~polyneuritis, etc.;~~

preferably, the systemic autoimmune diseases comprise systemic lupus erythematosus, rheumatoid arthritis, systemic vasculitis, scleroderma, pemphigus, dermatomyositis, mixed connective tissue disease, autoimmune hemolytic anemia, thyroid autoimmune diseases, ulcerative colitis, etc.;

- 5 preferably, the neurological diseases comprise nervous system diseases, peripheral nerve diseases such as trigeminal neuralgia, facial paralysis, hemifacial spasm, vestibular neuronitis, glossopharyngeal neuralgia, mononeuritis, brachial plexus neuralgia, multiple mononeuropathy, multiple Neuropathy, acute inflammatory demyelinating polyneuropathy, chronic
- 10 inflammatory demyelinating polyneuropathy; spinal cord diseases, e.g., myelitis, compressive myelopathy, subacute combined degeneration of the spinal cord, syringomyelia, spinal cord vascular disease, spinal cord arachnoiditis, etc.; cerebrovascular diseases, e.g., transient ischemic attack, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, intracranial venous system
- 15 thrombosis, etc.; infectious diseases of the central nervous system, e.g., meningitis, encephalitis, etc. caused by infections of viruses, bacteria, fungi, or parasites, etc., and lentiviral encephalitis caused by lentiviral infections; central nervous system demyelinating diseases, e.g., multiple sclerosis, neuromyelitis optica, acute disseminated encephalomyelitis, leukodystrophy, etc.; movement
- 20 disorders, e.g., Parkinson's disease, chorea, hepatolenticular degeneration, dystonia, essential tremor, tardive dyskinesia, etc. Epilepsy; headaches such as

~~migraines, tension headaches, cluster headaches, etc.;~~

~~nervous system degenerative diseases, e.g., motor neuron disease, Alzheimer's disease, Lewy body dementia, frontotemporal dementia, multiple system atrophy,~~

~~etc.; inherited nervous system diseases, e.g., hereditary ataxia, hereditary spastic~~

5 ~~paraplegia, Charcot-Marie-Tooth disease, neurofibromatosis, tuberous sclerosis, cerebral hemangiomas, etc.;~~

~~neurodevelopmental disorders, e.g., congenital hydrocephalus, cerebral palsy,~~

~~basilar depression, cerebellar subtonsillar disease, etc.; neuromuscular junction~~

~~and muscle diseases, e.g., myasthenia gravis, periodic paralysis, polymyositis,~~

10 ~~progressive muscular dystrophy, myotonic myopathy (myotonic dystrophy, myotonia congenita), metabolic myopathy (mitochondrial myopathy, lipid storage myopathy, glycogenosis), etc.; autonomic nervous system diseases, e.g.,~~

~~Raynaud's disease, erythromelalgia, hemifacial atrophy, generalized autonomic~~

~~insufficiency, spontaneous hyperhidrosis, progressive lipodystrophy, etc.;~~

15 ~~nervous system tumors, e.g., glioma, lymphoma, meningioma, etc.;~~

~~paraneoplastic syndromes of the nervous system, e.g., paraneoplastic cerebellar~~

~~degeneration, paraneoplastic encephalomyelitis, subacute necrotizing~~

~~myelopathy, subacute motor neuron disease, paraneoplastic sensory neuron~~

~~disease, etc.;~~

20 ~~preferably, metabolic diseases comprise diabetes, hyperlipidemia, gout and the like.~~

~~54. A method of stimulating an immune response in a subject, said method comprises administering an effective amount of the pharmaceutical composition of claim 46 to the subject.~~