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(54) Title: REPLICATION-DEFICIENT ARENAVIRUS PARTICLES AND TRI-SEGMENTED ARENAVIRUS PARTICLES AS
CANCER VACCINES

(57) Abstract: The present application relates generally to genetically modified arenaviruses that are suitable vaccines against neoplastic diseases, such as cancer. The arenaviruses described herein may be suitable as vaccines and/or for treatment of neoplastic diseases and/or for the use in immunotherapies. In particular, provided herein are methods and compositions for treating a neoplastic disease by administering a genetically modified arenavirus in combination with a chemotherapeutic agent, wherein the arenavirus has been engineered to include a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof.



**REPLICATION-DEFICIENT ARENAVIRUS PARTICLES AND TRI-SEGMENTED
ARENAVIRUS PARTICLES AS CANCER VACCINES**

[0001] This application claims the priority of and the benefit of the filing date of U.S. Provisional Application No. 62/417,865, filed November 4, 2016, and U.S. Provisional Application No. 62/417,891, filed November 4, 2016, which are herein incorporated in their entireties.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[0002] This application incorporates by reference a Sequence Listing submitted with this application as text file entitled "13194-025-228_ST25.TXT" created on October 31, 2017 and having a size of 113 kilobytes.

1. INTRODUCTION

[0003] The present application relates generally to genetically modified arenaviruses that are suitable vaccines against neoplastic diseases, such as cancer. The arenaviruses described herein may be suitable as vaccines and/or for treatment of neoplastic diseases and/or for the use in immunotherapies. In particular, provided herein are methods and compositions for treating a neoplastic disease by administering a genetically modified arenavirus in combination with a chemotherapeutic agent, wherein the arenavirus has been engineered to include a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof.

2. BACKGROUND

[0004] The generation of recombinant negative-stranded RNA viruses expressing foreign genes of interest has been pursued for a long time. Different strategies have been published for other viruses (Garcia-Sastre *et al.*, 1994, J Virol 68(10): 6254-6261; Percy *et al.*, 1994, J Virol 68(7): 4486-4492; Flick and Hobom, 1999, Virology 262(1): 93-103; Machado *et al.*, 2003, Virology 313(1): 235-249). In the past it has been shown that it is possible to introduce additional foreign genes into the genome of bi-segmented LCMV particles (Emonet *et al.*, 2009, PNAS, 106(9):3473-3478). Two foreign genes of interest were inserted into the bi-segmented

genome of LCMV, resulting in tri-segmented LCMV particles (r3LCMV) with two S segments and one L segment. In the tri-segmented virus, published by Emonet *et al.*, (2009), both NP and GP were kept in their respective natural position in the S segment and thus were expressed under their natural promoters in the flanking UTR.

2.1 Replication-deficient Arenavirus Vectors Expressing Genes of Interest

[0005] The use of infectious, replication-deficient arenaviruses as vectors for the expression of antigens has been reported (see Flatz *et al.*, 2010, Nat. Med., 16(3):339-345; Flatz *et al.*, 2012, J. Virol., 86(15), 7760-7770). These infectious, replication-deficient arenaviruses can infect a host cell, *i.e.*, attach to a host cell and release their genetic material into the host cell. However, they are replication-deficient, *i.e.*, the arenavirus is unable to produce further infectious progeny particles in a non-complementing cell, due to a deletion or functional inactivation of an open reading frame (ORF) encoding a viral protein, such as the GP protein. Instead, the ORF is substituted with a nucleotide sequence of an antigen of interest. In Flatz *et al.* 2010, the authors used infectious, replication-deficient arenaviruses as vectors to express OVA (SIINFEKL epitope). In Flatz *et al.* 2012, the authors used replication deficient arenaviruses as vectors to express HIV/SIV Env.

2.2 Recombinant LCMV Expressing Genes of Interest

[0006] Recently, it has been shown that an infectious arenavirus particle can be engineered to contain a genome with the ability to amplify and express its genetic material in infected cells but unable to produce further progeny in normal, not genetically engineered cells (*i.e.*, an infectious, replication-deficient arenavirus particle) (International Publication No.: WO 2009/083210 A1 and International Publication No.: WO 2014/140301 A1).

[0007] Recently published International Publication No.: WO 2016/075250 A1 shows that arenavirus genomic segments may be engineered to form tri-segmented arenavirus particles with rearrangements of their open reading frames ("ORF"), wherein the arenavirus genomic segment carries a viral ORF in a position other than the wild-type position of the ORF, comprising one L segment and two S segments or two L segments and one S segment that do not recombine into a replication-competent bi-segmented arenavirus particle.

2.3 Cancer and Chemotherapy

[0008] Chemotherapeutics are widely used to treat cancer, and traditionally act in the direct killing of tumor cells, such as through interference with DNA synthesis and replication. However, chemotherapeutics also are known for their severe side effects and are not always efficacious. Better treatment options are needed to more effectively treat cancer.

1. SUMMARY OF THE INVENTION

[0008a] In a first aspect of the invention, there is provided use of an arenavirus particle or a pharmaceutical composition thereof for the manufacture of a medicament for the treatment of a neoplastic disease in a subject in combination with a chemotherapeutic agent, wherein the arenavirus particle is a tri-segmented arenavirus particle comprising one L segment and two S segments, and wherein the arenavirus particle is engineered to contain an arenavirus genomic segment comprising:

- (i) a nucleotide sequence encoding a human papillomavirus (HPV)-associated antigen or an antigenic fragment thereof; and
- (ii) at least one arenavirus open reading frame (“ORF”) in a position other than the wild-type position of the ORF, wherein the ORF encodes the glycoprotein (“GP”), the nucleoprotein (“NP”), the matrix protein Z (“Z protein”) or the RNA dependent RNA polymerase L (“L protein”) of the arenavirus particle.

[0008b] In a second aspect of the invention, there is provided a method for treating a neoplastic disease in a subject in need thereof, wherein the method comprises administering to the subject in need thereof an arenavirus particle or a pharmaceutical composition thereof, and a chemotherapeutic agent, wherein the arenavirus particle is a tri-segmented arenavirus particle comprising one L segment and two S segments, and wherein the arenavirus particle is engineered to contain an arenavirus genomic segment comprising:

- (i) a nucleotide sequence encoding a human papillomavirus (HPV)-associated antigen or an antigenic fragment thereof; and

- (ii) at least one arenavirus open reading frame (“ORF”) in a position other than the wild-type position of the ORF, wherein the ORF encodes the glycoprotein (“GP”), the nucleoprotein (“NP”), the matrix protein Z (“Z protein”) or the RNA dependent RNA polymerase L (“L protein”) of the arenavirus particle.

[0008c] In a third aspect of the invention, there is provided a kit comprising two or more containers and instructions for use, wherein one of the containers comprises an arenavirus particle or a pharmaceutical composition thereof and another of the containers comprises a chemotherapeutic agent, wherein the arenavirus particle is a tri-segmented arenavirus particle comprising one L segment and two S segments, and wherein the arenavirus particle is engineered to contain an arenavirus genomic segment comprising:

- (i) a nucleotide sequence encoding a human papillomavirus (HPV)-associated antigen or an antigenic fragment thereof; and
- (ii) at least one arenavirus open reading frame (“ORF”) in a position other than the wild-type position of the ORF, wherein the ORF encodes the glycoprotein (“GP”), the nucleoprotein (“NP”), the matrix protein Z (“Z protein”) or the RNA dependent RNA polymerase L (“L protein”) of the arenavirus particle.

[0008d] In a fourth aspect of the invention, there is provided use of the kit of the third aspect for the manufacture of a medicament for the treatment of a neoplastic disease in a subject.

[0008e] In a fifth aspect of the invention, there is provided a method for treating a neoplastic disease in a subject in need thereof, wherein the method comprises administering to the subject in need thereof the arenavirus particle or a pharmaceutical composition thereof and the chemotherapeutic agent of the kit of the third aspect.

[0008f] In a sixth aspect of the invention, there is provided a method for treating a human papillomavirus (HPV) induced cancer in a subject in need thereof, wherein the method comprises administering to the subject an arenavirus particle or a pharmaceutical composition thereof, and a chemotherapeutic agent, wherein the chemotherapeutic agent is a platinum-based chemotherapy, a taxane, or a combination thereof, wherein the arenavirus particle is derived from lymphocytic

choriomeningitis virus ("LCMV") or Pichinde virus ("PICV") and is a tri-segmented arenavirus particle comprising one L segment, a first S segment, and a second S segment, and wherein:

- (i) the first S segment comprises an open reading frame encoding the arenaviral glycoprotein GP in a position under control of a genomic 3' untranslated region and an open reading frame encoding a HPV E7 and E6 fusion protein in a position under control of a genomic 5' untranslated region;
- (ii) the second S segment comprises an open reading frame encoding the arenaviral nucleoprotein NP in a position under control of a genomic 3' untranslated region and an open reading frame encoding a HPV E7 and E6 fusion protein in a position under control of a genomic 5' untranslated region; and
- (iii) the L segment comprises an open reading frame encoding ribonucleic acid (RNA) dependent RNA polymerase L in a position under control of a genomic 3' untranslated region and an open reading frame encoding the matrix protein Z in a position under control of a genomic 5' untranslated region.

[0008g] In a seventh aspect of the invention, there is provided use of an arenavirus particle or a pharmaceutical composition thereof for the manufacture of a medicament for the treatment of a human papillomavirus (HPV) induced cancer in a subject in combination with a chemotherapeutic agent, wherein the chemotherapeutic agent is a platinum-based chemotherapy, a taxane, or a combination thereof, wherein the arenavirus particle is derived from lymphocytic choriomeningitis virus ("LCMV") or Pichinde virus ("PICV") and is a tri-segmented arenavirus particle comprising one L segment, a first S segment, and a second S segment, and wherein:

- (i) the first S segment comprises an open reading frame encoding the arenaviral glycoprotein GP in a position under control of a genomic 3' untranslated region and an open reading frame encoding a HPV E7 and E6 fusion protein in a position under control of a genomic 5' untranslated region;
- (ii) the second S segment comprises an open reading frame encoding the arenaviral nucleoprotein NP in a position under control of a genomic 3' untranslated region and an open reading frame encoding a HPV E7 and E6 fusion protein in a position under control of a genomic 5' untranslated region; and

(iii) the L segment comprises an open reading frame encoding ribonucleic acid (RNA) dependent RNA polymerase L in a position under control of a genomic 3' untranslated region and an open reading frame encoding the matrix protein Z in a position under control of a genomic 5' untranslated region.

[0008h] In an eighth aspect of the invention, there is provided a kit comprising two or more containers and instructions for use, wherein one of the containers comprises an arenavirus particle or a pharmaceutical composition thereof and another of the containers comprises a chemotherapeutic agent, wherein the chemotherapeutic agent is a platinum-based chemotherapy, a taxane, or a combination thereof, wherein the arenavirus particle is derived from lymphocytic choriomeningitis virus ("LCMV") or Pichinde virus ("PICV") and is a tri-segmented arenavirus particle comprising one L segment, a first S segment, and a second S segment, and wherein:

- (i) the first S segment comprises an open reading frame encoding the arenaviral glycoprotein GP in a position under control of a genomic 3' untranslated region and an open reading frame encoding a HPV E7 and E6 fusion protein in a position under control of a genomic 5' untranslated region;
- (ii) the second S segment comprises an open reading frame encoding the arenaviral nucleoprotein NP in a position under control of a genomic 3' untranslated region and an open reading frame encoding a HPV E7 and E6 fusion protein in a position under control of a genomic 5' untranslated region; and
- (iii) the L segment comprises an open reading frame encoding ribonucleic acid (RNA) dependent RNA polymerase L in a position under control of a genomic 3' untranslated region and an open reading frame encoding the matrix protein Z in a position under control of a genomic 5' untranslated region.

[0008i] In a ninth aspect of the invention, there is provided use of the kit of the eighth aspect for the manufacture of a medicament for the treatment of a neoplastic disease in a subject.

[0008j] In a tenth aspect of the invention, there is provided a method for treating a neoplastic disease in a subject in need thereof, wherein the method comprises administering to the subject in need thereof the arenavirus particle or a pharmaceutical composition thereof and the chemotherapeutic agent of the kit of the eighth aspect.

[0009] Provided herein are methods and compositions for treating a neoplastic disease using an arenavirus particle comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof. Also provided herein are methods and compositions for treating a neoplastic disease using a chemotherapeutic agent. Thus, in certain embodiments, provided herein are methods for treating a neoplastic disease using an arenavirus particle comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof, and a chemotherapeutic agent. Also, in certain embodiments, provided herein are compositions comprising an arenavirus particle comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof, and a chemotherapeutic agent. In certain embodiments, the arenavirus particle provided herein is an infectious, replication deficient arenavirus particle.

[0010] In certain embodiments, the arenavirus particle provided herein is engineered to contain an arenavirus genomic segment having a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof and at least one arenavirus open reading frame ("ORF") in a position other than the wild-type position of the ORF. In certain embodiments, the arenavirus particle provided herein is an infectious, replication deficient arenavirus particle. In other embodiments, the arenavirus particle provided herein is a tri-segmented arenavirus particle, which can be replication-deficient or replication-competent. In still other embodiments, the tri-segmented arenavirus particle provided herein, when propagated, does not result in a replication-competent bi-segmented viral particle.

3.1 Infectious, Replication Deficient Arenavirus Particle

[0011] In certain embodiments, an arenavirus particle provided herein is infectious, *i.e.*, it is capable of entering into or injecting its genetic material into a host cell. In certain more specific embodiments, an arenavirus particle as provided herein is infectious, *i.e.*, is capable of entering into or injecting its genetic material into a host cell followed by amplification and expression of its genetic information inside the host cell. In certain embodiments, the arenavirus particle provided herein is engineered to be an infectious, replication-deficient arenavirus particle, *i.e.*, it contains a genome with the ability to amplify and express its genetic information in infected cells but unable to produce further infectious progeny particles in non-complementing cells.

[0012] In certain embodiments, provided herein is an arenavirus particle engineered to contain a genome comprising: a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and the ability to amplify and express its genetic information in infected cells but unable to produce further infectious progeny particles in non-complementing cells. In certain embodiments, the arenavirus particle is infectious and replication-deficient.

[0013] The tumor antigen or tumor associated antigen encoded by the nucleotide sequence included within an arenavirus particle provided herein can be one or more of the tumor antigens or tumor associated antigens selected from the group consisting of oncogenic viral antigens, cancer-testis antigens, oncofetal antigens, tissue differentiation antigens, mutant protein antigens, Adipophilin, AIM-2, ALDH1AI, BCLX (L), BING-4, CALCA, CD45, CPSF, cyclin D1, DKKI, ENAH (hMcna), Ga733 (EpCAM), EphA3, EZH2, FGF5, glypican-3, G250 /MN/CAIX, HER-2/neu, IDO1, IGF2B3, IL13Ralpha2, Intestinal carboxyl esterase, alpha-foetoprotein, Kallikrein 4, KIF20A, Lentsin, M-CSF, MCSP, mdm-2, Meloe, MMP-2, MMP-7, MUC1, MUC5AC, p53 (non-mutant), PAX5, PBF, PRAME, PSMA, RAGE, RAGE-1, RGS5, RhoC, RNF43, RU2AS, secernin 1, SOX10, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), survivin, Telomerase, VEGF, WT1, EGF-R, CEA, CD20, CD33, CD52, MELANA/MART1, MART2, NY-ESO-1, p53, MAGE A1, MAGE A3, MAGE-4, MAGE-5, MAGE-6, CDK4, alpha-actinin-4, ARTC1, BCR-ABL, BCR-ABL fusion protein (b3a2), B-RAF, CASP-5, CASP-8, beta-catenin, Cdc27, CDK4, CDKN2A, CLPP, COA-1, dek-can fusion protein, EFTUD2, Elongation factor 2, ETV6-AML, ETV6-AML1 fusion protein, FLT3-ITD,

FNI, GPNMB, LDLR-fucosyltransferaseAS fusion protein, NFYC, OGT, OS-9, pml-RARalpha fusion protein, PRDX5, PTPRK, H-ras, K-ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene), N-ras, RBAF600, SIRT2, SNRPDI, SSX, SSX2, SYT-SSX1 or-SSX2 fusion protein, TGF-betaRII, Triosephosphate isomerase, ormdm-2, LMP2, HPV E6 / E7, EGFRvIII (epidermal growth factor variant III), Idiotype, GD2, ganglioside G2), Ras-mutant, p53 (mutant), Proteinase3 (PR1), Tyrosinase, PSA, hTERT, Sarcoma translocation breakpoints, EphA2, prostatic acid phosphatase PAP, neo-PAP, ML-IAP, AFP, ERG (TMPRSS2 ETS Fusion gene), NA17, PAX3, ALK, Androgen Receptor, Cyclin B1, Polysialic acid, MYCN, TRP2, TRP2-Int2, GD3, Fucosyl GM1, Mesothelin, PSCA, sLe(a), cyp1B1, PLAC1, GM3, BORIS, Tn, GLoboh, NY-BR-1, SART3, STn, Carbonic Anhydrase IX, OY-TES1, Sperm protein 17, LCK, high molecular weight melanoma-associated antigen (HMWMAA), AKAP-4, SSX2, XAGE 1, B7H3, Legumain, Tie 2, Page4, VEGFR2, MAD-CT-1, FAP, PDGFR-beta, MAD-CT-2, For-related antigen 1, TRP-1, GP100, CA-125, CA19-9, Calretinin, Epithelial membrane antigen (EMA), Epithelial tumor antigen (ETA), CD19, CD34, CD99, CD117, Chromogranin, Cytokeratin, Desmin, Glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, Myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), BAGE BAGE-1, CAGE, CTAGE, FATE, GAGE, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, HCA661, HOM-TES-85, MAGEA, MAGEB, MAGEC, NA88, NY-SAR-35, SPANXB1, SPA17, SSX, SYCP1, TPTE, Carbohydrate / ganglioside GM2 (oncofetal antigen-immunogenic-1 OFA-I-1), GM3, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA 50, CAM 43, CEA, EBNA, EF2, Epstein-Barr virus antigen, HLA-A2, HLA-A11, HSP70-2, KIAA0205, MUM-1, MUM-2, MUM-3, Myosin class I, GnTV, Herv-K-mel, LAGE-1, LAGE-2, (sperm protein) SP17, SCP-1, P15(58), Hom/Mel-40, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, TSP-180, P185erbB2, p180erbB-3, c-met, nm-23H1, TAG-72, TAG-72-4, CA-72-4, CAM 17.1, NuMa, 13-catenin, P16, TAGE, CT7, 43-9F, 5T4, 791Tgp72, 13HCG, BCA225, BTAA, CD68\KP1, CO-029, HTgp-175, M344, MG7-Ag, MOV18, NB\70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TLP, TPS, CD22, CD27, CD30, CD70, prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, integrin $\alpha v \beta 3$ (CD61), galactin, or Ral-B, CD123, CLL-1, CD38, CS-1, CD138, and ROR1. In certain embodiments, the nucleotide

sequence encodes two, three, four, five, six, seven, eight, nine, ten or more tumor antigens, tumor associated antigens or antigenic fragments thereof. In certain embodiments, an antigenic fragment of a tumor antigen or tumor associated provided herein is encoded by the nucleotide sequence included within the arenavirus.

[0014] In certain embodiments, an infectious, replication-deficient arenavirus particle provided herein comprises at least one arenavirus open reading frame (“ORF”) that is at least partially removed or functionally inactivated. The ORF can encode the glycoprotein (“GP”), the nucleoprotein (“NP”), the matrix protein Z (“Z protein”) or the RNA dependent RNA polymerase L (“L protein”) of the arenavirus particle. Additionally, in certain embodiments, at least one ORF encoding the GP, NP, Z protein, or L protein is removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In certain embodiments, only one of the four ORFs encoding GP, NP, Z protein and L protein is removed. Thus, in certain embodiments, the ORF encoding GP is removed. In certain embodiments, the ORF encoding NP is removed. In certain embodiments, the ORF encoding Z protein is removed. In certain embodiments, the ORF encoding L protein is removed.

[0015] In certain embodiments, an infectious, replication-deficient arenavirus particle comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof as provided herein further comprises at least one nucleotide sequence encoding at least one immunomodulatory peptide, polypeptide or protein. In certain embodiments, the immunomodulatory peptide, polypeptide or protein is Calreticulin (CRT), or a fragment thereof; Ubiquitin or a fragment thereof; Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), or a fragment thereof; Invariant chain (CD74) or an antigenic fragment thereof; Mycobacterium tuberculosis Heat shock protein 70 or an antigenic fragment thereof; Herpes simplex virus 1 protein VP22 or an antigenic fragment thereof; CD40 ligand or an antigenic fragment thereof; or Fms-related tyrosine kinase 3 (Flt3) ligand or an antigenic fragment thereof.

[0016] In certain embodiments, an infectious, replication-deficient arenavirus particle provided herein is derived from a specific arenavirus species, such as lymphocytic choriomeningitis virus (“LCMV”), Junin virus (“JUNV”), or Pichinde virus (“PICV”). In other words, the genomic information encoding the infectious, replication-deficient arenavirus particle

is derived from a specific species of arenavirus. Thus, in certain embodiments, the infectious, replication-deficient arenavirus particle is derived from LCMV. In other embodiments, the infectious, replication-deficient arenavirus particle is derived from JUNV. In other embodiments, the infectious, replication-deficient arenavirus particle is derived from PICV. Additionally, in specific embodiments, the LCMV is MP strain, WE strain, Armstrong strain, or Armstrong Clone 13 strain. In other specific embodiments, the JUNV is JUNV vaccine Candid #1 strain, or JUNV vaccine XJ Clone 3 strain. In other specific embodiments, the PICV is strain Munchique CoAn4763 isolate P18, or P2 strain.

(a) Methods for Treating a Neoplastic Disease

[0017] In certain embodiments, provided herein are methods of treating a neoplastic disease in a subject. Such methods can include administering to a subject in need thereof an arenavirus particle provided herein in combination with a chemotherapeutic agent provided herein. In certain embodiments, the arenavirus particle used in the methods is an infectious, replication-deficient arenavirus particle. Thus, in certain embodiments, the infectious, replication-deficient arenavirus particle used in the methods is engineered to contain a genome comprising (1) a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and (2) the ability to amplify and express its genetic information in infected cells but unable to produce further infectious progeny particles in non-complementing cells.

[0018] In certain embodiments, the tumor antigen or tumor associated antigen encoded by the nucleotide sequence included within an arenavirus particle provided herein can be one or more of the tumor antigens or tumor associated antigens selected from the group consisting of oncogenic viral antigens, cancer-testis antigens, oncofetal antigens, tissue differentiation antigens, mutant protein antigens, Adipophilin, AIM-2, ALDH1A1, BCLX (L), BING-4, CALCA, CD45, CPSF, cyclin D1, DKK1, ENAH (hMena), Ga733 (EpCAM), EphA3, EZH2, FGF5, glypican-3, G250 /MN/CAIX, HER-2/neu, IDO1, IGF2B3, IL13Ralpha2, Intestinal carboxyl esterase, alpha-fetoprotein, Kallikrein 4, KIF20A, Lengsin, M-CSF, MCSP, mdm-2, Meloe, MMP-2, MMP-7, MUC1, MUC5AC, p53 (non-mutant), PAX5, PBF, PRAME, PSMA, RAGE, RAGE-1, RGS5, RhoC, RNF43, RU2AS, secernin 1, SOX10, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), survivin, Telomerase, VEGF, WT1, EGF-R, CEA, CD20, CD33, CD52, MELANA/MART1, MART2, NY-ESO-1, p53, MAGE A1, MAGE

A3, MAGE-4, MAGE-5, MAGE-6, CDK4, alpha-actinin-4, ARTC1, BCR-ABL, BCR-ABL fusion protein (b3a2), B-RAF, CASP-5, CASP-8, beta-catenin, Cdc27, CDK4, CDKN2A, CLPP, COA-1, dek-can fusion protein, EFTUD2, Elongation factor 2, ETV6-AML, ETV6-AML1 fusion protein, FLT3-ITD, FNI, GPNMB, LDLR-fucosyltransferaseAS fusion protein, NFYC, OGT, OS-9, pml-RARalpha fusion protein, PRDX5, PTPRK, H-ras, K-ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene), N-ras, RBAF600, SIRT2, SNRPDI, SSX, SSX2, SYT-SSX1 or-SSX2 fusion protein, TGF-betaRII, Triosephosphate isomerase, ormdm-2, LMP2, HPV E6 / E7, EGFRvIII (epidermal growth factor variant III), Idiotype, GD2, ganglioside G2), Ras-mutant, p53 (mutant), Proteinase3 (PR1), Tyrosinase, PSA, hTERT, Sarcoma translocation breakpoints, EphA2, prostatic acid phosphatase PAP, neo-PAP, ML-IAP, AFP, ERG (TMPRSS2 ETS Fusion gene), NA17, PAX3, ALK, Androgen Receptor, Cyclin B1, Polysialic acid, MYCN, TRP2, TRP2-Int2, GD3, Fucosyl GM1, Mesothelin, PSCA, sLe(a), cyp1B1, PLAC1, GM3, BORIS, Tn, GLoboH, NY-BR-1, SART3, STn, Carbonic Anhydrase IX, OY-TES1, Sperm protein 17, LCK, high molecular weight melanoma-associated antigen (HMWMAA), AKAP-4, SSX2, XAGE 1, B7H3, Legumain, Tie 2, Page4, VEGFR2, MAD-CT-1, FAP, PDGFR-beta, MAD-CT-2, For-related antigen 1, TRP-1, GP100, CA-125, CA19-9, Calretinin, Epithelial membrane antigen (EMA), Epithelial tumor antigen (ETA), CD19, CD34, CD99, CD117, Chromogranin, Cytokeratin, Desmin, Glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, Myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), BAGE BAGE-1, CAGE, CTAGE, FATE, GAGE, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, HCA661, HOM-TES-85, MAGEA, MAGEB, MAGEC, NA88, NY-SAR-35, SPANXB1, SPA17, SSX, SYCP1, TPTE, Carbohydrate / ganglioside GM2 (oncofetal antigen-immunogenic-1 OFA-I-1), GM3, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA 50, CAM 43, CEA, EBNA, EF2, Epstein-Barr virus antigen, HLA-A2, HLA-A11, HSP70-2, KIAA0205, MUM-1, MUM-2, MUM-3, Myosin class I, GnTV, Herv-K-mel, LAGE-1, LAGE-2, (sperm protein) SP17, SCP-1, P15(58), Hom/Mel-40, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, TSP-180, P185erbB2, p180erbB-3, c-met, nm-23H1, TAG-72, TAG-72-4, CA-72-4, CAM 17.1, NuMa, 13-catenin, P16, TAGE, CT7, 43-9F,5T4, 791Tgp72, 13HCG, BCA225, BTAA, CD68\KP1, CO-029, HTgp-175, M344, MG7-Ag, MOV18, NB\70K, NY-CO-

1, RCAS1, SDCCAG16, TA-90, TAAL6, TLP, TPS, CD22, CD27, CD30, CD70, prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, integrin $\alpha\beta 3$ (CD61), galactin, or Ral-B, CD123, CLL-1, CD38, CS-1, CD138, and ROR1. In certain embodiments, the nucleotide sequence encodes two, three, four, five, six, seven, eight, nine, ten or more tumor antigen, tumor associated antigens or antigenic fragments thereof. In certain embodiments, an antigenic fragment of a tumor antigen, tumor associated antigen provided herein is encoded by the nucleotide sequence included within the arenavirus. In specific embodiments, the tumor antigen is selected from the group consisting of GP100, Trp1, Trp2, and a combination thereof. In specific embodiments, the tumor antigen is GP100. In specific embodiments, the tumor antigen is Trp1. In specific embodiments, the tumor antigen is Trp2.

[0019] In certain embodiments, provided herein are methods for treating a neoplastic disease in a subject by administering a chemotherapeutic agent in combination with a replication-deficient arenavirus particle. In certain embodiments, the chemotherapeutic agent is an alkylating agent (*e.g.*, cyclophosphamide), a platinum-based therapeutic, an antimetabolite, a topoisomerase inhibitor, a cytotoxic antibiotic, an intercalating agent, a mitosis inhibitor, a taxane, or a combination of two or more thereof. In certain embodiments, the alkylating agent is a nitrogen mustard, a nitrosourea, an alkyl sulfonate, a non-classical alkylating agent, or a triazene. In certain embodiments, the chemotherapeutic agent comprises one or more of cyclophosphamide, thiotepa, mechlorethamine (chlormethine/mustine), uramustine, melphalan, chlorambucil, ifosfamide, chlornaphazine, cholophosphamide, estramustine, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, bendamustine, busulfan, improsulfan, piposulfan, carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine, streptozucin, cisplatin, carboplatin, nedaplatin, oxaliplatin, satraplatin, triplatin tetranitrate, procarbazine, altretamine, dacarbazine, mitozolomide, temozolomide, paclitaxel, docetaxel, vinblastine, vincristine, vinorelbine, cabazitaxel, dactinomycin (actinomycin D), calicheamicin, dynemicin, amsacrine, doxorubicin, daunorubicin, epirubicin, mitoxantrone, idarubicin, pirarubicin, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate, trimethylolomelamine, bullatacin, bullatacinone, camptothecin, topotecan, bryostatin, callystatin, CC-1065, adozelesin, carzelesin, bizelesin, cryptophycin, dolastatin, duocarmycin, KW-2189, CB1-TM1, eleutherobin, pancratistatin, sarcodictyin, spongistatin, clodronate, esperamicin, neocarzinostatin

chromophore, aclacinomycin, anthramycin, azaserine, bleomycin, cactinomycin, carabycin, carminomycin, carzinophilin, chromomycinis, detorubicin, 6-diazo-5-oxo-L-norleucine, esorubicin, idarubicin, marcellomycin, mitomycin, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, methotrexate, 5-fluorouracil (5-FU), denopterin, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiothane, testolactone, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, bestabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elformithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansine, ansamitocins, mitoguazone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, PSK polysaccharide complex, razoxane, rhizoxin, sizofiran, spirogermanium, tenuazonic acid, triaziquone, 2,2',2''-trichlorotriethylamine; T-2 toxin, verracurin A, roridin A and anguidine, urethan, vindesine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside ("Ara-C"), etoposide (VP-16), vinorelbine, novantrone, teniposide, edatrexate, aminopterin, xeloda, ibandronate, irinotecan (e.g., CPT-11), topoisomerase inhibitor RFS 2000, difluoromethylornithine (DMFO), retinoic acid, capecitabine, plicomycin, gemcitabine, navelbine, transplatinum, and pharmaceutically acceptable salts, acids, or derivatives of any of the above. In specific embodiments, the chemotherapeutic agent comprises cyclophosphamide. In certain embodiments, the nitrogen mustard is mechlorethamine, cyclophosphamide, melphalan, chlorambucil, ifosfamide, or busulfan. In certain embodiments, the chemotherapeutic agent alkylates DNA. In certain embodiments, the chemotherapeutic agent alkylates DNA, resulting in the formation of interstrand cross-links ("ICLs").

[0020] In certain embodiments, provided herein are methods for treating a neoplastic disease in a subject by administering a chemotherapeutic agent in combination with a replication-deficient arenavirus particle and an immune checkpoint inhibitor that inhibits, decreases or interferes with the activity of a negative checkpoint regulator. In certain embodiments, the negative checkpoint regulator is selected from the group consisting of Cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD80, CD86, Programmed cell death 1 (PD-1),

Programmed cell death ligand 1 (PD-L1), Programmed cell death ligand 2 (PD-L2), Lymphocyte activation gene-3 (LAG-3; also known as CD223), Galectin-3, B and T lymphocyte attenuator (BTLA), T-cell membrane protein 3 (TIM3), Galectin-9 (GAL9), B7-H1, B7-H3, B7-H4, T-Cell immunoreceptor with Ig and ITIM domains (TIGIT/Vstm3/WUCAM/VSIG9), V-domain Ig suppressor of T-Cell activation (VISTA), Glucocorticoid-induced tumor necrosis factor receptor-related (GITR) protein, Herpes Virus Entry Mediator (HVEM), OX40, CD27, CD28, CD137, CGEN-15001T, CGEN-15022, CGEN-15027, CGEN-15049, CGEN-15052, and CGEN-15092. In certain embodiments, the immune checkpoint inhibitor is an anti-PD-1 antibody.

[0021] In certain embodiments, the subject that is treated using the methods provided herein is suffering from, is susceptible to, or is at risk for a neoplastic disease. Thus, in some embodiments, the subject is suffering from a neoplastic disease. In some embodiments, the subject is susceptible to a neoplastic disease. In some embodiments, the subject is at risk for a neoplastic disease. In certain embodiments, the neoplastic disease that a subject treatable by the methods provided herein is selected from the group consisting of acute lymphoblastic leukemia; acute lymphoblastic lymphoma; acute lymphocytic leukaemia; acute myelogenous leukemia; acute myeloid leukemia (adult / childhood); adrenocortical carcinoma; AIDS-related cancers; AIDS-related lymphoma; anal cancer; appendix cancer; astrocytomas; atypical teratoid/rhabdoid tumor; basal-cell carcinoma; bile duct cancer, extrahepatic (cholangiocarcinoma); bladder cancer; bone osteosarcoma/malignant fibrous histiocytoma; brain cancer (adult / childhood); brain tumor, cerebellar astrocytoma (adult / childhood); brain tumor, cerebral astrocytoma/malignant glioma brain tumor; brain tumor, ependymoma; brain tumor, medulloblastoma; brain tumor, supratentorial primitive neuroectodermal tumors; brain tumor, visual pathway and hypothalamic glioma; brainstem glioma; breast cancer; bronchial adenomas/carcinoids; bronchial tumor; Burkitt lymphoma; cancer of childhood; carcinoid gastrointestinal tumor; carcinoid tumor; carcinoma of adult, unknown primary site; carcinoma of unknown primary; central nervous system embryonal tumor; central nervous system lymphoma, primary; cervical cancer; childhood adrenocortical carcinoma; childhood cancers; childhood cerebral astrocytoma; chordoma, childhood; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloid leukemia; chronic myeloproliferative disorders; colon cancer; colorectal cancer; craniopharyngioma; cutaneous T-cell lymphoma; desmoplastic small round cell tumor; emphysema; endometrial cancer; ependymoblastoma; ependymoma;

esophageal cancer; ewing's sarcoma in the Ewing family of tumors; extracranial germ cell tumor; extragonadal germ cell tumor; extrahepatic bile duct cancer; gallbladder cancer; gastric (stomach) cancer; gastric carcinoid; gastrointestinal carcinoid tumor; gastrointestinal stromal tumor; germ cell tumor: extracranial, extragonadal, or ovarian gestational trophoblastic tumor; gestational trophoblastic tumor, unknown primary site; glioma; glioma of the brain stem; glioma, childhood visual pathway and hypothalamic; hairy cell leukemia; head and neck cancer; heart cancer; hepatocellular (liver) cancer; hodgkin lymphoma; hypopharyngeal cancer; hypothalamic and visual pathway glioma; intraocular melanoma; islet cell carcinoma (endocrine pancreas); Kaposi Sarcoma; kidney cancer (renal cell cancer); langerhans cell histiocytosis; laryngeal cancer; lip and oral cavity cancer; liposarcoma; liver cancer (primary); lung cancer, non-small cell; lung cancer, small cell; lymphoma, primary central nervous system; macroglobulinemia, Waldenström; male breast cancer; malignant fibrous histiocytoma of bone/osteosarcoma; medulloblastoma; medulloepithelioma; melanoma; melanoma, intraocular (eye); merkel cell cancer; merkel cell skin carcinoma; mesothelioma; mesothelioma, adult malignant; metastatic squamous neck cancer with occult primary; mouth cancer; multiple endocrine neoplasia syndrome; multiple myeloma/plasma cell neoplasm; mycosis fungoides, myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; myelogenous leukemia, chronic; myeloid leukemia, adult acute; myeloid leukemia, childhood acute; myeloma, multiple (cancer of the bone-marrow); myeloproliferative disorders, chronic; nasal cavity and paranasal sinus cancer; nasopharyngeal carcinoma; neuroblastoma, non-small cell lung cancer; non-hodgkin lymphoma; oligodendroglioma; oral cancer; oral cavity cancer; oropharyngeal cancer; osteosarcoma/malignant fibrous histiocytoma of bone; ovarian cancer; ovarian epithelial cancer (surface epithelial-stromal tumor); ovarian germ cell tumor; ovarian low malignant potential tumor; pancreatic cancer; pancreatic cancer, islet cell; papillomatosis; paranasal sinus and nasal cavity cancer; parathyroid cancer; penile cancer; pharyngeal cancer; pheochromocytoma; pineal astrocytoma; pineal germinoma; pineal parenchymal tumors of intermediate differentiation; pineoblastoma and supratentorial primitive neuroectodermal tumors; pituitary tumor; pituitary adenoma; plasma cell neoplasia/multiple myeloma; pleuropulmonary blastoma; primary central nervous system lymphoma; prostate cancer; rectal cancer; renal cell carcinoma (kidney cancer); renal pelvis and ureter, transitional cell cancer; respiratory tract carcinoma involving the NUT gene on chromosome 15; retinoblastoma; rhabdomyosarcoma, childhood; salivary gland cancer;

sarcoma, Ewing family of tumors; Sézary syndrome; skin cancer (melanoma); skin cancer (non-melanoma); small cell lung cancer; small intestine cancer soft tissue sarcoma; soft tissue sarcoma; spinal cord tumor; squamous cell carcinoma; squamous neck cancer with occult primary, metastatic; stomach (gastric) cancer; supratentorial primitive neuroectodermal tumor; T-cell lymphoma, cutaneous (Mycosis Fungoides and Sézary syndrome); testicular cancer; throat cancer; thymoma; thymoma and thymic carcinoma; thyroid cancer; thyroid cancer, childhood; transitional cell cancer of the renal pelvis and ureter; urethral cancer; uterine cancer, endometrial; uterine sarcoma; vaginal cancer; vulvar cancer; and Wilms Tumor. In certain embodiments, the neoplastic disease of a subject treatable by the methods provided herein is melanoma. In specific embodiments, the neoplastic disease is melanoma and the chemotherapeutic agent is cyclophosphamide. In specific embodiments, the neoplastic disease is melanoma, the tumor antigen is selected from the group consisting of GP100, Trp1, Trp2, and a combination thereof, and the chemotherapeutic agent is cyclophosphamide. In specific embodiments, the neoplastic disease is melanoma, the tumor antigen is GP100, and the chemotherapeutic agent is cyclophosphamide. In specific embodiments, the neoplastic disease is melanoma, the tumor antigen is Trp2, and the chemotherapeutic agent is cyclophosphamide. In specific embodiments, the neoplastic disease is melanoma, the tumor antigen is Trp1, and the chemotherapeutic agent is cyclophosphamide. In more specific embodiments, the neoplastic disease is melanoma, the tumor antigen is Trp1, the chemotherapeutic agent is cyclophosphamide, and the method further comprises administering an anti-PD-1 antibody.

[0022] In certain embodiments, the arenavirus particle provided herein and chemotherapeutic agent provided herein, which are used in the methods provided herein, can be administered in a variety of different combinations. Thus, in certain embodiments, the arenavirus particle and the chemotherapeutic agent are co-administered simultaneously. In other embodiments, the arenavirus particle is administered prior to administration of the chemotherapeutic agent. In still other embodiments, the arenavirus particle is administered after administration of the chemotherapeutic agent. The interval between administration of the arenavirus particle and the chemotherapeutic agent be hours, days, weeks or months. Thus, in some embodiments, interval is about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about

6 days, about 1 week, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, or more.

[0023] In certain embodiments, the method provided here includes administering an arenavirus particle provided herein and a chemotherapeutic agent provided herein in a therapeutically effective amount. Thus, in certain embodiments, provided herein is a method for treating a neoplastic disease in a subject comprising, administering to a subject in need thereof a therapeutically effective amount of an infectious, replication-deficient arenavirus particle and a therapeutically effective amount of a chemotherapeutic agent, wherein the arenavirus particle is engineered to contain a genome comprising: a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and the ability to amplify and express its genetic information in infected cells but unable to produce further infectious progeny particles in non-complementing cells.

[0024] In certain embodiments, provided herein are methods of treating a neoplastic disease in a subject comprising, administering to the subject two or more arenaviruses expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof. In a more specific embodiment, the method provided herein includes administering to the subject a first infectious, replication-deficient arenavirus particle, and administering to the subject, after a period of time, a second infectious, replication-deficient arenavirus particle. In still another embodiment, the first infectious, replication-deficient arenavirus particle and the second infectious, replication-deficient arenavirus particle are derived from different arenavirus species and/or comprise nucleotide sequences encoding different tumor antigen, tumor associated antigens or antigenic fragments thereof.

[0025] In certain embodiments, the methods and compositions provided herein are used in combination with personalized medicine. Personalized medicine seeks to benefit patients by using information from a patient's unique genetic and/or epigenetic profile to predict a patient's response to different therapies and identify which therapies are more likely to be effective. Techniques that can be used in combination with the methods and compositions provided herein to obtain a patient's unique genetic and/or epigenetic profile include, but are not limited to,

genome sequencing, RNA sequencing, gene expression analysis and identification of a tumor antigen (e.g., neoantigen), tumor associated antigen or an antigenic fragment thereof. In certain embodiments, the selection of an arenavirus tumor antigen or tumor associated antigen for use in the methods and compositions provided herein is performed based on the genetic profile of the patient. In certain embodiments, the selection of an arenavirus tumor antigen or tumor associated antigen for use in the methods and compositions provided herein is performed based on the genetic profile of a tumor or tumor cell. In certain embodiments, the selection of a chemotherapeutic for use in the methods and compositions provided herein is performed based on the genetic profile of a tumor or tumor cell. In certain embodiments, the selection of an arenavirus tumor antigen or tumor associated antigen and the selection of a chemotherapeutic for use in the methods and compositions provided herein are performed based on the genetic profile of a tumor or tumor cell.

(b) Pharmaceutical Compositions and Kits

[0026] In certain embodiments, provided herein are compositions, *e.g.*, pharmaceutical, immunogenic or vaccine compositions, comprising an arenavirus particle provided herein, a chemotherapeutic agent provided herein, and a pharmaceutically acceptable carrier. Thus, in some embodiments, provided herein is a pharmaceutical composition comprising an infectious, replication-deficient arenavirus particle as provided herein, a chemotherapeutic agent as provided herein and a pharmaceutically acceptable carrier. In specific certain embodiments, the arenavirus particle is engineered to contain a genome comprising: (1) a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and (2) the ability to amplify and express its genetic information in infected cells but unable to produce further infectious progeny particles in non-complementing cells.

[0027] In certain embodiments, the tumor antigen or tumor associated antigen encoded by the nucleotide sequence included within an arenavirus particle provided herein can be one or more of the tumor antigens or tumor associated antigens selected from the group consisting of oncogenic viral antigens, cancer-testis antigens, oncofetal antigens, tissue differentiation antigens, mutant protein antigens, Adipophilin, AIM-2, ALDH1A1, BCLX (L), BING-4, CALCA, CD45, CPSF, cyclin D1, DKKI, ENAH (hMena), Ga733 (EpCAM), EphA3, EZH2, FGF5, glypican-3, G250 /MN/CAIX, HER-2/neu, IDO1, IGF2B3, IL13Ralpha2, Intestinal carboxyl esterase, alpha-fetoprotein, Kallikrein 4, KIF20A, Lentsin, M-CSF, MCSP, mdm-2,

Meloe, MMP-2, MMP-7, MUC1, MUC5AC, p53 (non-mutant), PAX5, PBF, PRAME, PSMA, RAGE, RAGE-1, RGS5, RhoC, RNF43, RU2AS, secernin 1, SOX10, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), survivin, Telomerase, VEGF, WT1, EGF-R, CEA, CD20, CD33, CD52, MELANA/MART1, MART2, NY-ESO-1, p53, MAGE A1, MAGE A3, MAGE-4, MAGE-5, MAGE-6, CDK4, alpha-actinin-4, ARTC1, BCR-ABL, BCR-ABL fusion protein (b3a2), B-RAF, CASP-5, CASP-8, beta-catenin, Cdc27, CDK4, CDKN2A, CLPP, COA-1, dek-can fusion protein, EFTUD2, Elongation factor 2, ETV6-AML, ETV6-AML1 fusion protein, FLT3-ITD, FNI, GPNMB, LDLR-fucosyltransferaseAS fusion protein, NFYC, OGT, OS-9, pml-RARalpha fusion protein, PRDX5, PTPRK, H-ras, K-ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene), N-ras, RBAF600, SIRT2, SNRPD1, SSX, SSX2, SYT-SSX1 or-SSX2 fusion protein, TGF-betaR2, Triosephosphate isomerase, ormdm-2, LMP2, HPV E6 / E7, EGFRvIII (epidermal growth factor variant III), Idiotype, GD2, ganglioside G2), Ras-mutant, p53 (mutant), Proteinase3 (PR1), Tyrosinase, PSA, hTERT, Sarcoma translocation breakpoints, EphA2, prostatic acid phosphatase PAP, neo-PAP, ML-IAP, AFP, ERG (TMPRSS2 ETS Fusion gene), NA17, PAX3, ALK, Androgen Receptor, Cyclin B1, Polysialic acid, MYCN, TRP2, TRP2-Int2, GD3, Fucosyl GM1, Mesothelin, PSCA, sLe(a), cyp1B1, PLAC1, GM3, BORIS, Tn, GLobH, NY-BR-1, SART3, STn, Carbonic Anhydrase IX, OY-TES1, Sperm protein 17, LCK, high molecular weight melanoma-associated antigen (HMWMAA), AKAP-4, SSX2, XAGE 1, B7H3, Legumain, Tie 2, Page4, VEGFR2, MAD-CT-1, FAP, PDGFR-beta, MAD-CT-2, For-related antigen 1, TRP-1, GP100, CA-125, CA19-9, Calretinin, Epithelial membrane antigen (EMA), Epithelial tumor antigen (ETA), CD19, CD34, CD99, CD117, Chromogranin, Cytokeratin, Desmin, Glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, Myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), BAGE BAGE-1, CAGE, CTAGE, FATE, GAGE, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, HCA661, HOM-TES-85, MAGEA, MAGEB, MAGEC, NA88, NY-SAR-35, SPANXB1, SPA17, SSX, SYCP1, TPTE, Carbohydrate / ganglioside GM2 (oncofetal antigen-immunogenic-1 OFA-I-1), GM3, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA 50, CAM 43, CEA, EBNA, EF2, Epstein-Barr virus antigen, HLA-A2, HLA-A11, HSP70-2, KIAA0205, MUM-1, MUM-2, MUM-3, Myosin class I, GnTV, Herv-K-mel, LAGE-

1, LAGE-2, (sperm protein) SP17, SCP-1, P15(58), Hom/Mel-40, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, TSP-180, P185erbB2, p180erbB-3, c-met, nm-23H1, TAG-72, TAG-72-4, CA-72-4, CAM 17.1, NuMa, 13-catenin, P16, TAGE, CT7, 43-9F, 5T4, 791Tgp72, 13HCG, BCA225, BTAA, CD68\KP1, CO-029, HTgp-175, M344, MG7-Ag, MOV18, NB\70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TLP, TPS, CD22, CD27, CD30, CD70, prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, integrin $\alpha\beta 3$ (CD61), galactin, or Ral-B, CD123, CLL-1, CD38, CS-1, CD138, and ROR1. In certain embodiments, the nucleotide sequence encodes two, three, four, five, six, seven, eight, nine, ten or more tumor antigen, tumor associated antigens or antigenic fragments thereof. In certain embodiments, an antigenic fragment of a tumor antigen or tumor associated antigen provided herein is encoded by the nucleotide sequence included within the arenavirus.

[0028] In certain embodiments, a composition provided herein, including a pharmaceutical, immunogenic or vaccine composition, includes a chemotherapeutic agent in combination with a replication-deficient arenavirus particle. In certain embodiments, the chemotherapeutic agent is an alkylating agent (*e.g.*, cyclophosphamide), a platinum-based therapeutic, an antimetabolite, a topoisomerase inhibitor, a cytotoxic antibiotic, an intercalating agent, a mitosis inhibitor, a taxane, or a combination of two or more thereof. In certain embodiments, the alkylating agent is a nitrogen mustard, a nitrosourea, an alkyl sulfonate, a non-classical alkylating agent, or a triazene. In certain embodiments, the chemotherapeutic agent comprises one or more of cyclophosphamide, thiotepa, mechlorethamine (chlormethine/mustine), uramustine, melphalan, chlorambucil, ifosfamide, chlornaphazine, cholophosphamide, estramustine, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, bendamustine, busulfan, improsulfan, piposulfan, carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine, streptozucin, cisplatin, carboplatin, nedaplatin, oxaliplatin, satraplatin, triplatin tetranitrate, procarbazine, altretamine, dacarbazine, mitozolomide, temozolomide, paclitaxel, docetaxel, vinblastine, vincristine, vinorelbine, cabazitaxel, dactinomycin (actinomycin D), calicheamicin, dynemicin, amsacrine, doxorubicin, daunorubicin, epirubicin, mitoxantrone, idarubicin, pirarubicin, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, trietylenephosphoramidate, triethylenethiophosphoramidate, trimethylolomelamine, bullatacin, bullatacinone, camptothecin, topotecan, bryostatin, callistatin, CC-1065, adozelesin, carzelesin, bizelesin, cryptophycin, dolastatin, duocarmycin, KW-2189,

CB1-TM1, eleutherobin, pancratistatin, sarcodictyin, spongistatin, clodronate, esperamicin, neocarzinostatin chromophore, aclacinomysin, anthramycin, azaserine, bleomycin, cactinomycin, carabycin, carminomycin, carzinophilin, chromomycinis, detorubicin, 6-diazo-5-oxo-L-norleucine, esorubicin, idarubicin, marcellomycin, mitomycin, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, methotrexate, 5-fluorouracil (5-FU), denopterin, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiothane, testolactone, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elformithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansine, ansamitocins, mitoguazone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, PSK polysaccharide complex, razoxane, rhizoxin, sizofiran, spirogermanium, tenuazonic acid, triaziquone, 2,2',2''-trichlorotriethylamine; T-2 toxin, verracurin A, roridin A and anguidine, urethan, vindesine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside ("Ara-C"), etoposide (VP-16), vinorelbine, novantrone, teniposide, edatrexate, aminopterin, xeloda, ibandronate, irinotecan (e.g., CPT-11), topoisomerase inhibitor RFS 2000, difluoromethylornithine (DMFO), retinoic acid, capecitabine, plicomycin, gemcitabine, navelbine, transplatinum, and pharmaceutically acceptable salts, acids, or derivatives of any of the above. In specific embodiments, the chemotherapeutic agent comprises cyclophosphamide. In certain embodiments, the nitrogen mustard is mechlorethamine, cyclophosphamide, melphalan, chlorambucil, ifosfamide, or busulfan. In certain embodiments, the chemotherapeutic agent alkylates DNA. In certain embodiments, the chemotherapeutic agent alkylates DNA, resulting in the formation of interstrand cross-links ("ICLs").

[0029] In certain embodiments, the composition provided herein, including a pharmaceutical, immunogenic or vaccine composition, includes a chemotherapeutic agent and an immune checkpoint inhibitor that inhibits, decreases or interferes with the activity of a negative checkpoint regulator. In certain embodiments, the negative checkpoint regulator is selected from the group consisting of Cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD80, CD86,

Programmed cell death 1 (PD-1), Programmed cell death ligand 1 (PD-L1), Programmed cell death ligand 2 (PD-L2), Lymphocyte activation gene-3 (LAG-3; also known as CD223), Galectin-3, B and T lymphocyte attenuator (BTLA), T-cell membrane protein 3 (TIM3), Galectin-9 (GAL9), B7-H1, B7-H3, B7-H4, T-Cell immunoreceptor with Ig and ITIM domains (TIGIT/Vstm3/WUCAM/VSIG9), V-domain Ig suppressor of T-Cell activation (VISTA), Glucocorticoid-induced tumor necrosis factor receptor-related (GITR) protein, Herpes Virus Entry Mediator (HVEM), OX40, CD27, CD28, CD137. CGEN-15001T, CGEN-15022, CGEN-15027, CGEN-15049, CGEN-15052, and CGEN-15092. In certain embodiments, the immune checkpoint inhibitor is an anti-PD-1 antibody.

[0030] In certain embodiments, the compositions provided herein, including a pharmaceutical, immunogenic or vaccine composition, can be used in the methods described herein. Thus, in certain embodiments, the compositions can be used for the treatment of a neoplastic disease. In specific certain embodiments, the compositions provided herein can be used for the treatment of a neoplastic disease selected from the group consisting of acute lymphoblastic leukemia; acute lymphoblastic lymphoma; acute lymphocytic leukaemia; acute myelogenous leukemia; acute myeloid leukemia (adult / childhood); adrenocortical carcinoma; AIDS-related cancers; AIDS-related lymphoma; anal cancer; appendix cancer; astrocytomas; atypical teratoid/rhabdoid tumor; basal-cell carcinoma; bile duct cancer, extrahepatic (cholangiocarcinoma); bladder cancer; bone osteosarcoma/malignant fibrous histiocytoma; brain cancer (adult / childhood); brain tumor, cerebellar astrocytoma (adult / childhood); brain tumor, cerebral astrocytoma/malignant glioma brain tumor; brain tumor, ependymoma; brain tumor, medulloblastoma; brain tumor, supratentorial primitive neuroectodermal tumors; brain tumor, visual pathway and hypothalamic glioma; brainstem glioma; breast cancer; bronchial adenomas/carcinoids; bronchial tumor; Burkitt lymphoma; cancer of childhood; carcinoid gastrointestinal tumor; carcinoid tumor; carcinoma of adult, unknown primary site; carcinoma of unknown primary; central nervous system embryonal tumor; central nervous system lymphoma, primary; cervical cancer; childhood adrenocortical carcinoma; childhood cancers; childhood cerebral astrocytoma; chordoma, childhood; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloid leukemia; chronic myeloproliferative disorders; colon cancer; colorectal cancer; craniopharyngioma; cutaneous T-cell lymphoma; desmoplastic small round cell tumor; emphysema; endometrial cancer; ependymoblastoma; ependymoma;

esophageal cancer; ewing's sarcoma in the Ewing family of tumors; extracranial germ cell tumor; extragonadal germ cell tumor; extrahepatic bile duct cancer; gallbladder cancer; gastric (stomach) cancer; gastric carcinoid; gastrointestinal carcinoid tumor; gastrointestinal stromal tumor; germ cell tumor: extracranial, extragonadal, or ovarian gestational trophoblastic tumor; gestational trophoblastic tumor, unknown primary site; glioma; glioma of the brain stem; glioma, childhood visual pathway and hypothalamic; hairy cell leukemia; head and neck cancer; heart cancer; hepatocellular (liver) cancer; hodgkin lymphoma; hypopharyngeal cancer; hypothalamic and visual pathway glioma; intraocular melanoma; islet cell carcinoma (endocrine pancreas); Kaposi Sarcoma; kidney cancer (renal cell cancer); langerhans cell histiocytosis; laryngeal cancer; lip and oral cavity cancer; liposarcoma; liver cancer (primary); lung cancer, non-small cell; lung cancer, small cell; lymphoma, primary central nervous system; macroglobulinemia, Waldenström; male breast cancer; malignant fibrous histiocytoma of bone/osteosarcoma; medulloblastoma; medulloepithelioma; melanoma; melanoma, intraocular (eye); merkel cell cancer; merkel cell skin carcinoma; mesothelioma; mesothelioma, adult malignant; metastatic squamous neck cancer with occult primary; mouth cancer; multiple endocrine neoplasia syndrome; multiple myeloma/plasma cell neoplasm; mycosis fungoides, myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; myelogenous leukemia, chronic; myeloid leukemia, adult acute; myeloid leukemia, childhood acute; myeloma, multiple (cancer of the bone-marrow); myeloproliferative disorders, chronic; nasal cavity and paranasal sinus cancer; nasopharyngeal carcinoma; neuroblastoma, non-small cell lung cancer; non-hodgkin lymphoma; oligodendroglioma; oral cancer; oral cavity cancer; oropharyngeal cancer; osteosarcoma/malignant fibrous histiocytoma of bone; ovarian cancer; ovarian epithelial cancer (surface epithelial-stromal tumor); ovarian germ cell tumor; ovarian low malignant potential tumor; pancreatic cancer; pancreatic cancer, islet cell; papillomatosis; paranasal sinus and nasal cavity cancer; parathyroid cancer; penile cancer; pharyngeal cancer; pheochromocytoma; pineal astrocytoma; pineal germinoma; pineal parenchymal tumors of intermediate differentiation; pineoblastoma and supratentorial primitive neuroectodermal tumors; pituitary tumor; pituitary adenoma; plasma cell neoplasia/multiple myeloma; pleuropulmonary blastoma; primary central nervous system lymphoma; prostate cancer; rectal cancer; renal cell carcinoma (kidney cancer); renal pelvis and ureter, transitional cell cancer; respiratory tract carcinoma involving the NUT gene on chromosome 15; retinoblastoma; rhabdomyosarcoma, childhood; salivary gland cancer;

sarcoma, Ewing family of tumors; Sézary syndrome; skin cancer (melanoma); skin cancer (non-melanoma); small cell lung cancer; small intestine cancer soft tissue sarcoma; soft tissue sarcoma; spinal cord tumor; squamous cell carcinoma; squamous neck cancer with occult primary, metastatic; stomach (gastric) cancer; supratentorial primitive neuroectodermal tumor; T-cell lymphoma, cutaneous (Mycosis Fungoides and Sézary syndrome); testicular cancer; throat cancer; thymoma; thymoma and thymic carcinoma; thyroid cancer; thyroid cancer, childhood; transitional cell cancer of the renal pelvis and ureter; urethral cancer; uterine cancer, endometrial; uterine sarcoma; vaginal cancer; vulvar cancer; and Wilms Tumor.

[0031] Also provided herein are kits that can be used to perform the methods described herein. Thus, in certain embodiments, the kit provided herein includes one or more containers and instructions for use, wherein the one or more containers comprise a composition (*e.g.*, pharmaceutical, immunogenic or vaccine composition) provided herein. In other certain embodiments, a kit provided herein includes containers that each contain the active ingredients for performing the methods described herein. Thus, in certain embodiments, the kit provided herein includes two or more containers and instructions for use, wherein one of the containers comprises an infectious, replication-deficient arenavirus particle provided herein and another container that comprises a chemotherapeutic agent provided herein. In a specific embodiment, a kit provided herein includes two or more containers and instructions for use, wherein one of the containers comprises an infectious, replication-deficient arenavirus particle provided herein and another container that comprises a chemotherapeutic agent provided herein, wherein the arenavirus particle is engineered to contain a genome comprising: a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and the ability to amplify and express its genetic information in infected cells but unable to produce further infectious progeny particles in non-complementing cells.

3.2 Arenavirus Particles having Non-natural Open Reading Frame

[0032] In certain embodiments, arenaviruses with rearrangements of their ORFs in their genomes and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof can be used with the methods and compositions provided herein, such as combinations with a chemotherapeutic agent. In a particular embodiment, an arenavirus particle provided herein includes an arenavirus genomic segment that has been engineered to carry an arenavirus ORF in a position other than the wild-type position. Thus, in certain

particular embodiments, provided herein is an arenavirus genomic segment comprising: a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and at least one arenavirus ORF in a position other than the wild-type position of said ORF, wherein the ORF encodes the glycoprotein (“GP”), the nucleoprotein (“NP”), the matrix protein Z (“Z protein”) or the RNA dependent RNA polymerase L (“L protein”) of an arenavirus particle. Also provided herein is an arenavirus particle that has been engineered to contain such an arenavirus genomic segment.

[0033] In certain embodiments, an arenavirus particle provided herein is infectious, *i.e.*, it is capable of entering into or injecting its genetic material into a host cell. In certain more specific embodiments, an arenavirus particle as provided herein is infectious, *i.e.*, is capable of entering into or injecting its genetic material into a host cell followed by amplification and expression of its genetic information inside the host cell. In certain embodiments, the arenavirus particle provided herein is engineered to be an infectious, replication-deficient arenavirus particle, *i.e.*, it contains a genome with the ability to amplify and express its genetic information in infected cells but unable to produce further infectious progeny particles in non-complementing cells.

[0034] The tumor antigen or tumor associated antigen encoded by the nucleotide sequence included within an arenavirus genomic segment or arenavirus particle provided herein can be one or more of the tumor antigens or tumor associated antigens selected from the group consisting of oncogenic viral antigens, cancer-testis antigens, oncofetal antigens, tissue differentiation antigens, mutant protein antigens, Adipophilin, AIM-2, ALDH1AI, BCLX (L), BING-4, CALCA, CD45, CPSF, cyclin D1, DKKI, ENAH (hMcna), Ga733 (EpCAM), EphA3, EZH2, FGF5, glypican-3, G250 /MN/CAIX, HER-2/neu, IDO1, IGF2B3, IL13Ralpha2, Intestinal carboxyl esterase, alpha-fetoprotein, Kallikrein 4, KIF20A, Lengsin, M-CSF, MCSP, mdm-2, Meloe, MMP-2, MMP-7, MUC1, MUC5AC, p53 (non-mutant), PAX5, PBF, PRAME, PSMA, RAGE, RAGE-1, RGS5, RhoC, RNF43, RU2AS, secernin 1, SOX10, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), survivin, Telomerase, VEGF, WT1, EGF-R, CEA, CD20, CD33, CD52, MELANA/MART1, MART2, NY-ESO-1, p53, MAGE A1, MAGE A3, MAGE-4, MAGE-5, MAGE-6, CDK4, alpha-actinin-4, ARTC1, BCR-ABL, BCR-ABL fusion protein (b3a2), B-RAF, CASP-5, CASP-8, beta-catenin, Cdc27, CDK4, CDKN2A, CLPP, COA-1, dek-can fusion protein, EFTUD2, Elongation factor 2, ETV6-AML, ETV6-AML1

fusion protein, FLT3-ITD, FNL, GPNMB, LDLR-fucosyltransferaseAS fusion protein, NFYC, OGT, OS-9, pml-RARalpha fusion protein, PRDX5, PTPRK, H-ras, K-ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene), N-ras, RBAF600, SIRT2, SNRPD1, SSX, SSX2, SYT-SSX1 or-SSX2 fusion protein, TGF-betaRII, Triosephosphate isomerase, ormdm-2, LMP2, HPV E6 / E7, EGFRvIII (epidermal growth factor variant III), Idiotypic, GD2, ganglioside G2), Ras-mutant, p53 (mutant), Proteinase3 (PR1), Tyrosinase, PSA, hTERT, Sarcoma translocation breakpoints, EphA2, prostatic acid phosphatase PAP, neo-PAP, ML-IAP, AFP, ERG (TMPRSS2 ETS Fusion gene), NA17, PAX3, ALK, Androgen Receptor, Cyclin B1, Polysialic acid, MYCN, TRP2, TRP2-Int2, GD3, Fucosyl GM1, Mesothelin, PSCA, sLe(a), cyp1B1, PLAC1, GM3, BORIS, Tn, GLoboH, NY-BR-1, SART3, STn, Carbonic Anhydrase IX, OY-TES1, Sperm protein 17, LCK, high molecular weight melanoma-associated antigen (HMWMAA), AKAP-4, SSX2, XAGE 1, B7H3, Legumain, Tie 2, Page4, VEGFR2, MAD-CT-1, FAP, PDGFR-beta, MAD-CT-2, For-related antigen 1, TRP-1, GP100, CA-125, CA19-9, Calretinin, Epithelial membrane antigen (EMA), Epithelial tumor antigen (ETA), CD19, CD34, CD99, CD117, Chromogranin, Cytokeratin, Desmin, Glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, Myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), BAGE BAGE-1, CAGE, CTAGE, FATE, GAGE, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, HCA661, HOM-TES-85, MAGEA, MAGEB, MAGEC, NA88, NY-SAR-35, SPANXB1, SPA17, SSX, SYCP1, TPTE, Carbohydrate / ganglioside GM2 (oncofetal antigen-immunogenic-1 OFA-I-1), GM3, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA 50, CAM 43, CEA, EBNA, EF2, Epstein-Barr virus antigen, HLA-A2, HLA-A11, HSP70-2, KIAA0205, MUM-1, MUM-2, MUM-3, Myosin class I, GnTV, Herv-K-mel, LAGE-1, LAGE-2, (sperm protein) SP17, SCP-1, P15(58), Hom/Mel-40, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, TSP-180, P185erbB2, p180erbB-3, c-met, nm-23H1, TAG-72, TAG-72-4, CA-72-4, CAM 17.1, NuMa, 13-catenin, P16, TAGE, CT7, 43-9F, 5T4, 791Tgp72, 13HCG, BCA225, BTAA, CD68\KP1, CO-029, HTgp-175, M344, MG7-Ag, MOV18, NB\70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TLP, TPS, CD22, CD27, CD30, CD70, prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, integrin $\alpha\text{v}\beta\text{3}$ (CD61), galactin, or Ral-B, CD123, CLL-1, CD38, CS-1, CD138, and ROR1. In certain embodiments,

the nucleotide sequence encodes two, three, four, five, six, seven, eight, nine, ten or more tumor antigens, tumor associated antigens or antigenic fragments thereof. In certain embodiments, an antigenic fragment of a tumor antigen or tumor associated antigen provided herein is encoded by the nucleotide sequence included within the arenavirus.

[0035] Accordingly, in certain embodiments, provided herein is an arenavirus genomic segment comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In certain embodiments, the genomic segment is engineered to carry an arenavirus ORF in a position other than the wild-type position of the ORF. In some embodiments, the arenavirus genomic segment is selected from the group consisting of:

- (i) an S segment, wherein the ORF encoding the NP is under control of an arenavirus 5' UTR;
- (ii) an S segment, wherein the ORF encoding the Z protein is under control of an arenavirus 5' UTR;
- (iii) an S segment, wherein the ORF encoding the L protein is under control of an arenavirus 5' UTR;
- (iv) an S segment, wherein the ORF encoding the GP is under control of an arenavirus 3' UTR;
- (v) an S segment, wherein the ORF encoding the L protein is under control of an arenavirus 3' UTR;
- (vi) an S segment, wherein the ORF encoding the Z protein is under control of an arenavirus 3' UTR;
- (vii) an L segment, wherein the ORF encoding the GP is under control of an arenavirus 5' UTR;
- (viii) an L segment, wherein the ORF encoding the NP is under control of an arenavirus 5' UTR;
- (ix) an L segment, wherein the ORF encoding the L protein is under control of an arenavirus 5' UTR;
- (x) an L segment, wherein the ORF encoding the GP is under control of an arenavirus 3' UTR;

- (xi) an L segment, wherein the ORF encoding the NP is under control of an arenavirus 3' UTR; and
- (xii) an L segment, wherein the ORF encoding the Z protein is under control of an arenavirus 3' UTR.

[0036] In certain embodiments, the arenavirus 3' UTR is the 3' UTR of the arenavirus S segment or the arenavirus L segment. In certain embodiments, the arenavirus 5' UTR is the 5' UTR of the arenavirus S segment or the arenavirus L segment.

[0037] In certain embodiments, the arenavirus particle provided herein comprises a second arenavirus genomic segment so that the arenavirus particle comprises an S segment and an L segment.

[0038] In certain embodiments, an arenavirus particle provided herein is infectious, *i.e.*, it is capable of entering into or injecting its genetic material into a host cell. In certain more specific embodiments, an arenavirus particle as provided herein is infectious, *i.e.*, is capable of entering into or injecting its genetic material into a host cell followed by amplification and expression of its genetic information inside the host cell. In certain embodiments, the arenavirus particle is an infectious, replication-deficient arenavirus particle engineered to contain a genome with the ability to amplify and express its genetic information in infected cells but unable to produce further infectious progeny particles in non-complementing cells. In certain embodiments, the arenavirus particle is replication-competent and able to produce further infectious progeny particles in normal, not genetically engineered cells. In certain more specific embodiments, such a replication-competent particle is attenuated relative to the wild type virus from which the replication-competent particle is derived.

[0039] In certain embodiments, an arenavirus genomic segment provided herein, including an arenavirus particle comprising the arenavirus genomic segment, comprises at least one arenavirus ORF that is at least partially removed or functionally inactivated. The ORF can encode the GP, NP, Z protein, or L protein of an arenavirus particle. Additionally, in certain embodiments, at least one ORF encoding the GP, NP, Z protein, or L protein is removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In certain embodiments, only one of the four ORFs encoding GP, NP, Z protein, and L protein is removed. Thus, in certain embodiments, the ORF encoding GP is removed. In certain embodiments, the ORF encoding NP is removed. In certain

embodiments, the ORF encoding Z protein is removed. In certain embodiments, the ORF encoding L protein is removed.

[0040] In certain embodiments, an arenavirus particle provided herein is derived from a specific arenavirus species, such as lymphocytic choriomeningitis virus (“LCMV”), Junin virus (“JUNV”), or Pichinde virus (“PICV”). In other words, the genomic information encoding the arenavirus particle is derived from a specific species of arenavirus. Thus, in certain embodiments, the arenavirus particle is derived from LCMV. In other embodiments, the arenavirus particle is derived from JUNV. In other embodiments, the arenavirus particle is derived from PICV. Additionally, in specific embodiments, the LCMV is MP strain, WE strain, Armstrong strain, or Armstrong Clone 13 strain. In other specific embodiments, the JUNV is JUNV vaccine Candid #1 strain, or JUNV vaccine XJ Clone 3 strain. In other specific embodiments, the PICV is strain Munchique CoAn4763 isolate P18, or P2 strain.

(a) Tri-segmented Arenaviruses

[0041] In certain embodiments, tri-segmented arenavirus particles comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof can be used with the methods and compositions provided herein, such as combinations with a chemotherapeutic agent. Thus, in certain embodiments, an arenavirus particle provided herein can comprise one L segment and two S segments or two L segments and one S segment. In certain embodiments, the tri-segmented arenavirus particle provided herein does not recombine into a replication-competent bi-segmented arenavirus particle. Accordingly, in certain embodiments, propagation of the tri-segmented arenavirus particle does not result in a replication-competent bi-segmented particle after 70 days of persistent infection in mice lacking type I interferon receptor, type II interferon receptor and recombination activating gene 1 (RAG1) and having been infected with 10^4 PFU of the tri-segmented arenavirus particle. The tri-segmented arenavirus particles provided herein, in certain embodiments, can be engineered to improve genetic stability and ensure lasting transgene expression. Moreover, in certain embodiments, inter-segmental recombination of the two S segments or two L segments, uniting two arenavirus ORFs on only one instead of two separate segments, abrogates viral promoter activity.

[0042] In certain embodiments, a tri-segmented arenavirus particle, as provided herein, is infectious, *i.e.*, it is capable of entering into or injecting its genetic material into a host cell. In

certain more specific embodiments, a tri-segmented arenavirus particle as provided herein is infectious, *i.e.*, is capable of entering into or injecting its genetic material into a host cell followed by amplification and expression of its genetic information inside the host cell. In certain embodiments, the tri-segmented arenavirus particle is an infectious, replication-deficient arenavirus particle engineered to contain a genome with the ability to amplify and express its genetic information in infected cells but unable to produce further infectious progeny particles in non-complementing cells. In certain embodiments, the tri-segmented arenavirus particle is replication-competent and able to produce further infectious progeny particles in normal, not genetically engineered cells. In certain more specific embodiments, such a replication-competent particle is attenuated relative to the wild type virus from which the replication-competent particle is derived.

[0043] The tumor antigen or tumor associated antigen encoded by the nucleotide sequence included within a tri-segmented arenavirus particle provided herein can be one or more of the tumor antigens or tumor associated antigens selected from the group consisting of oncogenic viral antigens, cancer-testis antigens, oncofetal antigens, tissue differentiation antigens, mutant protein antigens, Adipophilin, AIM-2, ALDH1A1, BCLX (L), BING-4, CALCA, CD45, CPSF, cyclin D1, DKK1, ENAH (hMena), Ga733 (EpCAM), EphA3, EZH2, FGF5, glypican-3, G250 /MN/CAIX, HER-2/neu, IDO1, IGF2B3, IL13Ralpha2, Intestinal carboxyl esterase, alpha-foetoprotein, Kallikrein 4, KIF20A, Lengsin, M-CSF, MCSP, mdm-2, Meloe, MMP-2, MMP-7, MUC1, MUC5AC, p53 (non-mutant), PAX5, PBF, PRAME, PSMA, RAGE, RAGE-1, RGS5, RhoC, RNF43, RU2AS, secernin 1, SOX10, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), survivin, Telomerase, VEGF, WT1, EGF-R, CEA, CD20, CD33, CD52, MELANA/MART1, MART2, NY-ESO-1, p53, MAGE A1, MAGE A3, MAGE-4, MAGE-5, MAGE-6, CDK4, alpha-actinin-4, ARTC1, BCR-ABL, BCR-ABL fusion protein (b3a2), B-RAF, CASP-5, CASP-8, beta-catenin, Cdc27, CDK4, CDKN2A, CLPP, COA-1, dek-can fusion protein, EFTUD2, Elongation factor 2, ETV6-AML, ETV6-AML1 fusion protein, FLT3-ITD, FN1, GPNMB, LDLR-fucosyltransferaseAS fusion protein, NFYC, OGT, OS-9, pml-RARalpha fusion protein, PRDX5, PTPRK, H-ras, K-ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene), N-ras, RBAF600, SIRT2, SNRPD1, SSX, SSX2, SYT-SSX1 or-SSX2 fusion protein, TGF-betaRII, Triosephosphate isomerase, ormdm-2, LMP2, HPV E6 / E7, EGFRvIII (epidermal growth factor variant III), Idiotype, GD2, ganglioside G2), Ras-mutant,

p53 (mutant), Proteinase3 (PR1), Tyrosinase, PSA, hTERT, Sarcoma translocation breakpoints, EphA2, prostatic acid phosphatase PAP, neo-PAP, ML-IAP, AFP, ERG (TMPRSS2 ETS Fusion gene), NA17, PAX3, ALK, Androgen Receptor, Cyclin B1, Polysialic acid, MYCN, TRP2, TRP2-Int2, GD3, Fucosyl GM1, Mesothelin, PSCA, sLe(a), cyp1B1, PLAC1, GM3, BORIS, Tn, GLobH, NY-BR-1, SART3, STn, Carbonic Anhydrase IX, OY-TES1, Sperm protein 17, LCK, high molecular weight melanoma-associated antigen (HMWMAA), AKAP-4, SSX2, XAGE 1, B7H3, Legumain, Tie 2, Page4, VEGFR2, MAD-CT-1, FAP, PDGFR-beta, MAD-CT-2, For-related antigen 1, TRP-1, GP100, CA-125, CA19-9, Calretinin, Epithelial membrane antigen (EMA), Epithelial tumor antigen (ETA), CD19, CD34, CD99, CD117, Chromogranin, Cytokeratin, Desmin, Glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, Myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), BAGE BAGE-1, CAGE, CTAGE, FATE, GAGE, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, HCA661, HOM-TES-85, MAGEA, MAGEB, MAGEC, NA88, NY-SAR-35, SPANXB1, SPA17, SSX, SYCP1, TPTE, Carbohydrate / ganglioside GM2 (oncofetal antigen-immunogenic-1 OFA-I-1), GM3, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA 50, CAM 43, CEA, EBNA, EF2, Epstein-Barr virus antigen, HLA-A2, HLA-A11, HSP70-2, KIAA0205, MUM-1, MUM-2, MUM-3, Myosin class I, GnTV, Herv-K-mel, LAGE-1, LAGE-2, (sperm protein) SP17, SCP-1, P15(58), Hom/Mel-40, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, TSP-180, P185erbB2, p180erbB-3, c-met, nm-23H1, TAG-72, TAG-72-4, CA-72-4, CAM 17.1, NuMa, 13-catenin, P16, TAGE, CT7, 43-9F, 5T4, 791Tgp72, 13HCG, BCA225, BTAA, CD68\KP1, CO-029, HTgp-175, M344, MG7-Ag, MOV18, NB\70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TLP, TPS, CD22, CD27, CD30, CD70, prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, integrin $\alpha\beta 3$ (CD61), galactin, or Ral-B, CD123, CLL-1, CD38, CS-1, CD138, and ROR1. In certain embodiments, the nucleotide sequence encodes two, three, four, five, six, seven, eight, nine, ten or more tumor antigens, tumor associated antigens or antigenic fragments thereof. In certain embodiments, an antigenic fragment of a tumor antigen or tumor associated antigen provided herein is encoded by the nucleotide sequence included within the tri-segmented arenavirus.

[0044] In certain embodiments, provided herein are tri-segmented arenaviruses with rearrangements of their ORFs in their genomes and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In a particular embodiment, a tri-segmented arenavirus particle provided herein has been engineered to carry an arenavirus ORF in a position other than the wild-type position. Thus, in certain particular embodiments, provided herein is a tri-segmented arenavirus comprising: a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and at least one arenavirus ORF in a position other than the wild-type position of said ORF, wherein the ORF encodes the GP, NP, Z protein or L protein of an arenavirus particle.

[0045] In certain embodiments, one of the two S segments included in the tri-segmented arenavirus particle provided herein is selected from the group consisting of:

- (i) an S segment, wherein the ORF encoding the NP is under control of an arenavirus 5' UTR
- (ii) an S segment, wherein the ORF encoding the Z protein is under control of an arenavirus 5' UTR;
- (iii) an S segment, wherein the ORF encoding the L protein is under control of an arenavirus 5' UTR;
- (iv) an S segment, wherein the ORF encoding the GP is under control of an arenavirus 3' UTR;
- (v) an S segment, wherein the ORF encoding the L protein is under control of an arenavirus 3' UTR; and
- (vi) an S segment, wherein the ORF encoding the Z protein is under control of an arenavirus 3' UTR.

[0046] In certain embodiments, one of the two L segments included in the tri-segmented arenavirus particle provided herein is selected from the group consisting of:

- (xiii) an L segment, wherein the ORF encoding the GP is under control of an arenavirus 5' UTR;
- (xiv) an L segment, wherein the ORF encoding the NP is under control of an arenavirus 5' UTR;
- (xv) an L segment, wherein the ORF encoding the L protein is under control of an arenavirus 5' UTR;

- (xvi) an L segment, wherein the ORF encoding the GP is under control of an arenavirus 3' UTR;
- (xvii) an L segment, wherein the ORF encoding the NP is under control of an arenavirus 3' UTR; and
- (xviii) an L segment, wherein the ORF encoding the Z protein is under control of an arenavirus 3' UTR.

[0047] In certain embodiments, the tri-segmented arenavirus particle 3' UTR is the 3' UTR of the arenavirus S segment or the arenavirus L segment. In other embodiments, the tri-segmented arenavirus particle 5' UTR is the 5' UTR of the arenavirus S segment or the arenavirus L segment.

[0048] In certain embodiments, the two S segments comprise: (i) one or two nucleotide sequences each encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; or (ii) one or two duplicated arenavirus ORFs; or (iii) one nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof and one duplicated arenavirus ORF.

[0049] In certain embodiments, the two L segments comprise (i) one or two nucleotide sequences each encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; or (ii) one or two duplicated arenavirus ORFs; or (iii) one nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof and one duplicated arenavirus ORF.

[0050] In certain embodiments, a tri-segmented arenavirus particle provided herein, comprises at least one arenavirus ORF that is at least partially removed or functionally inactivated. The ORF can encode the GP, NP, Z protein, or L protein of an arenavirus particle. Additionally, in certain embodiments, at least one ORF encoding the GP, NP, Z protein, or L protein is removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In certain embodiments, only one of the four ORFs encoding GP, NP, Z protein, and L protein is removed. Thus, in certain embodiments, the ORF encoding GP is removed. In certain embodiments, the ORF encoding NP is removed. In certain embodiments, the ORF encoding Z protein is removed. In certain embodiments, the ORF encoding L protein is removed.

[0051] In certain embodiments, an arenavirus particle provided herein is derived from a specific arenavirus species, such as lymphocytic choriomeningitis virus (“LCMV”), Junin virus (“JUNV”), or Pichinde virus (“PICV”). In other words, the genomic information encoding the arenavirus particle is derived from a specific species of arenavirus. Thus, in certain embodiments, the arenavirus particle is derived from LCMV. In other embodiments, the arenavirus particle is derived from JUNV. In other embodiments, the arenavirus particle is derived from PICV. Additionally, in specific embodiments, the LCMV is MP strain, WE strain, Armstrong strain, or Armstrong Clone 13 strain. In other specific embodiments, the JUNV is JUNV vaccine Candid #1 strain, or JUNV vaccine XJ Clone 3 strain. In other specific embodiments, the PICV is strain Munchique CoAn4763 isolate P18, or P2 strain.

(b) Methods for Treating a Neoplastic Disease

[0052] In certain embodiments, provided herein are methods of treating a neoplastic disease in a subject. Such methods can include administering to a subject in need thereof an arenavirus particle, including a tri-segmented arenavirus particle, provided herein in combination with a chemotherapeutic agent provided herein.

[0053] In certain embodiments, the arenavirus particle used in the methods is an infectious, replication-deficient arenavirus particle provided herein. In certain embodiments, the arenavirus particle used in the methods is a tri-segmented arenavirus particle provided herein, including an infectious, replication-deficient tri-segmented arenavirus particle or a replication-competent tri-segmented arenavirus particle. Thus, in certain embodiments, the arenavirus particle, including a tri-segmented arenavirus particle, used in the methods is replication deficient, wherein the tri-segmented arenavirus particle is engineered to contain a genome comprising: (1) a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and (2) the ability to amplify and express its genetic information in infected cells but unable to produce further infectious progeny particles in non-complementing cells. Moreover, in certain embodiments, a tri-segmented arenavirus particle used in the methods is replication-competent, wherein the tri-segmented arenavirus particle is engineered to contain a genome comprising: (1) a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; (2) the ability to amplify and express its genetic information in infected cells; and (3) the ability to produce further infectious progeny particles in normal, not genetically engineered cells.

[0054] In certain embodiments, the tumor antigen or tumor associated antigen encoded by the nucleotide sequence included within an arenavirus particle, including a tri-segmented arenavirus particle, provided herein can be one or more of the tumor antigens or tumor associated antigens selected from the group consisting of oncogenic viral antigens, cancer-testis antigens, oncofetal antigens, tissue differentiation antigens, mutant protein antigens, Adipophilin, AIM-2, ALDH1AI, BCLX (L), BING-4, CALCA, CD45, CPSF, cyclin D1, DKKI, ENAH (hMena), Ga733 (EpCAM), EphA3, EZH2, FGF5, glypican-3, G250 /MN/CAIX, HER-2/neu, IDO1, IGF2B3, IL13Ralpha2, Intestinal carboxyl esterase, alpha-foetoprotein, Kallikrein 4, KIF20A, Lengsin, M-CSF, MCSP, mdm-2, Meloe, MMP-2, MMP-7, MUC1, MUC5AC, p53 (non-mutant), PAX5, PBF, PRAME, PSMA, RAGE, RAGE-1, RGS5, RhoC, RNF43, RU2AS, secernin 1, SOX10, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), survivin, Telomerase, VEGF, WT1, EGF-R, CEA, CD20, CD33, CD52, MELANA/MART1, MART2, NY-ESO-1, p53, MAGE A1, MAGE A3, MAGE-4, MAGE-5, MAGE-6, CDK4, alpha-actinin-4, ARTC1, BCR-ABL, BCR-ABL fusion protein (b3a2), B-Raf, CASP-5, CASP-8, beta-catenin, Cdc27, CDK4, CDKN2A, CLPP, COA-1, dek-can fusion protein, EFTUD2, Elongation factor 2, ETV6-AML, ETV6-AML1 fusion protein, FLT3-ITD, FNL, GPNMB, LDLR-fucosyltransferaseAS fusion protein, NFYC, OGT, OS-9, pml-RARalpha fusion protein, PRDX5, PTPRK, H-ras, K-ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene), N-ras, RBAF600, SIRT2, SNRPDI, SSX, SSX2, SYT-SSX1 or-SSX2 fusion protein, TGF-betaRII, Triosephosphate isomerase, ormdm-2, LMP2, HPV E6 / E7, EGFRvIII (epidermal growth factor variant III), Idiotype, GD2, ganglioside G2), Ras-mutant, p53 (mutant), Proteinase3 (PR1), Tyrosinase, PSA, hTERT, Sarcoma translocation breakpoints, EphA2, prostatic acid phosphatase PAP, neo-PAP, ML-IAP, AFP, ERG (TMPRSS2 ETS Fusion gene), NA17, PAX3, ALK, Androgen Receptor, Cyclin B1, Polysialic acid, MYCN, TRP2, TRP2-Int2, GD3, Fucosyl GM1, Mesothelin, PSCA, sLe(a), cyp1B1, PLAC1, GM3, BORIS, Tn, GLobH, NY-BR-1, SART3, STn, Carbonic Anhydrase IX, OY-TES1, Sperm protein 17, LCK, high molecular weight melanoma-associated antigen (HMWMAA), AKAP-4, SSX2, XAGE 1, B7H3, Legumain, Tie 2, Page4, VEGFR2, MAD-CT-1, FAP, PDGFR-beta, MAD-CT-2, For-related antigen 1, TRP-1, GP100, CA-125, CA19-9, Calretinin, Epithelial membrane antigen (EMA), Epithelial tumor antigen (ETA), CD19, CD34, CD99, CD117, Chromogranin, Cytokeratin, Desmin, Glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45

antigen, Myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), BAGE BAGE-1, CAGE, CTAGE, FATE, GAGE, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, HCA661, HOM-TES-85, MAGEA, MAGEB, MAGEC, NA88, NY-SAR-35, SPANXB1, SPA17, SSX, SYCP1, TPTE, Carbohydrate / ganglioside GM2 (oncofetal antigen-immunogenic-1 OFA-I-1), GM3, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA 50, CAM 43, CEA, EBNA, EF2, Epstein-Barr virus antigen, HLA-A2, HLA-A11, HSP70-2, KIAA0205, MUM-1, MUM-2, MUM-3, Myosin class I, GnTV, Herv-K-mel, LAGE-1, LAGE-2, (sperm protein) SP17, SCP-1, P15(58), Hom/Mel-40, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, TSP-180, P185erbB2, p180erbB-3, c-met, nm-23H1, TAG-72, TAG-72-4, CA-72-4, CAM 17.1, NuMa, 13-catenin, P16, TAGE, CT7, 43-9F, 5T4, 791Tgp72, 13HCG, BCA225, BTAA, CD68\KP1, CO-029, HTgp-175, M344, MG7-Ag, MOV18, NB\70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TLP, TPS, CD22, CD27, CD30, CD70, prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, integrin $\alpha\beta$ 3 (CD61), galactin, or Ral-B, CD123, CLL-1, CD38, CS-1, CD138, and ROR1. In certain embodiments, the nucleotide sequence encodes two, three, four, five, six, seven, eight, nine, ten or more tumor antigen, tumor associated antigens or antigenic fragments thereof. In certain embodiments, an antigenic fragment of a tumor antigen, tumor associated antigen provided herein is encoded by the nucleotide sequence included within the arenavirus, including a tri-segmented arenavirus. In specific embodiments, the tumor antigen is selected from the group consisting of GP100, Trp1, Trp2, and a combination thereof. In specific embodiments, the tumor antigen is GP100. In specific embodiments, the tumor antigen is Trp1. In specific embodiments, the tumor antigen is Trp2.

[0055] In certain embodiments, provided herein are methods for treating a neoplastic disease in a subject by administering a chemotherapeutic agent in combination with a tri-segmented arenavirus particle. In certain embodiments, the chemotherapeutic agent is an alkylating agent (*e.g.*, cyclophosphamide), a platinum-based therapeutic, an antimetabolite, a topoisomerase inhibitor, a cytotoxic antibiotic, an intercalating agent, a mitosis inhibitor, a taxane, or a combination of two or more thereof. In certain embodiments, the alkylating agent is a nitrogen mustard, a nitrosourea, an alkyl sulfonate, a non-classical alkylating agent, or a

triazene. In certain embodiments, the chemotherapeutic agent comprises one or more of cyclophosphamide, thiotepa, mechlorethamine (chlormethine/mustine), uramustine, melphalan, chlorambucil, ifosfamide, chlornaphazine, cholophosphamide, estramustine, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, bendamustine, busulfan, improsulfan, piposulfan, carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine, streptozucin, cisplatin, carboplatin, nedaplatin, oxaliplatin, satraplatin, triplatin tetranitrate, procarbazine, altretamine, dacarbazine, mitozolomide, temozolomide, paclitaxel, docetaxel, vinblastine, vincristine, vinorelbine, cabazitaxel, dactinomycin (actinomycin D), calicheamicin, dynemicin, amsacrine, doxorubicin, daunorubicin, epirubicin, mitoxantrone, idarubicin, pirarubicin, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolomelamine, bullatacin, bullatacinone, camptothecin, topotecan, bryostatin, callystatin, CC-1065, adozelesin, carzelesin, bizelesin, cryptophycin, dolastatin, duocarmycin, KW-2189, CB1-TM1, eleutherobin, pancratistatin, sarcodictyin, spongistatin, clodronate, esperamicin, neocarzinostatin chromophore, aclacinomycin, anthramycin, azaserine, bleomycin, cactinomycin, carabycin, carminomycin, carzinophilin, chromomycinis, detorubicin, 6-diazo-5-oxo-L-norleucine, esorubicin, idarubicin, marcellomycin, mitomycin, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, methotrexate, 5-fluorouracil (5-FU), denopterin, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiothane, testolactone, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elformithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansine, ansamitocins, mitoguazone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, PSK polysaccharide complex, razoxane, rhizoxin, sizofiran, spirogermanium, tenuazonic acid, triaziquone, 2,2',2''-trichlorotriethylamine; T-2 toxin, verracurin A, roridin A and anguidine, urethan, vindesine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside ("Ara-C"), etoposide (VP-16), vinorelbine, novantrone, teniposide, edatrexate, aminopterin, xeloda,

ibandronate, irinotecan (e.g., CPT-11), topoisomerase inhibitor RFS 2000, difluoromethylthylornithine (DMFO), retinoic acid, capecitabine, plicomycin, gemcitabine, navelbine, transplatin, and pharmaceutically acceptable salts, acids, or derivatives of any of the above. In specific embodiments, the chemotherapeutic agent comprises cyclophosphamide. In certain embodiments, the nitrogen mustard is mechlorethamine, cyclophosphamide, melphalan, chlorambucil, ifosfamide, or busulfan. In certain embodiments, the chemotherapeutic agent alkylates DNA. In certain embodiments, the chemotherapeutic agent alkylates DNA, resulting in the formation of interstrand cross-links (“ICLs”).

[0056] In certain embodiments, provided herein are methods for treating a neoplastic disease in a subject by administering a chemotherapeutic agent in combination with a tri-segmented arenavirus particle and an immune checkpoint inhibitor that inhibits, decreases or interferes with the activity of a negative checkpoint regulator. In certain embodiments, the negative checkpoint regulator is selected from the group consisting of Cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD80, CD86, Programmed cell death 1 (PD-1), Programmed cell death ligand 1 (PD-L1), Programmed cell death ligand 2 (PD-L2), Lymphocyte activation gene-3 (LAG-3; also known as CD223), Galectin-3, B and T lymphocyte attenuator (BTLA), T-cell membrane protein 3 (TIM3), Galectin-9 (GAL9), B7-H1, B7-H3, B7-H4, T-Cell immunoreceptor with Ig and ITIM domains (TIGIT/Vstm3/WUCAM/VSIG9), V-domain Ig suppressor of T-Cell activation (VISTA), Glucocorticoid-induced tumor necrosis factor receptor-related (GITR) protein, Herpes Virus Entry Mediator (HVEM), OX40, CD27, CD28, CD137, CGEN-15001T, CGEN-15022, CGEN-15027, CGEN-15049, CGEN-15052, and CGEN-15092. In certain embodiments, the immune checkpoint inhibitor is an anti-PD-1 antibody.

[0057] In certain embodiments, the subject that is treated using the methods provided herein is suffering from, is susceptible to, or is at risk for a neoplastic disease. Thus, in some embodiments, the subject is suffering from a neoplastic disease. In some embodiments, the subject is susceptible to a neoplastic disease. In some embodiments, the subject is at risk for a neoplastic disease. In certain embodiments, the neoplastic disease of a subject treatable by the methods provided herein is selected from the group consisting of acute lymphoblastic leukemia; acute lymphoblastic lymphoma; acute lymphocytic leukaemia; acute myelogenous leukemia; acute myeloid leukemia (adult / childhood); adrenocortical carcinoma; AIDS-related cancers; AIDS-related lymphoma; anal cancer; appendix cancer; astrocytomas; atypical teratoid/rhabdoid

tumor; basal-cell carcinoma; bile duct cancer, extrahepatic (cholangiocarcinoma); bladder cancer; bone osteosarcoma/malignant fibrous histiocyoma; brain cancer (adult / childhood); brain tumor, cerebellar astrocytoma (adult / childhood); brain tumor, cerebral astrocytoma/malignant glioma brain tumor; brain tumor, ependymoma; brain tumor, medulloblastoma; brain tumor, supratentorial primitive neuroectodermal tumors; brain tumor, visual pathway and hypothalamic glioma; brainstem glioma; breast cancer; bronchial adenomas/carcinoids; bronchial tumor; Burkitt lymphoma; cancer of childhood; carcinoid gastrointestinal tumor; carcinoid tumor; carcinoma of adult, unknown primary site; carcinoma of unknown primary; central nervous system embryonal tumor; central nervous system lymphoma, primary; cervical cancer; childhood adrenocortical carcinoma; childhood cancers; childhood cerebral astrocytoma; chordoma, childhood; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloid leukemia; chronic myeloproliferative disorders; colon cancer; colorectal cancer; craniopharyngioma; cutaneous T-cell lymphoma; desmoplastic small round cell tumor; emphysema; endometrial cancer; ependymoblastoma; ependymoma; esophageal cancer; ewing's sarcoma in the Ewing family of tumors; extracranial germ cell tumor; extragonadal germ cell tumor; extrahepatic bile duct cancer; gallbladder cancer; gastric (stomach) cancer; gastric carcinoid; gastrointestinal carcinoid tumor; gastrointestinal stromal tumor; germ cell tumor: extracranial, extragonadal, or ovarian gestational trophoblastic tumor; gestational trophoblastic tumor, unknown primary site; glioma; glioma of the brain stem; glioma, childhood visual pathway and hypothalamic; hairy cell leukemia; head and neck cancer; heart cancer; hepatocellular (liver) cancer; hodgkin lymphoma; hypopharyngeal cancer; hypothalamic and visual pathway glioma; intraocular melanoma; islet cell carcinoma (endocrine pancreas); Kaposi Sarcoma; kidney cancer (renal cell cancer); langerhans cell histiocytosis; laryngeal cancer; lip and oral cavity cancer; liposarcoma; liver cancer (primary); lung cancer, non-small cell; lung cancer, small cell; lymphoma, primary central nervous system; macroglobulinemia, Waldenström; male breast cancer; malignant fibrous histiocyoma of bone/osteosarcoma; medulloblastoma; medulloepithelioma; melanoma; melanoma, intraocular (eye); merkel cell cancer; merkel cell skin carcinoma; mesothelioma; mesothelioma, adult malignant; metastatic squamous neck cancer with occult primary; mouth cancer; multiple endocrine neoplasia syndrome; multiple myeloma/plasma cell neoplasm; mycosis fungoides, myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; myelogenous leukemia, chronic;

myeloid leukemia, adult acute; myeloid leukemia, childhood acute; myeloma, multiple (cancer of the bone-marrow); myeloproliferative disorders, chronic; nasal cavity and paranasal sinus cancer; nasopharyngeal carcinoma; neuroblastoma, non-small cell lung cancer; non-hodgkin lymphoma; oligodendroglioma; oral cancer; oral cavity cancer; oropharyngeal cancer; osteosarcoma/malignant fibrous histiocytoma of bone; ovarian cancer; ovarian epithelial cancer (surface epithelial-stromal tumor); ovarian germ cell tumor; ovarian low malignant potential tumor; pancreatic cancer; pancreatic cancer, islet cell; papillomatosis; paranasal sinus and nasal cavity cancer; parathyroid cancer; penile cancer; pharyngeal cancer; pheochromocytoma; pineal astrocytoma; pineal germinoma; pineal parenchymal tumors of intermediate differentiation; pineoblastoma and supratentorial primitive neuroectodermal tumors; pituitary tumor; pituitary adenoma; plasma cell neoplasia/multiple myeloma; pleuropulmonary blastoma; primary central nervous system lymphoma; prostate cancer; rectal cancer; renal cell carcinoma (kidney cancer); renal pelvis and ureter, transitional cell cancer; respiratory tract carcinoma involving the NUT gene on chromosome 15; retinoblastoma; rhabdomyosarcoma, childhood; salivary gland cancer; sarcoma, Ewing family of tumors; Sézary syndrome; skin cancer (melanoma); skin cancer (non-melanoma); small cell lung cancer; small intestine cancer soft tissue sarcoma; soft tissue sarcoma; spinal cord tumor; squamous cell carcinoma; squamous neck cancer with occult primary, metastatic; stomach (gastric) cancer; supratentorial primitive neuroectodermal tumor; T-cell lymphoma, cutaneous (Mycosis Fungoides and Sézary syndrome); testicular cancer; throat cancer; thymoma; thymoma and thymic carcinoma; thyroid cancer; thyroid cancer, childhood; transitional cell cancer of the renal pelvis and ureter; urethral cancer; uterine cancer, endometrial; uterine sarcoma; vaginal cancer; vulvar cancer; and Wilms Tumor. In certain embodiments, the neoplastic disease of a subject treatable by the methods provided herein is melanoma. In specific embodiments, the neoplastic disease is melanoma and the chemotherapeutic agent is cyclophosphamide. In specific embodiments, the neoplastic disease is melanoma, the tumor antigen is selected from the group consisting of GP100, Trp1, Trp2, and a combination thereof, and the chemotherapeutic agent is cyclophosphamide. In specific embodiments, the neoplastic disease is melanoma, the tumor antigen is GP100, and the chemotherapeutic agent is cyclophosphamide. In specific embodiments, the neoplastic disease is melanoma, the tumor antigen is Trp2, and the chemotherapeutic agent is cyclophosphamide. In specific embodiments, the neoplastic disease is melanoma, the tumor antigen is Trp1, and the chemotherapeutic agent is

cyclophosphamide. In more specific embodiments, the neoplastic disease is melanoma, the tumor antigen is Trp1, the chemotherapeutic agent is cyclophosphamide, and the method further comprises administering an anti-PD-1 antibody.

[0058] In certain embodiments, the arenavirus particle, including a tri-segmented arenavirus, provided herein and chemotherapeutic agents, which are used in the methods provided herein, can be administered in a variety of different combinations. Thus, in certain embodiments, the arenavirus particle and the chemotherapeutic agent are co-administered simultaneously. In other embodiments, the arenavirus particle is administered prior to administration of the chemotherapeutic agent. In still other embodiments, the arenavirus particle is administered after administration of the chemotherapeutic agent. The interval between administration of the arenavirus particle and the chemotherapeutic agent can be hours, days, weeks or months. Thus, in some embodiments, the interval is about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, or more.

[0059] In certain embodiments, the method provided here includes administering an arenavirus particle, including a tri-segmented arena virus, provided herein and the chemotherapeutic agent provided herein in a therapeutically effective amount. Thus, in certain embodiments, provided herein is a method for treating a neoplastic disease in a subject comprising, administering to a subject in need thereof a therapeutically effective amount of an arenavirus particle and a therapeutically effective amount of a chemotherapeutic agent, wherein the arenavirus particle is engineered to contain a genomic segment comprising: a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and at least one arenavirus ORF in a position other than the wild-type position of the ORF, wherein the ORF encodes the GP, NP, Z protein or L protein of the arenavirus particle.

[0060] In certain embodiments, provided herein are methods of treating a neoplastic disease in a subject comprising, administering to the subject two or more arenaviruses, including

a tri-segmented arenavirus, provided herein expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof. In a more specific embodiment, the method provided herein includes administering to the subject a first arenavirus particle, and administering to the subject, after a period of time, a second arenavirus particle. In still another embodiment, the first arenavirus particle and the second arenavirus particle are derived from different arenavirus species and/or comprise nucleotide sequences encoding different tumor antigen, tumor associated antigens or antigenic fragments thereof.

[0061] In certain embodiments, the methods and compositions provided herein are used in combination with personalized medicine. Personalized medicine seeks to benefit patients by using information from a patient's unique genetic and/or epigenetic profile to predict a patient's response to different therapies and identify which therapies are more likely to be effective. Techniques that can be used in combination with the methods and compositions provided herein to obtain a patient's unique genetic and/or epigenetic profile include, but are not limited to, genome sequencing, RNA sequencing, gene expression analysis and identification of a tumor antigen (e.g., neoantigen), tumor associated antigen or an antigenic fragment thereof. In certain embodiments, the selection of an arenavirus tumor antigen or tumor associated antigen for use in the methods and compositions provided herein is performed based on the genetic profile of the patient. In certain embodiments, the selection of an arenavirus tumor antigen or tumor associated antigen for use in the methods and compositions provided herein is performed based on the genetic profile of a tumor or tumor cell. In certain embodiments, the selection of a chemotherapeutic for use in the methods and compositions provided herein is performed based on the genetic profile of a tumor or tumor cell. In certain embodiments, the selection of an arenavirus tumor antigen or tumor associated antigen and the selection of a chemotherapeutic for use in the methods and compositions provided herein are performed based on the genetic profile of a tumor or tumor cell.

[0062] In one embodiment, disclosed herein is a method for treating a neoplastic disease in a subject comprising administering to a subject in need thereof an arenavirus particle and a chemotherapeutic agent, wherein said arenavirus particle is engineered to contain an arenavirus genomic segment comprising: (i) a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and (ii) at least one arenavirus open reading frame ("ORF") in a position other than the wild-type position of said ORF, wherein said ORF

encodes the glycoprotein (“GP”), the nucleoprotein (“NP”), the matrix protein Z (“Z protein”) or the RNA dependent RNA polymerase L (“L protein”) of said arenavirus particle. In certain embodiments, said tumor antigen or tumor associated antigen is selected from the group consisting of GP100, Trp1, and Trp2. In certain embodiments, said chemotherapeutic agent is cyclophosphamide. In certain embodiments, said subject is suffering from, is susceptible to, or is at risk for melanoma. In certain embodiments, the arenavirus particle is a tri-segmented arenavirus particle comprising one L segment and two S segments. In certain embodiments, one of said two S segments is an S segment, wherein the ORF encoding the GP is under control of an arenavirus 3’ UTR. In certain embodiments, each of the two S segments comprise a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof. In certain embodiments, said arenavirus particle is derived from LCMV. In specific embodiments, said arenavirus particle is derived from LCMV Clone 13. In specific embodiments, said arenavirus particle is derived from LCMV strain WE. In specific embodiments, said arenavirus particle is derived from LCMV Clone 13 and strain WE.

[0063] In one embodiment, disclosed herein is a method for treating melanoma in a subject comprising administering to a subject in need thereof an arenavirus particle and a chemotherapeutic agent, wherein said arenavirus particle is engineered to contain an arenavirus genomic segment comprising: (i) a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and (ii) at least one arenavirus open reading frame (“ORF”) in a position other than the wild-type position of said ORF, wherein said ORF encodes the glycoprotein (“GP”), the nucleoprotein (“NP”), the matrix protein Z (“Z protein”) or the RNA dependent RNA polymerase L (“L protein”) of said arenavirus particle, wherein said tumor antigen or tumor associated antigen is selected from the group consisting of GP100, Trp1, and Trp2, said chemotherapeutic agent is cyclophosphamide, said arenavirus particle is derived from LCMV and is a tri-segmented arenavirus particle comprising one L segment and two S segments, and wherein, in one of said two S segments the ORF encoding the GP is under control of an arenavirus 3’ UTR, and each of the two S segments comprise a nucleotide sequence encoding said tumor antigen, tumor associated antigen or antigenic fragment thereof.

(c) Pharmaceutical Compositions and Kits

[0064] In certain embodiments, provided herein are compositions, *e.g.*, pharmaceutical, immunogenic or vaccine compositions, comprising an arenavirus particle, including a tri-segmented arenavirus particle, provided herein, a chemotherapeutic agent provided herein, and a pharmaceutically acceptable carrier. Thus, in some embodiments, provided herein is a pharmaceutical composition comprising an arenavirus particle as provided herein, a chemotherapeutic agent as provided herein and a pharmaceutically acceptable carrier.

[0065] In certain embodiments, the arenavirus particle contained within the compositions is an infectious, replication-deficient arenavirus particle provided herein. In certain embodiments, the arenavirus particle contained within the compositions is a tri-segmented arenavirus particle provided herein, including an infectious, replication-deficient tri-segmented arenavirus particle or a replication-competent tri-segmented arenavirus particle. Thus, in certain embodiments, the compositions providing herein, including a pharmaceutical, immunogenic or vaccine composition, comprise an arenavirus particle, including a tri-segmented arenavirus particle, that is replication-deficient, wherein the arenavirus particle is engineered to contain a genome comprising: (1) a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and (2) the ability to amplify and express its genetic information in infected cells but unable to produce further infectious progeny particles in non-complementing cells. Moreover, in certain embodiments, the compositions providing herein, including a pharmaceutical, immunogenic or vaccine composition, comprise a tri-segmented arenavirus particle, that is replication-competent, wherein the arenavirus particle is engineered to contain a genome comprising: (1) a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; (2) the ability to amplify and express its genetic information in infected cells; and (3) the ability to produce further infectious progeny particles in normal, not genetically engineered cells.

[0066] In certain embodiments, the tumor antigen or tumor associated antigen encoded by the nucleotide sequence included within an arenavirus particle provided herein can be one or more of the tumor antigens or tumor associated antigens selected from the group consisting of oncogenic viral antigens, cancer-testis antigens, oncofetal antigens, tissue differentiation antigens, mutant protein antigens, Adipophilin, AIM-2, ALDH1A1, BCLX (L), BING-4, CALCA, CD45, CPSF, cyclin D1, DKK1, ENAH (hMcna), Ga733 (EpCAM), EphA3, EZH2,

FGF5, glypican-3, G250 /MN/CAIX, HER-2/neu, IDO1, IGF2B3, IL13Ralpha2, Intestinal carboxyl esterase, alpha-foetoprotein, Kallikrein 4, KIF20A, Lengsin, M-CSF, MCSP, mdm-2, Meloe, MMP-2, MMP-7, MUC1, MUC5AC, p53 (non-mutant), PAX5, PBF, PRAME, PSMA, RAGE, RAGE-1, RGS5, RhoC, RNF43, RU2AS, secernin 1, SOX10, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), survivin, Telomerase, VEGF, WT1, EGF-R, CEA, CD20, CD33, CD52, MELANA/MART1, MART2, NY-ESO-1, p53, MAGE A1, MAGE A3, MAGE-4, MAGE-5, MAGE-6, CDK4, alpha-actinin-4, ARTC1, BCR-ABL, BCR-ABL fusion protein (b3a2), B-RAF, CASP-5, CASP-8, beta-catenin, Cdc27, CDK4, CDKN2A, CLPP, COA-1, dek-can fusion protein, EFTUD2, Elongation factor 2, ETV6-AML, ETV6-AML1 fusion protein, FLT3-ITD, FNL, GPNMB, LDLR-fucosyltransferaseAS fusion protein, NFYC, OGT, OS-9, pml-RARalpha fusion protein, PRDX5, PTPRK, H-ras, K-ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene), N-ras, RBAF600, SIRT2, SNRPDI, SSX, SSX2, SYT-SSX1 or-SSX2 fusion protein, TGF-betaRII, Triosephosphate isomerase, ormdm-2, LMP2, HPV E6 / E7, EGFRvIII (epidermal growth factor variant III), Idiotype, GD2, ganglioside G2), Ras-mutant, p53 (mutant), Proteinase3 (PR1), Tyrosinase, PSA, hTERT, Sarcoma translocation breakpoints, EphA2, prostatic acid phosphatase PAP, neo-PAP, ML-IAP, AFP, ERG (TMPRSS2 ETS Fusion gene), NA17, PAX3, ALK, Androgen Receptor, Cyclin B1, Polysialic acid, MYCN, TRP2, TRP2-Int2, GD3, Fucosyl GM1, Mesothelin, PSCA, sLe(a), cyp1B1, PLAC1, GM3, BORIS, Tn, GLoboH, NY-BR-1, SART3, STn, Carbonic Anhydrase IX, OY-TES1, Sperm protein 17, LCK, high molecular weight melanoma-associated antigen (HMWMAA), AKAP-4, SSX2, XAGE 1, B7H3, Legumain, Tie 2, Page4, VEGFR2, MAD-CT-1, FAP, PDGFR-beta, MAD-CT-2, For-related antigen 1, TRP-1, GP100, CA-125, CA19-9, Calretinin, Epithelial membrane antigen (EMA), Epithelial tumor antigen (ETA), CD19, CD34, CD99, CD117, Chromogranin, Cytokeratin, Desmin, Glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, Myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), BAGE BAGE-1, CAGE, CTAGE, FATE, GAGE, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, HCA661, HOM-TES-85, MAGEA, MAGEB, MAGEC, NA88, NY-SAR-35, SPANXB1, SPA17, SSX, SYCP1, TPTE, Carbohydrate / ganglioside GM2 (oncofetal antigen-immunogenic-1 OFA-I-1), GM3, CA 15-3 (CA 27.29\BCAA), CA 195, CA

242, CA 50, CAM 43, CEA, EBNA, EF2, Epstein-Barr virus antigen, HLA-A2, HLA-A11, HSP70-2, KIAA0205, MUM-1, MUM-2, MUM-3, Myosin class I, GnTV, Herv-K-mel, LAGE-1, LAGE-2, (sperm protein) SP17, SCP-1, P15(58), Hom/Mel-40, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, TSP-180, P185erbB2, p180erbB-3, c-met, nm-23H1, TAG-72, TAG-72-4, CA-72-4, CAM 17.1, NuMa, 13-catenin, P16, TAGE, CT7, 43-9F, 5T4, 791Tgp72, 13HCG, BCA225, BTAA, CD68\KP1, CO-029, HTgp-175, M344, MG7-Ag, MOV18, NB\70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TLP, TPS, CD22, CD27, CD30, CD70, prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, integrin $\alpha\text{v}\beta\text{3}$ (CD61), galactin, or Ral-B, CD123, CLL-1, CD38, CS-1, CD138, and ROR1. In certain embodiments, the nucleotide sequence encodes two, three, four, five, six, seven, eight, nine, ten or more tumor antigen, tumor associated antigens or antigenic fragments thereof. In certain embodiments, an antigenic fragment of a tumor antigen or tumor associated antigen provided herein is encoded by the nucleotide sequence included within the arenavirus.

[0067] In certain embodiments, the composition provided herein, including a pharmaceutical, immunogenic or vaccine composition, includes a chemotherapeutic agent. In certain embodiments, the chemotherapeutic agent is an alkylating agent (*e.g.*, cyclophosphamide), a platinum-based therapeutic, an antimetabolite, a topoisomerase inhibitor, a cytotoxic antibiotic, an intercalating agent, a mitosis inhibitor, a taxane, or a combination of two or more thereof. In certain embodiments, the alkylating agent is a nitrogen mustard, a nitrosourea, an alkyl sulfonate, a non-classical alkylating agent, or a triazene. In certain embodiments, the chemotherapeutic agent comprises one or more of cyclophosphamide, thiotepa, mechlorethamine (chlormethine/mustine), uramustine, melphalan, chlorambucil, ifosfamide, chlornaphazine, cholophosphamide, estramustine, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, bendamustine, busulfan, improsulfan, piposulfan, carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine, streptozucin, cisplatin, carboplatin, nedaplatin, oxaliplatin, satraplatin, triplatin tetranitrate, procarbazine, altretamine, dacarbazine, mitozolomide, temozolomide, paclitaxel, docetaxel, vinblastine, vincristine, vinorelbine, cabazitaxel, dactinomycin (actinomycin D), calicheamicin, dynemicin, amsacrine, doxorubicin, daunorubicin, epirubicin, mitoxantrone, idarubicin, pirarubicin, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate, trimethylolomelamine, bullatacin,

bullatacinone, camptothecin, topotecan, bryostatin, callystatin, CC-1065, adozelesin, carzelesin, bizelesin, cryptophycin, dolastatin, duocarmycin, KW-2189, CB1-TM1, eleutherobin, pancratistatin, sarcodictyin, spongistatin, clodronate, esperamicin, neocarzinostatin chromophore, aclacinomycin, anthramycin, azaserine, bleomycin, cactinomycin, carabycin, carminomycin, carzinophilin, chromomycinis, detorubicin, 6-diazo-5-oxo-L-norleucine, esorubicin, idarubicin, marcellomycin, mitomycin, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, methotrexate, 5-fluorouracil (5-FU), denopterin, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiothane, testolactone, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elformithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansine, ansamitocins, mitoguazone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, PSK polysaccharide complex, razoxane, rhizoxin, sizofiran, spirogermanium, tenuazonic acid, triaziquone, 2,2',2''-trichlorotriethylamine; T-2 toxin, verracurin A, roridin A and anguidine, urethan, vindesine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside ("Ara-C"), etoposide (VP-16), vinorelbine, novantrone, teniposide, edatrexate, aminopterin, xeloda, ibandronate, irinotecan (e.g., CPT-11), topoisomerase inhibitor RFS 2000, difluoromethylornithine (DMFO), retinoic acid, capecitabine, plicomycin, gemcitabine, navelbine, transplatinum, and pharmaceutically acceptable salts, acids, or derivatives of any of the above. In specific embodiments, the chemotherapeutic agent comprises cyclophosphamide. In certain embodiments, the nitrogen mustard is mechlorethamine, cyclophosphamide, melphalan, chlorambucil, ifosfamide, or busulfan. In certain embodiments, the chemotherapeutic agent alkylates DNA. In certain embodiments, the chemotherapeutic agent alkylates DNA, resulting in the formation of interstrand cross-links ("ICLs").

[0068] In certain embodiments, the composition provided herein, including a pharmaceutical, immunogenic or vaccine composition, includes a chemotherapeutic agent and an immune checkpoint inhibitor that inhibits, decreases or interferes with the activity of a negative

checkpoint regulator. In certain embodiments, the negative checkpoint regulator is selected from the group consisting of Cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD80, CD86, Programmed cell death 1 (PD-1), Programmed cell death ligand 1 (PD-L1), Programmed cell death ligand 2 (PD-L2), Lymphocyte activation gene-3 (LAG-3; also known as CD223), Galectin-3, B and T lymphocyte attenuator (BTLA), T-cell membrane protein 3 (TIM3), Galectin-9 (GAL9), B7-H1, B7-H3, B7-H4, T-Cell immunoreceptor with Ig and ITIM domains (TIGIT/Vstm3/WUCAM/VSIG9), V-domain Ig suppressor of T-Cell activation (VISTA), Glucocorticoid-induced tumor necrosis factor receptor-related (GITR) protein, Herpes Virus Entry Mediator (HVEM), OX40, CD27, CD28, CD137. CGEN-15001T, CGEN-15022, CGEN-15027, CGEN-15049, CGEN-15052, and CGEN-15092. In certain embodiments, the immune checkpoint inhibitor is an anti-PD-1 antibody.

[0069] In certain embodiments, the compositions provided herein, a pharmaceutical, immunogenic or vaccine composition, can be used in the methods described herein. Thus, in certain embodiments, the compositions can be used for the treatment of a neoplastic disease. In specific certain embodiments, the compositions provided herein can be used for the treatment of a neoplastic disease selected from the group consisting of acute lymphoblastic leukemia; acute lymphoblastic lymphoma; acute lymphocytic leukaemia; acute myelogenous leukemia; acute myeloid leukemia (adult / childhood); adrenocortical carcinoma; AIDS-related cancers; AIDS-related lymphoma; anal cancer; appendix cancer; astrocytomas; atypical teratoid/rhabdoid tumor; basal-cell carcinoma; bile duct cancer, extrahepatic (cholangiocarcinoma); bladder cancer; bone osteosarcoma/malignant fibrous histiocyoma; brain cancer (adult / childhood); brain tumor, cerebellar astrocytoma (adult / childhood); brain tumor, cerebral astrocytoma/malignant glioma brain tumor; brain tumor, ependymoma; brain tumor, medulloblastoma; brain tumor, supratentorial primitive neuroectodermal tumors; brain tumor, visual pathway and hypothalamic glioma; brainstem glioma; breast cancer; bronchial adenomas/carcinoids; bronchial tumor; Burkitt lymphoma; cancer of childhood; carcinoid gastrointestinal tumor; carcinoid tumor; carcinoma of adult, unknown primary site; carcinoma of unknown primary; central nervous system embryonal tumor; central nervous system lymphoma, primary; cervical cancer; childhood adrenocortical carcinoma; childhood cancers; childhood cerebral astrocytoma; chordoma, childhood; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloid leukemia; chronic myeloproliferative disorders; colon cancer; colorectal cancer;

craniopharyngioma; cutaneous T-cell lymphoma; desmoplastic small round cell tumor; emphysema; endometrial cancer; ependymoblastoma; ependymoma; esophageal cancer; ewing's sarcoma in the Ewing family of tumors; extracranial germ cell tumor; extragonadal germ cell tumor; extrahepatic bile duct cancer; gallbladder cancer; gastric (stomach) cancer; gastric carcinoid; gastrointestinal carcinoid tumor; gastrointestinal stromal tumor; germ cell tumor: extracranial, extragonadal, or ovarian gestational trophoblastic tumor; gestational trophoblastic tumor, unknown primary site; glioma; glioma of the brain stem; glioma, childhood visual pathway and hypothalamic; hairy cell leukemia; head and neck cancer; heart cancer; hepatocellular (liver) cancer; hodgkin lymphoma; hypopharyngeal cancer; hypothalamic and visual pathway glioma; intraocular melanoma; islet cell carcinoma (endocrine pancreas); Kaposi Sarcoma; kidney cancer (renal cell cancer); langerhans cell histiocytosis; laryngeal cancer; lip and oral cavity cancer; liposarcoma; liver cancer (primary); lung cancer, non-small cell; lung cancer, small cell; lymphoma, primary central nervous system; macroglobulinemia, Waldenström; male breast cancer; malignant fibrous histiocytoma of bone/osteosarcoma; medulloblastoma; medulloepithelioma; melanoma; melanoma, intraocular (eye); merkel cell cancer; merkel cell skin carcinoma; mesothelioma; mesothelioma, adult malignant; metastatic squamous neck cancer with occult primary; mouth cancer; multiple endocrine neoplasia syndrome; multiple myeloma/plasma cell neoplasm; mycosis fungoides, myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; myelogenous leukemia, chronic; myeloid leukemia, adult acute; myeloid leukemia, childhood acute; myeloma, multiple (cancer of the bone-marrow); myeloproliferative disorders, chronic; nasal cavity and paranasal sinus cancer; nasopharyngeal carcinoma; neuroblastoma, non-small cell lung cancer; non-hodgkin lymphoma; oligodendroglioma; oral cancer; oral cavity cancer; oropharyngeal cancer; osteosarcoma/malignant fibrous histiocytoma of bone; ovarian cancer; ovarian epithelial cancer (surface epithelial-stromal tumor); ovarian germ cell tumor; ovarian low malignant potential tumor; pancreatic cancer; pancreatic cancer, islet cell; papillomatosis; paranasal sinus and nasal cavity cancer; parathyroid cancer; penile cancer; pharyngeal cancer; pheochromocytoma; pineal astrocytoma; pineal germinoma; pineal parenchymal tumors of intermediate differentiation; pineoblastoma and supratentorial primitive neuroectodermal tumors; pituitary tumor; pituitary adenoma; plasma cell neoplasia/multiple myeloma; pleuropulmonary blastoma; primary central nervous system lymphoma; prostate cancer; rectal cancer; renal cell carcinoma (kidney cancer);

renal pelvis and ureter, transitional cell cancer; respiratory tract carcinoma involving the NUT gene on chromosome 15; retinoblastoma; rhabdomyosarcoma, childhood; salivary gland cancer; sarcoma, Ewing family of tumors; Sézary syndrome; skin cancer (melanoma); skin cancer (non-melanoma); small cell lung cancer; small intestine cancer soft tissue sarcoma; soft tissue sarcoma; spinal cord tumor; squamous cell carcinoma; squamous neck cancer with occult primary, metastatic; stomach (gastric) cancer; supratentorial primitive neuroectodermal tumor; T-cell lymphoma, cutaneous (Mycosis Fungoides and Sézary syndrome); testicular cancer; throat cancer; thymoma; thymoma and thymic carcinoma; thyroid cancer; thyroid cancer, childhood; transitional cell cancer of the renal pelvis and ureter; urethral cancer; uterine cancer, endometrial; uterine sarcoma; vaginal cancer; vulvar cancer; and Wilms Tumor.

[0070] Also provided herein are kits that can be used to perform the methods described herein. Thus, in certain embodiments, the kit provided herein includes one or more containers and instructions for use, wherein the one or more containers comprise a composition (*e.g.*, pharmaceutical, immunogenic or vaccine composition) provided herein. In other certain embodiments, a kit provided herein includes containers that each contains the active ingredients for performing the methods described herein. Thus, in certain embodiments, the kit provided herein includes two or more containers and instructions for use, wherein one of the containers comprises an arenavirus particle, including a tri-segmented arenavirus particle, provided herein and another container comprises a chemotherapeutic agent provided herein. In a specific embodiment, a kit provided herein includes two or more containers and instructions for use, wherein one of the containers comprises an arenavirus particle, including a tri-segmented arenavirus particle, provided herein and another container comprises a chemotherapeutic agent provided herein, wherein the arenavirus particle is engineered to contain a genome comprising: a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and the ability to amplify and express its genetic information in infected cells but unable to produce further infectious progeny particles in non-complementing cells. Moreover, in certain embodiments, one of the containers comprises a tri-segmented arenavirus particle that is engineered to contain a genome comprising: a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; the ability to amplify and express its genetic information in infected cells; and the ability to produce further infectious progeny particles in normal, not genetically engineered cells.

3.3 Conventions and Abbreviations

Abbreviation	Convention
APC	Antigen presenting cells
C-cell	Complementing cell line
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CMI	Cell-mediated immunity
GP	Glycoprotein
GS-plasmid	Plasmid expressing genome segments
IGR	Intergenic region
JUNV	Junin virus
L protein	RNA-dependent RNA polymerase
L segment	Long segment
LCMV	Lymphocytic choriomeningitis virus
MHC	Major Histocompatibility Complex
NP	Nucleoprotein
ORF	Open reading frame
S segment	Short segment
TF-plasmid	Plasmid expressing transacting factors
UTR	Untranslated region
Z protein	Matrix Protein Z

4. BRIEF DESCRIPTION OF THE FIGURES

[0071] Fig. 1. The genome of wild type arenaviruses consists of a short (1; ~3.4 kb) and a large (2; ~7.2 kb) RNA segment. The short segment carries open reading frames encoding the nucleoprotein (3) and glycoprotein (4). The large segment encodes the RNA-dependent RNA polymerase L (5) and the matrix protein Z (6). Wild type arenaviruses can be rendered replication-deficient vaccine vectors by deleting the glycoprotein gene and inserting, instead of the glycoprotein gene, a tumor antigen, tumor associated antigen, or antigenic fragment thereof described herein (7) against which immune responses are to be induced.

[0072] Fig. 2. Schematic representation of the genomic organization of bi- and tri-segmented LCMV. The bi-segmented genome of wild-type LCMV consists of one S segment encoding the GP and NP and one L segment encoding the Z protein and the L protein (i). Both segments are flanked by the respective 5' and 3' UTRs. The genome of recombinant tri-segmented LCMV (r3LCMV) consists of one L and two S segments with one position where to insert a gene of interest (here GFP, which can alternatively be a tumor antigen, tumor associated

antigen or antigenic fragment thereof as described herein) into each one of the S segments.

r3LCMV-GFP^{natural} (nat) has all viral genes in their natural position (ii), whereas the GP ORF in r3LCMV-GFP^{artificial} (art) is artificially juxtaposed to and expressed under control of the 3' UTR (iii).

[0073] Fig. 3A-C. Tumor growth in C57BL/6 mice after tumor challenge with B16F10 tumor cells (A) as well as animal survival (B and C) were monitored. Results are shown for C57BL/6 mice left untreated (group 1), treated with cyclophosphamide (group 2), treated with vector mix (each of r3LCMV-GP100, r3LCMV-Trp1 and r3LCMV-Trp2) (group 3), or treated with a combination of cyclophosphamide and vector mix (group 4). Symbols represent the mean $\pm$ SEM of three mice (groups 1 – 3) or four mice (group 4) per group.

[0074] Fig. 4A-B. Relative (left panel) and absolute (right panel) numbers of (A) Trp2-specific CD8⁺ T cells or (B) GP100-specific CD8⁺ T cells induced in mice treated with a combination of cyclophosphamide and r3LCMV-vectors compared to animals treated with r3LCMV vectors only.

[0075] Fig. 5. C57BL/6 mice (5 mice per group) were immunized intravenously on day 0 with 10⁵ RCV FFU of r3LCMV-E7E6 (group 1) or 10⁵ RCV FFU of r3PICV-E7E6 (group 2) or were left untreated (group 3). On day 13 mice in groups 1 and 2 were boosted with 10⁵ RCV FFU of r3LCMV-E7E6. Mice of group 3 were again left untreated. E7-specific CD8⁺ T cell frequencies were subsequently analyzed by tetramer staining (Db-E7 (49-57)-Tetramer) on days 20 (A) and 42 (B) in the blood, and on day 51 in the spleen (C) of test animals.

[0076] Fig. 6. On day 0 of the experiment female C57BL/6 mice (n=5 or n=3 animals per group for experimental groups and buffer group, respectively) were challenged subcutaneously with 1x10⁵ TC-1 tumor cells, derived from mouse primary epithelial cells, co-transformed with HPV16 E6 and E7 and c-Ha-ras oncogenes. Ten days later (day 10 of the experiment) mice were immunized intravenously with either buffer (group 1) or 10⁵ RCV FFU r3LCMV-E7E6 (group 2) or 10⁵ RCV FFU r3PICV-E7E6 (group 3). 14 days post prime (day 24 of the experiment) mice in groups 2 and 3 received a boost administration of 10⁵ RCV FFU r3LCMV-E7E6. Tumor growth was subsequently monitored over time. Arithmetic means $\pm$ SEM are shown. Arrows indicate time points of vaccination.

[0077] Fig 7A-B. 1x10⁵ B16F10 tumor cells were implanted subcutaneously into C57BL/6 mice on day 0. Mice were subsequently left untreated (group 1), treated intraperitoneally with 2

mg cyclophosphamide (CTX) on day 6 and 200 µg each of anti PD-1 and anti-CTLA-4 on days 10, 13, 16, 19 and 22 (group 2), treated intraperitoneally with 2 mg cyclophosphamide on day 6 and injected intravenously with 1.2×10^5 FFU (in total) of a r3LCMV vector mix (r3LCMV-GP100, r3LCMV-Trp1 and r3LCMV-Trp2) on day 7 (group 3), or treated with cyclophosphamide on day 6, an r3LCMV-vector mix on day 7 and anti PD-1 and anti-CTLA-4 on days 10, 13, 16, 19 and 22 (group 4). Tumor size (A) and percent animal survival (B) were monitored.

5. DETAILED DESCRIPTION OF THE INVENTION

5.1 Replication-Deficient Arenavirus Particles

[0078] In certain embodiments, replication-deficient arenavirus particles comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof in combination with chemotherapeutic agent, can be used as immunotherapies for treating a neoplastic disease, such as cancer. The term “neoplastic” or “neoplasm” refers to an abnormal new growth of cells or tissue. This abnormal new growth can form a mass, also known as a tumor or neoplasia. A neoplasm includes a benign neoplasm, an in situ neoplasm, a malignant neoplasm, and a neoplasm of uncertain or unknown behavior. In certain embodiments, the neoplastic disease treated using the methods and compositions described herein is cancer.

[0079] Provided herein are combination treatments for the treatment and/or prevention of a neoplastic disease, such as cancer. Specifically, such combination treatments comprise administering arenavirus particles or viral vectors that comprise a nucleotide sequence encoding one or more tumor antigens, tumor associated antigens or antigenic fragments thereof in combination with one or more chemotherapeutic agents. These genetically modified viruses can be administered to a subject for the treatment of a neoplastic disease, such as cancer. Detailed descriptions of the arenaviruses provided herein, including the nucleotide sequences encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof can be found in Sections 5.1.(a) and 5.1.(b). Additionally, methods for generation of arenavirus particles or viral vectors for use in the methods and compositions described herein are described in more detail in Section 5.1.(c).

[0080] In addition to administering arenavirus particles or viral vectors to a subject, the immunotherapies for treating a neoplastic disease provided herein can include a chemotherapeutic agent. “Chemotherapeutic agents” are cytotoxic anti-cancer agents, and can be categorized by their mode of activity within a cell, for example, at what stage they affect the cell cycle (*e.g.*, a mitosis inhibitor). Alternatively, chemotherapeutic agents can be characterized based on ability to cross-link DNA, to intercalate into DNA, or to induce chromosomal aberrations by affecting nucleic acid synthesis (*e.g.*, alkylating agents), among other mechanisms of action. Chemotherapeutic agents can also be characterized based on chemical components or structure (*e.g.*, platinum-based therapeutics). Thus, in certain embodiments, provided herein are methods and compositions for treating a neoplastic disease using an arenavirus particle or viral vector comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof and a chemotherapeutic agent.

[0081] Thus, in certain embodiments, provided herein are methods and compositions for treating a neoplastic disease using an arenavirus particle or viral vector comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof and a chemotherapeutic agent. Also, in certain embodiments, provided herein are compositions comprising an arenavirus particle or viral vector comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof, and a chemotherapeutic agent. In certain embodiments, the arenavirus particle provided herein is an infectious, replication deficient arenavirus particle.

[0082] Methods of using arenavirus particles for viral vectors for the treatment of a neoplastic disease, *e.g.*, non-malignant neoplasm or cancer, are provided herein. Specifically, provided herein are methods for treating a neoplastic disease, such as cancer, in a subject comprising administering to the subject one or more arenaviruses expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof. In a specific embodiment, provided herein are methods for treating cancer in a subject comprising administering to the subject one or more arenaviruses expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof, alone or in combination with one or more chemotherapeutic agents. In certain embodiments, immunization with an arenavirus that expresses a tumor antigen, tumor associated antigen or an antigenic fragment thereof, as described herein provides a cytotoxic T-cell response, which can be enhanced by the administration of a chemotherapeutic agent. Methods

and compositions for using an arenavirus particle or viral vector and a chemotherapeutic agent provided herein are described in more detail in Sections 5.1.(e) and 5.1.(f).

[0083] In addition to administering arenavirus particles or viral vectors to a subject in combination with a chemotherapeutic agent, the immunotherapies for treating a neoplastic disease provided herein can also include an immune checkpoint modulator. The term “immune checkpoint modulator” (also referred to as “checkpoint modulator” or as “checkpoint regulator”) refers to a molecule or to a compound that modulates (*e.g.*, totally or partially reduces, inhibits, interferes with, activates, stimulates, increases, reinforces or supports) the function of one or more checkpoint molecules. Thus, an immune checkpoint modulator may be an immune checkpoint inhibitor or an immune checkpoint activator.

[0084] An “immune checkpoint inhibitor” refers to a molecule that inhibits, decreases or interferes with the activity of a negative checkpoint regulator. In certain embodiments, immune checkpoint inhibitors for use with the methods and compositions disclosed herein can inhibit the activity of a negative checkpoint regulator directly, or decrease the expression of a negative checkpoint regulator, or interfere with the interaction of a negative checkpoint regulator and a binding partner (*e.g.*, a ligand). Immune checkpoint inhibitors for use with the methods and compositions disclosed herein include a protein, a polypeptide, a peptide, an antisense oligonucleotide, an antibody, an antibody fragment, or an inhibitory RNA molecule that targets the expression of a negative checkpoint regulator.

[0085] A “negative checkpoint regulator” refers to a molecule that down-regulates immune responses (*e.g.*, T-cell activation) by delivery of a negative signal to T-cells following their engagement by ligands or counter-receptors. Exemplary functions of a negative-checkpoint regulator are to prevent out-of-proportion immune activation, minimize collateral damage, and/or maintain peripheral self-tolerance. In certain embodiments, a negative checkpoint regulator is a ligand or receptor expressed by an antigen presenting cell. In certain embodiments, a negative checkpoint regulator is a ligand or receptor expressed by a T-cell. In certain embodiments, a negative checkpoint regulator is a ligand or receptor expressed by both an antigen presenting cell and a T-cell.

(a) Infectious, Replication-Deficient Arenavirus Particles

[0086] In certain embodiments, a genetically modified arenavirus provided herein, where the arenavirus:

- is infectious;
- cannot form infectious progeny virus in a non-complementary cell (*i.e.*, a cell that does not express the functionality that is missing from the replication-deficient arenavirus and causes it to be replication-deficient);
- is capable of replicating its genome and expressing its genetic information; and
- encodes a tumor antigen, tumor associated antigen or an antigenic fragment thereof,

can be used with the methods and compositions provided herein, such as combinations with a chemotherapeutic agent.

[0087] A genetically modified arenavirus described herein is infectious, *i.e.*, it can attach to a host cell and release its genetic material into the host cell. A genetically modified arenavirus described herein is replication-deficient, *i.e.*, the arenavirus is unable to produce further infectious progeny particles in a non-complementing cell. In particular, the genome of the arenavirus is modified (*e.g.*, by removal or functional inactivation of an ORF) such that a virus carrying the modified genome can no longer produce infectious progeny viruses. A non-complementing cell is a cell that does not provide the functionality that has been eliminated from the replication-deficient arenavirus by modification of the virus genome (*e.g.*, if the ORF encoding the GP protein is removed or functionally inactivated, a non-complementing cell does not provide the GP protein). However, a genetically modified arenavirus provided herein is capable of producing infectious progeny viruses in complementing cells. Complementing cells are cells that provide (in trans) the functionality that has been eliminated from the replication-deficient arenavirus by modification of the virus genome (*e.g.*, if the ORF encoding the GP protein is removed or functionally inactivated, a complementing cell does provide the GP protein). Expression of the complementing functionality (*e.g.*, the GP protein) can be accomplished by any method known to the skilled artisan (*e.g.*, transient or stable expression). A genetically modified arenavirus described herein can amplify and express its genetic information in a cell that has been infected by the virus. A genetically modified arenavirus provided herein can comprise a nucleotide sequence that encodes a tumor antigen, tumor associated antigen or an antigenic fragment thereof such as, but not limited to, the tumor antigen, tumor associated antigen or an antigenic fragment thereof described in Section 5.1.(b).

[0088] In certain embodiments, provided herein is a genetically modified arenavirus in which an ORF of the arenavirus genome is removed or functionally inactivated such that the

resulting virus cannot produce further infectious progeny virus particles in non-complementing cells. An arenavirus particle comprising a genetically modified genome in which an ORF is removed or functionally inactivated can be produced in complementing cells (*i.e.*, in cells that express the arenaviral ORF that has been removed or functionally inactivated). The genetic material of the resulting arenavirus particles can be transferred upon infection of a host cell into the host cell, wherein the genetic material can be expressed and amplified. In addition, the genome of the genetically modified arenavirus particles provided herein encodes a tumor antigen, tumor associated antigen or antigenic fragment thereof that can be expressed in the host cell.

[0089] In certain embodiments, an ORF of the arenavirus is deleted or functionally inactivated and replaced with a nucleotide encoding a tumor antigen or tumor associated antigen as described herein. In a specific embodiment, the ORF that encodes the glycoprotein GP of the arenavirus is deleted or functionally inactivated. In certain embodiments, functional inactivation of a gene eliminates any translation product. In certain embodiments, functional inactivation refers to a genetic alteration that allows some translation, the translation product, however, is not longer functional and cannot replace the wild type protein.

[0090] In certain embodiments, the ORF that encodes the glycoprotein (GP) of the arenavirus is deleted to generate a replication-deficient arenavirus for use in the methods and compositions provided herein. In a specific embodiment, the replication-deficient arenavirus comprises a genomic segment comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof. Thus, in certain embodiments, a genetically modified arenavirus particle provided herein comprises a genomic segment that a) has a deletion or functional inactivation of an ORF that is present in the wild type form of the genomic segment; and b) encodes (either in sense or antisense) a tumor antigen, tumor associated antigen or antigenic fragment thereof.

[0091] In certain embodiments, the antigen encoded by the nucleotide that is inserted into the genome of replication-deficient arenavirus can encode, for example, a tumor antigen, tumor associated antigen or antigenic fragment thereof or combinations of tumor antigens, tumor associated antigens or antigenic fragments thereof including, but not limited to, oncogenic viral antigens, cancer-testis antigens, oncofetal antigens, tissue differentiation antigens, mutant protein antigens, Adipophilin, AIM-2, ALDH1AI, BCLX (L), BING-4, CALCA, CD45, CPSF, cyclin

D1, DKKI, ENAH (hMcna), Ga733 (EpCAM), EphA3, EZH2, FGF5, glypican-3, G250 /MN/CAIX, HER-2/neu, IDO1, IGF2B3, IL13Ralpha2, Intestinal carboxyl esterase, alpha-foetoprotein, Kallikrein 4, KIF20A, Lengsin, M-CSF, MCSP, mdm-2, Meloe, MMP-2, MMP-7, MUC1, MUC5AC, p53 (non-mutant), PAX5, PBF, PRAME, PSMA, RAGE, RAGE-1, RGS5, RhoC, RNF43, RU2AS, secernin 1, SOX10, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), survivin, Telomerase, VEGF, WT1, EGF-R, CEA, CD20, CD33, CD52, gp 100 protein, MELANA/MART1, MART2, NY-ESO-1, p53, MAGE A1, MAGE A3, MAGE-4, MAGE-5, MAGE-6, CDK4, alpha-actinin-4, ARTC1, BCR-ABL, BCR-ABL fusion protein (b3a2), B-RAF, CASP-5, CASP-8, beta-catenin, Cdc27, CDK4, CDKN2A, CLPP, COA-1, dekan fusion protein, EFTUD2, Elongation factor 2, ETV6-AML, ETV6-AML1 fusion protein, FLT3-ITD, FNI, GPNMB, LDLR-fucosyltransferaseAS fusion protein, NFYC, OGT, OS-9, pml-RARalpha fusion protein, PRDX5, PTPRK, H-ras, K-ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene), N-ras, RBAF600, SIRT2, SNRPDI, SSX, SSX2, SYT-SSX1 or-SSX2 fusion protein, TGF-betaRII, Triosephosphate isomerase, ormdm-2, LMP2, HPV E6 / E7, EGFRvIII (epidermal growth factor variant III), Idiotypic, GD2, ganglioside G2), Ras-mutant, p53 (mutant), Proteinase3 (PR1), Tyrosinase, PSA, hTERT, Sarcoma translocation breakpoints, EphA2, prostatic acid phosphatase PAP, neo-PAP, ML-IAP, AFP, ERG (TMPRSS2 ETS Fusion gene), NA17, PAX3, ALK, Androgen Receptor, Cyclin B1, Polysialic acid, MYCN, TRP2, TRP2-Int2, GD3, Fucosyl GM1, Mesothelin, PSCA, sLe(a), cyp1B1, PLAC1, GM3, BORIS, Tn, GLobH, NY-BR-1, SART3, STn, Carbonic Anhydrase IX, OY-TES1, Sperm protein 17, LCK, high molecular weight melanoma-associated antigen (HMWMAA), AKAP-4, SSX2, XAGE 1, B7H3, Legumain, Tie 2, Page4, VEGFR2, MAD-CT-1, FAP, PDGFR-beta, MAD-CT-2, For-related antigen 1, TRP-1, CA-125, CA19-9, Calretinin, Epithelial membrane antigen (EMA), Epithelial tumor antigen (ETA), CD19, CD34, CD99, CD117, Chromogranin, Cytokeratin, Desmin, Glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, Myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), BAGE BAGE-1, CAGE, CTAGE, FATE, GAGE, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, HCA661, HOM-TES-85, MAGEA, MAGEB, MAGEC, NA88, NY-SAR-35, SPANXB1, SPA17, SSX, SYCP1, TPTE, Carbohydrate / ganglioside GM2 (oncofetal antigen-

immunogenic-1 OFA-I-1), GM3, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA 50, CAM 43, CEA, EBNA, EF2, Epstein-Barr virus antigen, HLA-A2, HLA-A11, HSP70-2, KIAA0205, MUM-1, MUM-2, MUM-3, Myosin class I, GnTV, Herv-K-mel, LAGE-1, LAGE-2, (sperm protein) SP17, SCP-1, P15(58), Hom/Mel-40, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, TSP-180, P185erbB2, p180erbB-3, c-met, nm-23H1, TAG-72, TAG-72-4, CA-72-4, CAM 17.1, NuMa, 13-catenin, P16, TAGE, CT7, 43-9F, 5T4, 791Tgp72, 13HCG, BCA225, BTAA, CD68\KP1, CO-029, HTgp-175, M344, MG7-Ag, MOV18, NB\70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TLP, TPS, CD22, CD27, CD30, CD70, prostatein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, integrin $\alpha\beta 3$ (CD61), galactin, or Ral-B, CD123, CLL-1, CD38, CS-1, CD138, and ROR1. A detailed description of the antigens described herein is provided in Section 5.1.(b).

[0092] Arenaviruses for use with the methods and compositions provided herein can be Old World viruses, for example Lassa virus, Lymphocytic choriomeningitis virus (LCMV), Mobala virus, Mopeia virus, or Ippy virus, or New World viruses, for example Amapari virus, Flexal virus, Guanarito virus, Junin virus, Latino virus, Machupo virus, Oliveros virus, Parana virus, Pichinde virus, Pirital virus, Sabia virus, Tacaribe virus, Tamiami virus, Bear Canyon virus, or Whitewater Arroyo virus.

[0093] The wild type arenavirus genome consists of a short (~3.4 kb) and a large (~7.2 kb) RNA segment. The short segment carries the ORFs encoding the nucleoprotein NP and glycoprotein GP genes. The large segment comprises the RNA-dependent RNA polymerase L and the matrix protein Z genes. Wild type arenaviruses can be rendered replication-deficient to generate vaccine vectors by substituting the glycoprotein gene for one or more tumor antigens, tumor associated antigens or antigenic fragments thereof, against which immune responses are to be induced.

[0094] Infectious, replication-deficient arenavirus particles expressing a tumor antigen, tumor associated antigen, or antigenic fragment thereof, or a combination of tumor antigens, tumor associated antigens or antigenic fragments thereof as described herein, can be used to treat (in an immunotherapeutic manner) subjects having a neoplastic disease described herein.

[0095] Arenavirus disease and immunosuppression in wild type arenavirus infection are known to result from unchecked viral replication. By abolishing replication, *i.e.*, the ability to produce infectious progeny virus particles, of arenavirus particles by deleting from their genome,

e.g., the Z gene which is required for particle release, or the GP gene which is required for infection of target cells, the total number of infected cells can be limited by the inoculum administered, *e.g.*, to a vaccine recipient, or accidentally transmitted to personnel involved in medical or biotechnological applications, or to animals. Therefore, abolishing replication of arenavirus particles prevents pathogenesis as a result of intentional or accidental transmission of vector particles. In this invention, one important aspect consists in exploiting the above necessity of abolishment of replication in a beneficial way for the purpose of expressing tumor antigens, tumor associated antigens or antigenic fragments thereof. In certain embodiments, an arenavirus particle is rendered replication deficient by genetic modification of its genome. Such modifications to the genome can include:

- deletion of an ORF (*e.g.*, the ORF encoding the GP, NP, L, or Z protein);
- functional inactivation of an ORF (*e.g.*, the ORF encoding the GP, NP, L, or Z protein). For example, this can be achieved by introducing a missense or a nonsense mutation.;
- change of the sequence of the ORF (*e.g.*, the exchange of an S1P cleavage site with the cleavage site of another protease);
- mutagenesis of one of the 5' or 3' termini of one of the genomic segments;
- mutagenesis of an intergenic region (*i.e.*, of the L or the S genomic segment).

[0096] In certain embodiments, an infectious, replication-deficient arenavirus expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof described herein is a Lymphocytic choriomeningitis virus (LCMV) wherein the S segment of the virus is modified by substituting the ORF encoding the GP protein with an ORF encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof.

[0097] In certain embodiments, a wild type arenavirus vector genome can be designed to retain at least the essential regulatory elements on the 5' and 3' untranslated regions (UTRs) of both segments, and/or also the intergenic regions (IGRs). Without being bound by theory, the minimal transacting factors for gene expression in infected cells remain in the vector genome as ORFs that can be expressed, yet they can be placed differently in the genome and can be placed under control of a different promoter than naturally, or can be expressed from internal ribosome entry sites. In certain embodiments, the nucleic acid encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof is transcribed from one of the endogenous arenavirus promoters (*i.e.*, 5' UTR, 3' UTR of the S segment, 5' UTR, 3' UTR of the L segment). In other

embodiments, the nucleic acid encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof is expressed from a heterologous introduced promoter sequences that can be read by the viral RNA-dependent RNA polymerase, by cellular RNA polymerase I, RNA polymerase II or RNA polymerase III, such as duplications of viral promoter sequences that are naturally found in the viral UTRs, the 28S ribosomal RNA promoter, the beta-actin promoter or the 5S ribosomal RNA promoter, respectively. In certain embodiments, ribonucleic acids coding for a tumor antigen, tumor associated antigen or antigenic fragment thereof are transcribed and translated either by themselves or as read-through by fusion to arenavirus protein ORFs, and expression of proteins in the host cell may be enhanced by introducing in the viral transcript sequence at the appropriate place(s) one or more, *e.g.*, two, three or four, internal ribosome entry sites.

[0098] In certain embodiments, the vector generated to encode one or more tumor antigens, tumor associated antigens or antigenic fragments thereof may be based on a specific strain of LCMV. Strains of LCMV include Clone 13, MP strain, Arm CA 1371, Arm E-250, WE, UBC, Traub, Pasteur, 810885, CH-5692, Marseille #12, HP65-2009, 200501927, 810362, 811316, 810316, 810366, 20112714, Douglas, GR01, SN05, CABN and their derivatives. In certain embodiments, the vector generated to encode one or more tumor antigens, tumor associated antigens or antigenic fragments thereof may be based on LCMV Clone 13. In other embodiments, the vector generated to encode one or more tumor antigens, tumor associated antigens or antigenic fragments thereof may be based on LCMV MP strain.

[0099] In certain embodiments, the vector generated to encode one or more tumor antigens, tumor associated antigens or antigenic fragments thereof may be based on a specific strain of Junin virus. Strains of Junin virus include vaccine strains XJ13, XJ#44, and Candid#1 as well as IV4454, a human isolate. In certain embodiments, the vector generated to encode one or more tumor antigens, tumor associated antigens or antigenic fragments thereof is based on Junin virus Candid #1 strain.

(b) Tumor Antigens, Tumor Associated Antigens and Antigenic Fragments

[00100] In certain embodiments, arenavirus particles with a nucleotide sequence encoding a tumor antigen, tumor associated antigen, or an antigenic fragment thereof provided herein can be used with the methods and compositions provided herein, such as combinations with a chemotherapeutic agent. In certain embodiments, a tumor antigen or tumor associated antigen

for use with the methods and compositions described herein is an immunogenic protein expressed in or on a neoplastic cell or tumor, such as a cancer cell or malignant tumor. In certain embodiments, a tumor antigen or tumor associated antigen for use with the methods and compositions described herein is a non-specific, mutant, overexpressed or abnormally expressed protein, which can be present on both a neoplastic cell or tumor and a normal cell or tissue. In certain embodiments, a tumor antigen or tumor associated antigen for use with the methods and compositions described herein is a tumor-specific antigen which is restricted to tumor cells. In certain embodiments, a tumor antigen for use with the methods and compositions described herein is a cancer-specific antigen which is restricted to cancer cells.

[00101] In certain embodiments, a tumor antigen or tumor associated antigen can exhibit one, two, three, or more, including all, of the following characteristics: overexpressed / accumulated (*i.e.*, expressed by both normal and neoplastic tissue, but highly expressed in neoplasia), oncofetal (*i.e.*, usually only expressed in fetal tissues and in cancerous somatic cells), oncoviral or oncogenic viral (*i.e.*, encoded by tumorigenic transforming viruses), cancer-testis (*i.e.*, expressed only by cancer cells and adult reproductive tissues, *e.g.*, the testis), lineage-restricted (*i.e.*, expressed largely by a single cancer histotype), mutated (*i.e.*, only expressed in neoplastic tissue as a result of genetic mutation or alteration in transcription), post-translationally altered (*e.g.*, tumor-associated alterations in glycosylation), or idiotypic (*i.e.*, developed from malignant clonal expansions of B or T lymphocytes).

[00102] In certain embodiments, the tumor antigen or tumor associated antigen for use with the methods and compositions described herein includes antigens from neoplastic diseases including acute lymphoblastic leukemia; acute lymphoblastic lymphoma; acute lymphocytic leukaemia; acute myelogenous leukemia; acute myeloid leukemia (adult / childhood); adrenocortical carcinoma; AIDS-related cancers; AIDS-related lymphoma; anal cancer; appendix cancer; astrocytomas; atypical teratoid/rhabdoid tumor; basal-cell carcinoma; bile duct cancer, extrahepatic (cholangiocarcinoma); bladder cancer; bone osteosarcoma/malignant fibrous histiocytoma; brain cancer (adult / childhood); brain tumor, cerebellar astrocytoma (adult / childhood); brain tumor, cerebral astrocytoma/malignant glioma brain tumor; brain tumor, ependymoma; brain tumor, medulloblastoma; brain tumor, supratentorial primitive neuroectodermal tumors; brain tumor, visual pathway and hypothalamic glioma; brainstem glioma; breast cancer; bronchial adenomas/carcinoids; bronchial tumor; Burkitt lymphoma;

cancer of childhood; carcinoid gastrointestinal tumor; carcinoid tumor; carcinoma of adult, unknown primary site; carcinoma of unknown primary; central nervous system embryonal tumor; central nervous system lymphoma, primary; cervical cancer; childhood adrenocortical carcinoma; childhood cancers; childhood cerebral astrocytoma; chordoma, childhood; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloid leukemia; chronic myeloproliferative disorders; colon cancer; colorectal cancer; craniopharyngioma; cutaneous T-cell lymphoma; desmoplastic small round cell tumor; emphysema; endometrial cancer; ependymblastoma; ependymoma; esophageal cancer; ewing's sarcoma in the Ewing family of tumors; extracranial germ cell tumor; extragonadal germ cell tumor; extrahepatic bile duct cancer; gallbladder cancer; gastric (stomach) cancer; gastric carcinoid; gastrointestinal carcinoid tumor; gastrointestinal stromal tumor; germ cell tumor: extracranial, extragonadal, or ovarian gestational trophoblastic tumor; gestational trophoblastic tumor, unknown primary site; glioma; glioma of the brain stem; glioma, childhood visual pathway and hypothalamic; hairy cell leukemia; head and neck cancer; heart cancer; hepatocellular (liver) cancer; hodgkin lymphoma; hypopharyngeal cancer; hypothalamic and visual pathway glioma; intraocular melanoma; islet cell carcinoma (endocrine pancreas); Kaposi Sarcoma; kidney cancer (renal cell cancer); langerhans cell histiocytosis; laryngeal cancer; lip and oral cavity cancer; liposarcoma; liver cancer (primary); lung cancer, non-small cell; lung cancer, small cell; lymphoma, primary central nervous system; macroglobulinemia, Waldenström; male breast cancer; malignant fibrous histiocytoma of bone/osteosarcoma; medulloblastoma; medulloepithelioma; melanoma; melanoma, intraocular (eye); merkel cell cancer; merkel cell skin carcinoma; mesothelioma; mesothelioma, adult malignant; metastatic squamous neck cancer with occult primary; mouth cancer; multiple endocrine neoplasia syndrome; multiple myeloma/plasma cell neoplasm; mycosis fungoides, myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; myelogenous leukemia, chronic; myeloid leukemia, adult acute; myeloid leukemia, childhood acute; myeloma, multiple (cancer of the bone-marrow); myeloproliferative disorders, chronic; nasal cavity and paranasal sinus cancer; nasopharyngeal carcinoma; neuroblastoma, non-small cell lung cancer; non-hodgkin lymphoma; oligodendroglioma; oral cancer; oral cavity cancer; oropharyngeal cancer; osteosarcoma/malignant fibrous histiocytoma of bone; ovarian cancer; ovarian epithelial cancer (surface epithelial-stromal tumor); ovarian germ cell tumor; ovarian low malignant potential tumor; pancreatic cancer; pancreatic cancer, islet cell; papillomatosis;

paranasal sinus and nasal cavity cancer; parathyroid cancer; penile cancer; pharyngeal cancer; pheochromocytoma; pineal astrocytoma; pineal germinoma; pineal parenchymal tumors of intermediate differentiation; pineoblastoma and supratentorial primitive neuroectodermal tumors; pituitary tumor; pituitary adenoma; plasma cell neoplasia/multiple myeloma; pleuropulmonary blastoma; primary central nervous system lymphoma; prostate cancer; rectal cancer; renal cell carcinoma (kidney cancer); renal pelvis and ureter, transitional cell cancer; respiratory tract carcinoma involving the NUT gene on chromosome 15; retinoblastoma; rhabdomyosarcoma, childhood; salivary gland cancer; sarcoma, Ewing family of tumors; Sézary syndrome; skin cancer (melanoma); skin cancer (non-melanoma); small cell lung cancer; small intestine cancer soft tissue sarcoma; soft tissue sarcoma; spinal cord tumor; squamous cell carcinoma; squamous neck cancer with occult primary, metastatic; stomach (gastric) cancer; supratentorial primitive neuroectodermal tumor; T-cell lymphoma, cutaneous (Mycosis Fungoides and Sézary syndrome); testicular cancer; throat cancer; thymoma; thymoma and thymic carcinoma; thyroid cancer; thyroid cancer, childhood; transitional cell cancer of the renal pelvis and ureter; urethral cancer; uterine cancer, endometrial; uterine sarcoma; vaginal cancer; vulvar cancer; and Wilms Tumor.

[00103] In certain embodiments, the tumor antigen or tumor associated antigen for use with the methods and compositions disclosed herein includes oncogenic viral antigens, cancer-testis antigens, oncofetal antigens, tissue differentiation antigens, mutant protein antigens, Adipophilin, AIM-2, ALDH1A1, BCLX (L), BING-4, CALCA, CD45, CPSF, cyclin D1, DKKI, ENAH (hMcna), Ga733 (EpCAM), EphA3, EZH2, FGF5, glypican-3, G250 /MN/CAIX, HER-2/neu, IDO1, IGF2B3, IL13Ralpha2, Intestinal carboxyl esterase, alpha-foetoprotein, Kallikrein 4, KIF20A, Lengsin, M-CSF, MCSP, mdm-2, Meloe, MMP-2, MMP-7, MUC1, MUC5AC, p53 (non-mutant), PAX5, PBF, PRAME, PSMA, RAGE, RAGE-1, RGS5, RhoC, RNF43, RU2AS, secernin 1, SOX10, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), survivin, Telomerase, VEGF, WT1, EGF-R, CEA, CD20, CD33, CD52, MELANA/MART1, MART2, NY-ESO-1, p53, MAGE A1, MAGE A3, MAGE-4, MAGE-5, MAGE-6, CDK4, alpha-actinin-4, ARTC1, BCR-ABL, BCR-ABL fusion protein (b3a2), B-Raf, CASP-5, CASP-8, beta-catenin, Cdc27, CDK4, CDKN2A, CLPP, COA-1, dek-can fusion protein, EFTUD2, Elongation factor 2, ETV6-AML, ETV6-AML1 fusion protein, FLT3-ITD, FNL, GPNMB, LDLR-fucosyltransferaseAS fusion protein, NFYC, OGT, OS-9, pml-RARalpha fusion protein,

PRDX5, PTPRK, H-ras, K-ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene), N-ras, RBAF600, SIRT2, SNRPD1, SSX, SSX2, SYT-SSX1 or-SSX2 fusion protein, TGF-betaRII, Triosephosphate isomerase, ormdm-2, LMP2, HPV E6 / E7, EGFRvIII (epidermal growth factor variant III), Idiotype, GD2, ganglioside G2), Ras-mutant, p53 (mutant), Proteinase3 (PR1), Tyrosinase, PSA, hTERT, Sarcoma translocation breakpoints, EphA2, prostatic acid phosphatase PAP, neo-PAP, ML-IAP, AFP, ERG (TMPRSS2 ETS Fusion gene), NA17, PAX3, ALK, Androgen Receptor, Cyclin B1, Polysialic acid, MYCN, TRP2, TRP2-Int2, GD3, Fucosyl GM1, Mesothelin, PSCA, sLe(a), cyp1B1, PLAC1, GM3, BORIS, Tn, GLobH, NY-BR-1, SART3, STn, Carbonic Anhydrase IX, OY-TES1, Sperm protein 17, LCK, high molecular weight melanoma-associated antigen (HMWMAA), AKAP-4, SSX2, XAGE 1, B7H3, Legumain, Tie 2, Page4, VEGFR2, MAD-CT-1, FAP, PDGFR-beta, MAD-CT-2, For-related antigen 1, TRP-1, GP100, CA-125, CA19-9, Calretinin, Epithelial membrane antigen (EMA), Epithelial tumor antigen (ETA), CD19, CD34, CD99, CD117, Chromogranin, Cytokeratin, Desmin, Glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, Myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), BAGE BAGE-1, CAGE, CTAGE, FATE, GAGE, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, HCA661, HOM-TES-85, MAGEA, MAGEB, MAGEC, NA88, NY-SAR-35, SPANXB1, SPA17, SSX, SYCP1, TPTE, Carbohydrate / ganglioside GM2 (oncofetal antigen-immunogenic-1 OFA-I-1), GM3, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA 50, CAM 43, CEA, EBNA, EF2, Epstein-Barr virus antigen, HLA-A2, HLA-A11, HSP70-2, KIAA0205, MUM-1, MUM-2, MUM-3, Myosin class I, GnTV, Herv-K-mel, LAGE-1, LAGE-2, (sperm protein) SP17, SCP-1, P15(58), Hom/Mel-40, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, TSP-180, P185erbB2, p180erbB-3, c-met, nm-23H1, TAG-72, TAG-72-4, CA-72-4, CAM 17.1, NuMa, 13-catenin, P16, TAGE, CT7, 43-9F, 5T4, 791Tgp72, 13HCG, BCA225, BTAA, CD68\KP1, CO-029, HTgp-175, M344, MG7-Ag, MOV18, NB\70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TLP, TPS, CD22, CD27, CD30, CD70, prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, integrin $\alpha v \beta 3$ (CD61), galactin, or Ral-B, CD123, CLL-1, CD38, CS-1, CD138, and ROR1.

[00104] In certain embodiments, the tumor antigen or tumor associated antigen is a neoantigen. A “neoantigen,” as used herein, means an antigen that arises by mutation in a tumor cell and such an antigen is not generally expressed in normal cells or tissue. Without being bound by theory, because healthy tissues generally do not possess these antigens, neoantigens represent a preferred target. Additionally, without being bound by theory, in the context of the present invention, since the T cells that recognize the neoantigen may not have undergone negative thymic selection, such cells can have high avidity to the antigen and mount a strong immune response against tumors, while lacking the risk to induce destruction of normal tissue and autoimmune damage. In certain embodiments, the neoantigen is an MHC class I-restricted neoantigen. In certain embodiments, the neoantigen is an MHC class II-restricted neoantigen. In certain embodiments, a mutation in a tumor cell of the patient results in a novel protein that produces the neoantigen.

[00105] In certain embodiments, the tumor antigen or tumor associated antigen can be an antigen ortholog, *e.g.*, a mammalian (*i.e.*, non-human primate, pig, dog, cat, or horse) to a human tumor antigen or tumor associated antigen.

[00106] In certain embodiments, an antigenic fragment of a tumor antigen or tumor associated antigen described herein is encoded by the nucleotide sequence included within the arenavirus. In certain embodiments, a fragment is antigenic when it is capable of (i) eliciting an antibody immune response in a host (*e.g.*, mouse, rabbit, goat, donkey or human) wherein the resulting antibodies bind specifically to an immunogenic protein expressed in or on a neoplastic cell (*e.g.*, a cancer cell); and/or (ii) eliciting a specific T cell immune response.

[00107] In certain embodiments, the nucleotide sequence encoding antigenic fragment of a tumor antigen or tumor associated antigen is 8 to 100 nucleotides in length, 15 to 100 nucleotides in length, 25 to 100 nucleotides in length, 50 to 200 nucleotide in length, 50 to 400 nucleotide in length, 200 to 500 nucleotide in length, or 400 to 600 nucleotides in length, 500 to 800 nucleotide in length. In other embodiments, the nucleotide sequence is 750 to 900 nucleotides in length, 800 to 100 nucleotides in length, 850 to 1000 nucleotides in length, 900 to 1200 nucleotides in length, 1000 to 1200 nucleotides in length, 1000 to 1500 nucleotides or 10 to 1500 nucleotides in length, 1500 to 2000 nucleotides in length, 1700 to 2000 nucleotides in length, 2000 to 2300 nucleotides in length, 2200 to 2500 nucleotides in length, 2500 to 3000 nucleotides in length, 3000 to 3200 nucleotides in length, 3000 to 3500 nucleotides in length, 3200 to 3600

nucleotides in length, 3300 to 3800 nucleotides in length, 4000 nucleotides to 4400 nucleotides in length, 4200 to 4700 nucleotides in length, 4800 to 5000 nucleotides in length, 5000 to 5200 nucleotides in length, 5200 to 5500 nucleotides in length, 5500 to 5800 nucleotides in length, 5800 to 6000 nucleotides in length, 6000 to 6400 nucleotides in length, 6200 to 6800 nucleotides in length, 6600 to 7000 nucleotides in length, 7000 to 7200 nucleotides in lengths, 7200 to 7500 nucleotides in length, or 7500 nucleotides in length. In some embodiments, the nucleotide sequence encodes a peptide or polypeptide that is 5 to 10 amino acids in length, 10 to 25 amino acids in length, 25 to 50 amino acids in length, 50 to 100 amino acids in length, 100 to 150 amino acids in length, 150 to 200 amino acids in length, 200 to 250 amino acids in length, 250 to 300 amino acids in length, 300 to 400 amino acids in length, 400 to 500 amino acids in length, 500 to 750 amino acids in length, 750 to 1000 amino acids in length, 1000 to 1250 amino acids in length, 1250 to 1500 amino acids in length, 1500 to 1750 amino acids in length, 1750 to 2000 amino acids in length, 2000 to 2500 amino acids in length, or more than 2500 or more amino acids in length. In some embodiments, the nucleotide sequence encodes a polypeptide that does not exceed 2500 amino acids in length. In specific embodiments the nucleotide sequence does not contain a stop codon. In certain embodiments, the nucleotide sequence is codon-optimized. In certain embodiments the nucleotide composition, nucleotide pair composition or both can be optimized. Techniques for such optimizations are known in the art and can be applied to optimize a nucleotide sequence of a tumor antigen or tumor associated antigen.

[00108] Nucleic acid sequences encoding a tumor antigen, tumor associated antigen, or antigenic fragment thereof can be introduced in the genome of an infectious, replication-deficient arenavirus by substitution of the nucleic acid sequence of the ORF of glycoprotein GP, the matrix protein Z, the nucleoprotein NP, or the polymerase protein L. In other embodiments, the nucleic acid sequence encoding the a tumor antigen, tumor associated antigen, or antigenic fragment thereof is fused to the ORF of glycoprotein GP, the matrix protein Z, the nucleoprotein NP, or the polymerase protein L. The nucleotide sequence encoding the a tumor antigen, tumor associated antigen, or antigenic fragment thereof, once inserted into the genome of an infectious, replication-deficient arenavirus, can be transcribed and/or expressed under control of the four arenavirus promoters (5' UTR and 3' UTR of the S segment, and 5' UTR and 3' UTR of the L segment), as well as ribonucleic acids that can be inserted with regulatory elements that can be read by the viral RNA-dependent RNA polymerase, cellular RNA polymerase I, RNA

polymerase II or RNA polymerase III, such as duplications of viral promoter sequences that are naturally found in the viral UTRs, the 28S ribosomal RNA promoter, the beta-actin promoter or the 5S ribosomal RNA promoter, respectively. The nucleic acids encoding the a tumor antigen, tumor associated antigen, or antigenic fragment thereof can be transcribed and/or expressed either by themselves or as read-through by fusion to arenavirus ORFs and genes, respectively, and/or in combination with one or more, *e.g.*, two, three or four, internal ribosome entry sites.

[00109] In certain embodiments, an arenavirus particle comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof as provided herein further comprises at least one nucleotide sequence encoding at least one immunomodulatory peptide, polypeptide or protein. In certain embodiments, the immunomodulatory peptide, polypeptide or protein is Calreticulin (CRT), or a fragment thereof; Ubiquitin or a fragment thereof; Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), or a fragment thereof; Invariant chain (CD74) or an antigenic fragment thereof; Mycobacterium tuberculosis Heat shock protein 70 or an antigenic fragment thereof; Herpes simplex virus 1 protein VP22 or an antigenic fragment thereof; CD40 ligand or an antigenic fragment thereof; or Fms-related tyrosine kinase 3 (Flt3) ligand or an antigenic fragment thereof.

[00110] In certain embodiments, an arenavirus particle provided herein comprises a genomic segment that a) has a removal or functional inactivation of an ORF that is present in the wild type form of the genomic segment; and b) encodes (either in sense or antisense): (i) one or more tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and (ii) one or more immunomodulatory peptide, polypeptide or protein provided herein.

[00111] In certain embodiments, the nucleotide sequence encoding the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the nucleotide sequence encoding the immunomodulatory peptide, polypeptide or protein provided herein, are on the same position of the viral genome. In certain embodiments, the nucleotide sequence encoding the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the nucleotide sequence encoding the immunomodulatory peptide, polypeptide or protein provided herein, are on different positions of the viral genome.

[00112] In certain embodiments, the nucleotide sequence encoding the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the nucleotide sequence encoding the immunomodulatory peptide, polypeptide or protein provided herein, are

separated via a spacer sequence. In certain embodiments, the sequence encoding the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the nucleotide sequence encoding the immunomodulatory peptide, polypeptide or protein provided herein, are separated by an internal ribosome entry site, or a sequence encoding a protease cleavage site. In certain embodiments, the nucleotide sequence encoding the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the nucleotide sequence encoding the immunomodulatory peptide, polypeptide or protein provided herein, are separated by a nucleotide sequence encoding a linker or a self-cleaving peptide. Any linker peptide or self-cleaving peptide known to the skilled artisan can be used with the compositions and methods provided herein. A non-limiting example of a peptide linker is GSG. Non-limiting examples of a self-cleaving peptide are Porcine teschovirus-1 2A peptide, Thoseaasignavirus 2A peptide, or Foot-and-mouth disease virus 2A peptide.

[00113] In certain embodiments, the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the immunomodulatory peptide, polypeptide or protein provided herein, are directly fused together. In certain embodiments, the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the immunomodulatory peptide, polypeptide or protein provided herein, are fused together via a peptide linker. In certain embodiments, the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the immunomodulatory peptide, polypeptide or protein provided herein are separated from each other via a self-cleaving peptide. A non-limiting example of a peptide linker is GSG. Non-limiting examples of a self-cleaving peptide are Porcine teschovirus-1 2A peptide, Thoseaasignavirus 2A peptide, or Foot-and-mouth disease virus 2A peptide.

[00114] In certain embodiments, the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the immunomodulatory peptide, polypeptide or protein provided herein are expressed on the same arenavirus particle. In certain embodiments, the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the immunomodulatory peptide, polypeptide or protein provided herein are expressed on different arenavirus particles. In certain embodiments, the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the immunomodulatory peptide, polypeptide or protein provided herein are expressed on different viruses of the same strain. In

certain embodiments, the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the immunomodulatory peptide, polypeptide or protein provided herein are expressed on different viruses of different strains.

[00115] In certain embodiments, an arenavirus particle generated to encode one or more tumor antigens, tumor associated antigens or antigenic fragments thereof comprises one or more nucleotide sequences encoding tumor antigens, tumor associated antigens or antigenic fragments thereof provided herein. In specific embodiments the tumor antigens, tumor associated antigens or antigenic fragments thereof provided herein are separated by various one or more linkers, spacers, or cleavage sites as described herein.

(c) Generation of Infectious, Replication-Deficient Arenavirus Expressing a Tumor Antigen, Tumor Associated Antigen or Antigenic Fragment Thereof

[00116] Generally, arenavirus particles for use in the methods and compositions provided herein, such as combinations with a chemotherapeutic agent, can be recombinantly produced by standard reverse genetic techniques as described for LCMV (L. Flatz, A. Bergthaler, J. C. de la Torre, and D. D. Pinschewer, Proc Natl Acad Sci USA 103:4663-4668, 2006; A. B. Sanchez and J. C. de la Torre, Virology 350:370, 2006; E. Ortiz-Riano, B.Y. Cheng, J. C. de la Torre, L. Martinez-Sobrido. J Gen Virol. 94:1175-88, 2013). To generate infectious, replication-deficient arenaviruses for use with the present invention these techniques can be used, however, the genome of the rescued virus is modified as described herein. These modifications can be: i) one or more, *e.g.*, two, three or four, of the four arenavirus ORFs (glycoprotein (GP); nucleoprotein (NP); the matrix protein Z; the RNA-dependent RNA polymerase L) are removed or functionally inactivated to prevent formation of infectious particles in normal cells albeit still allowing gene expression in arenavirus vector-infected host cells; and ii) nucleotides encoding for a tumor antigen, tumor associated antigen, or antigenic fragment thereof can be introduced. Infectious, replication-deficient viruses as described herein can be produced as described in International Patent Application Publication No. WO 2009/083210 (application number PCT/EP2008/010994) and International Patent Application Publication No. WO 2014/140301 (application number PCT/EP2014/055144), each of which is incorporated by reference herein in its entirety.

[00117] Once generated from cDNA, the infectious, replication-deficient arenaviruses provided herein can be propagated in complementing cells. Complementing cells are cells that

provide the functionality that has been eliminated from the replication-deficient arenavirus by modification of its genome (*e.g.*, if the ORF encoding the GP protein is deleted or functionally inactivated, a complementing cell does provide the GP protein).

[00118] Owing to the removal or functional inactivation of one or more of the viral genes in arenavirus vectors (here deletion of the glycoprotein, GP, will be taken as an example), arenavirus vectors can be generated and expanded in cells providing in trans the deleted viral gene(s), *e.g.*, the GP in the present example. Such a complementing cell line, henceforth referred to as C-cells, is generated by transfecting a mammalian cell line such as BHK-21, HEK 293, VERO or other (here BHK-21 will be taken as an example) with one or more plasmid(s) for expression of the viral gene(s) of interest (complementation plasmid, referred to as C-plasmid). The C-plasmid(s) express the viral gene(s) deleted in the arenavirus vector to be generated under control of one or more expression cassettes suitable for expression in mammalian cells, *e.g.*, a mammalian polymerase II promoter such as the CMV or EF1alpha promoter with a polyadenylation signal. In addition, the complementation plasmid features a mammalian selection marker, *e.g.*, puromycin resistance, under control of an expression cassette suitable for gene expression in mammalian cells, *e.g.*, polymerase II expression cassette as above, or the viral gene transcript(s) are followed by an internal ribosome entry site, such as the one of encephalomyocarditis virus, followed by the mammalian resistance marker. For production in *E. coli*, the plasmid additionally features a bacterial selection marker, such as an ampicillin resistance cassette.

[00119] Cells that can be used, *e.g.*, BHK-21, HEK 293, MC57G or other, are kept in culture and are transfected with the complementation plasmid(s) using any of the commonly used strategies such as calcium-phosphate, liposome-based protocols or electroporation. A few days later the suitable selection agent, *e.g.*, puromycin, is added in titrated concentrations. Surviving clones are isolated and subcloned following standard procedures, and high-expressing C-cell clones are identified using Western blot or flow cytometry procedures with antibodies directed against the viral protein(s) of interest. As an alternative to the use of stably transfected C-cells transient transfection of normal cells can complement the missing viral gene(s) in each of the steps where C-cells will be used below. In addition, a helper virus can be used to provide the missing functionality in trans.

[00120] Plasmids that can be used can be of two types: i) Two plasmids, referred to as TF-plasmids for expressing intracellularly in C-cells the minimal transacting factors of the arenavirus, is derived from *e.g.*, NP and L proteins of LCMV in the present example; and ii) Plasmids, referred to as GS-plasmids, for expressing intracellularly in C-cells the arenavirus vector genome segments, *e.g.*, the segments with designed modifications. TF-plasmids express the NP and L proteins of the respective arenavirus vector under control of an expression cassette suitable for protein expression in mammalian cells, typically *e.g.*, a mammalian polymerase II promoter such as the CMV or EF1alpha promoter, either one of them preferentially in combination with a polyadenylation signal. GS-plasmids express the small (S) and the large (L) genome segments of the vector. Typically, polymerase I-driven expression cassettes or T7 bacteriophage RNA polymerase (T7-) driven expression cassettes can be used, the latter preferentially with a 3'-terminal ribozyme for processing of the primary transcript to yield the correct end. In the case of using a T7-based system, expression of T7 in C-cells must be provided by either including in the recovery process an additional expression plasmid, constructed analogously to TF-plasmids, providing T7, or C-cells are constructed to additionally express T7 in a stable manner. In certain embodiments, TF and GS plasmids can be the same, *i.e.* the genome sequence and transacting factors can be transcribed by T7, polII and polIII promoters from one plasmid.

[00121] For recovering of the arenavirus vector, the following procedures can be used. First day: C-cells, typically 80% confluent in M6-well plates, are transfected with a mixture of the two TF-plasmids plus the two GS-plasmids. In certain embodiments, the TF and GS plasmids can be the same, *i.e.* the genome sequence and transacting factors can be transcribed by T7, polII and polIII promoters from one plasmid. For this one can exploit any of the commonly used strategies such as calcium-phosphate, liposome-based protocols or electroporation.

[00122] 3-5 days later: The culture supernatant (arenavirus vector preparation) is harvested, aliquoted and stored at 4°C, -20°C or -80°C depending on how long the arenavirus vector should be stored prior to use. Then the arenavirus vector preparation's infectious titer is assessed by an immunofocus assay on C-cells.

[00123] The invention furthermore relates to expression of a tumor antigen, tumor associated antigen, or antigenic fragment thereof in a cell culture wherein the cell culture is infected with an infectious, replication-deficient arenavirus expressing a tumor antigen, tumor

associated antigen, or antigenic fragment thereof. When used for expression of a tumor antigen, tumor associated antigen, or antigenic fragment thereof in cultured cells, the following two procedures can be used:

i) The cell type of interest is infected with the arenavirus vector preparation described herein at a multiplicity of infection (MOI) of one or more, *e.g.*, two, three or four, resulting in production of the tumor antigen, tumor associated antigen, or antigenic fragment thereof in all cells already shortly after infection.

ii) Alternatively, a lower MOI can be used and individual cell clones can be selected for their level of virally driven expression of a tumor antigen, tumor associated antigen, or antigenic fragment thereof. Subsequently individual clones can be expanded infinitely owing to the non-cytolytic nature of arenavirus vectors. Irrespective of the approach, the tumor antigen, tumor associated antigen, or antigenic fragment thereof can subsequently be collected (and purified) either from the culture supernatant or from the cells themselves, depending on the properties of the tumor antigen, tumor associated antigen, or antigenic fragment thereof produced. However, the invention is not limited to these two strategies, and other ways of driving expression of a tumor antigen, tumor associated antigen, or antigenic fragment thereof using infectious, replication-deficient arenaviruses as vectors may be considered.

[00124] Alternatively, a rescue system consisting of three plasmids can be used: (1) the first plasmid expresses the protein NP by transcription via Polymerase II and subsequent translation in transfected cells; (2) the second plasmid gives rise to the (negative-stranded) L-Segment of the LCMV genome by transcription via Polymerase I as well as the L protein by transcription via Polymerase II from the same template in the opposite direction of the Polymerase I promoter; (3) the third plasmid gives rise to the S-segment of the LCMV genome (encoding the antigen coding sequence instead of the LCMV glycoprotein) via transcription by Polymerase I. 3µg of each plasmid is used for electroporation of C-cells, followed by seeding of cells in 6-well plates and incubation at 37°C. After incubation, cells and supernatant from transfections are combined with freshly seeded C-cells, and vectors are harvested and cleared from cells & debris at a defined timepoint post infection. Once the vector has been generated, a nucleic acid encoding a tumor antigen, tumor associated antigen, or antigenic fragment thereof can be inserted into a plasmid from which a genomic segment of an infectious replication-deficient vector is transcribed by any technique known to the skilled artisan.

[00125] Owing to the removal or functional inactivation of one or more of the viral genes in arenavirus vectors (here deletion of the glycoprotein, GP, will be taken as an example) arenavirus vectors can be generated and expanded in cells that provide the deleted or functionally inactivated viral gene(s) (*e.g.*, the GP) *in trans*. The resulting virus itself is infectious but is unable to produce further infectious progeny particles in non-complementing cells due to the lack of the deleted or functionally inactivated viral gene(s) (*e.g.*, the GP). The complementing cell can provide the missing functionality either by stable transfection, transient transfection, or by infection with a helper virus that expresses the missing functionality.

[00126] In certain embodiments, the complementing cell provides the viral gene that has been deleted or functionally inactivated from the arenavirus vector genome. In a specific embodiment, the complementing cell provides the viral gene from a viral strain that is the same as the viral strain that was used to generate the genome of the arenavirus vector. In another embodiment, the complementing cell provides the viral gene from a viral strain that is different from the viral strain that was used to generate the genome of the arenavirus vector. For example, the viral gene provided in the complementing cell is obtained from the MP strain of LCMV. In another example, the viral gene provided in the complementing cell is obtained from the Clone 13 strain of LCMV. In another example, the viral gene provided in the complementing cell is obtained from the WE strain of LCMV.

[00127] In a specific embodiment, the complementing cell provides the GP of the MP strain of LCMV and the arenavirus vector comprises an ORF of a tumor antigen, tumor associated antigen, or antigenic fragment thereof as described herein in place of the ORF encoding the GP protein. In an even more specific embodiment, the complementing cell provides the GP of the MP strain of LCMV and the arenavirus vector is obtained from LCMV Clone 13 and comprises an ORF of a tumor antigen, tumor associated antigen, or antigenic fragment thereof as described herein in place of the ORF encoding the GP protein.

[00128] In a specific embodiment, the complementing cell provides the GP of the Clone 13 strain of LCMV and the arenavirus vector comprises an ORF of a tumor antigen, tumor associated antigen, or antigenic fragment thereof as described herein in place of the ORF encoding the GP protein. In an even more specific embodiment, the complementing cell provides the GP of the Clone 13 strain of LCMV and the arenavirus vector is obtained from

LCMV MP strain and comprises an ORF of a tumor antigen, tumor associated antigen, or antigenic fragment thereof as described herein in place of the ORF encoding the GP protein.

[00129] In a specific embodiment, the complementing cell provides the GP of the WE strain of LCMV and the arenavirus vector comprises an ORF of a tumor antigen, tumor associated antigen, or antigenic fragment thereof as described herein in place of the ORF encoding the GP protein. In an even more specific embodiment, the complementing cell provides the GP of the WE strain of LCMV and the arenavirus vector is obtained from LCMV Clone 13 and comprises an ORF of a tumor antigen, tumor associated antigen, or antigenic fragment thereof as described herein in place of the ORF encoding the GP protein.

[00130] In a specific embodiment, the complementing cell provides the GP of the WE strain of LCMV and the arenavirus vector comprises an ORF of a tumor antigen, tumor associated antigen, or antigenic fragment thereof as described herein in place of the ORF encoding the GP protein. In an even more specific embodiment, the complementing cell provides the GP of the WE strain of LCMV and the arenavirus vector is obtained from LCMV MP strain and comprises an ORF of a tumor antigen, tumor associated antigen, or antigenic fragment thereof as described herein in place of the ORF encoding the GP protein.

(d) Nucleic Acids, Vector Systems and Cell Lines

[00131] In one embodiment, described herein is a nucleic acid sequence which is the cDNA of the large genomic segment (L segment) of an infectious, replication-deficient arenavirus described herein, in which one ORF of the genomic segment is deleted or functionally inactivated, and the genomic segment comprises a nucleotide sequence encoding a tumor antigen, tumor associated antigen, or antigenic fragment thereof, which can be used with the methods and compositions provided herein, such as combinations with a chemotherapeutic agent.

[00132] In one embodiment, described herein is a nucleic acid sequence that encodes the short genomic segment (S segment) of an infectious, replication-deficient arenavirus described herein, in which one ORF of the genomic segment is deleted or functionally inactivated and wherein the short genomic segment comprises a nucleotide sequence encoding a tumor antigen, tumor associated antigen, or antigenic fragment thereof. In another embodiment, described herein is a nucleic acid sequence that encodes the short genomic segment (S segment) of an infectious, replication-deficient arenavirus described herein, in which the ORF of the

glycoprotein gene is deleted or functionally inactivated and wherein the short genomic segment comprises a nucleotide sequence encoding a tumor antigen, tumor associated antigen, or antigenic fragment thereof. In certain, more specific embodiments, the tumor antigen, tumor associated antigen, or antigenic fragment thereof is an antigen described in Section 5.1.(b).

[00133] In certain embodiments, the nucleic acid sequences provided herein can be derived from a particular strain of LCMV. Strains of LCMV include Clone 13, MP strain, Arm CA 1371, Arm E-250, WE, UBC, Traub, Pasteur, 810885, CH-5692, Marseille #12, HP65-2009, 200501927, 810362, 811316, 810316, 810366, 20112714, Douglas, GR01, SN05, CABN and their derivatives. In specific embodiments, the nucleic acid is derived from LCMV Clone 13. In other specific embodiments, the nucleic acid is derived from LCMV MP strain.

[00134] In a more specific embodiment, provided herein is a nucleic acid that comprises an arenavirus genomic segment; and (ii) a nucleotide sequence encoding a tumor antigen, tumor associated antigen, or antigenic fragment thereof.

[00135] In one embodiment, described herein is a vector system comprising one or more vectors that together comprise the genome of an infectious, replication-deficient arenavirus particle described herein. Specifically, provided herein is a vector system wherein the one or more vectors comprise two arenavirus genomic segments, namely an L segment and an S segment, of an infectious, replication-deficient arenavirus described herein. Such a vector system can comprise (on one or more separate DNA molecules):

- An arenavirus S genomic segment that is modified such that an arenavirus particle carrying this modified S genomic segment cannot produce infectious progeny virus particles and an arenavirus L genomic segment that comprises a nucleotide sequence encoding (in sense or antisense) a tumor antigen, tumor associated antigen, or antigenic fragment thereof;
- An arenavirus L genomic segment that is modified such that an arenavirus particle carrying this modified L genomic segment cannot produce infectious progeny virus particles and an arenavirus S genomic segment that comprises a nucleotide sequence encoding (in sense or antisense) a tumor antigen, tumor associated antigen, or antigenic fragment thereof;
- An arenavirus S genomic segment that is modified such that an arenavirus particle carrying this modified S genomic segment cannot produce infectious progeny virus particles and wherein the arenavirus S genomic segment comprises a nucleotide sequence encoding (in

sense or antisense) a tumor antigen, tumor associated antigen, or antigenic fragment thereof and comprising a wild type arenavirus L genomic segment; or

- An arenavirus L genomic segment that is modified such that an arenavirus particle carrying this modified L genomic segment cannot produce infectious progeny virus particles and wherein the arenavirus L genomic segment comprises a nucleotide sequence encoding (in sense or antisense) a tumor antigen, tumor associated antigen, or antigenic fragment thereof and comprising a wild type arenavirus S genomic segment.

[00136] In certain embodiments, described herein is a nucleic acid sequence comprising an arenavirus (*e.g.*, LCMV) genomic segment in which the ORF encoding the GP of the S genomic segment is substituted with a nucleotide sequence encoding a tumor antigen, tumor associated antigen, or antigenic fragment thereof, which is selected from the group consisting of oncogenic viral antigens, cancer-testis antigens, oncofetal antigens, tissue differentiation antigens, mutant protein antigens, Adipophilin, AIM-2, ALDH1AI, BCLX (L), BING-4, CALCA, CD45, CPSF, cyclin D1, DKKI, ENAH (hMena), Ga733 (EpCAM), EphA3, EZH2, FGF5, glypican-3, G250 /MN/CAIX, HER-2/neu, IDO1, IGF2B3, IL13Ralpha2, Intestinal carboxyl esterase, alpha-foetoprotein, Kallikrein 4, KIF20A, Lengsin, M-CSF, MCSP, mdm-2, Meloe, MMP-2, MMP-7, MUC1, MUC5AC, p53 (non-mutant), PAX5, PBF, PRAME, PSMA, RAGE, RAGE-1, RGS5, RhoC, RNF43, RU2AS, secernin 1, SOX10, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), survivin, Telomerase, VEGF, WT1, EGF-R, CEA, CD20, CD33, CD52, gp 100 protein, MELANA/MART1, MART2, NY-ESO-1, p53, MAGE A1, MAGE A3, MAGE-4, MAGE-5, MAGE-6, CDK4, alpha-actinin-4, ARTC1, BCR-ABL, BCR-ABL fusion protein (b3a2), B-RAF, CASP-5, CASP-8, beta-catenin, Cdc27, CDK4, CDKN2A, CLPP, COA-1, dek-can fusion protein, EFTUD2, Elongation factor 2, ETV6-AML, ETV6-AML1 fusion protein, FLT3-ITD, FNI, GPNMB, LDLR-fucosyltransferaseAS fusion protein, NFYC, OGT, OS-9, pml-RARalpha fusion protein, PRDX5, PTPRK, H-ras, K-ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene), N-ras, RBAF600, SIRT2, SNRPDI, SSX, SSX2, SYT-SSX1 or-SSX2 fusion protein, TGF-betaRII, Triosephosphate isomerase, ormdm-2, LMP2, HPV E6 / E7, EGFRvIII (epidermal growth factor variant III), Idiotypic, GD2, ganglioside G2), Ras-mutant, p53 (mutant), Proteinase3 (PR1), Tyrosinase, PSA, hTERT, Sarcoma translocation breakpoints, EphA2, prostatic acid phosphatase PAP, neo-PAP, ML-IAP, AFP, ERG (TMPRSS2 ETS Fusion gene), NA17, PAX3, ALK, Androgen Receptor, Cyclin B1, Polysialic acid, MYCN,

TRP2, TRP2-Int2, GD3, Fucosyl GM1, Mesothelin, PSCA, sLe(a), cyp1B1, PLAC1, GM3, BORIS, Tn, GLoboH, NY-BR-1, SART3, STn, Carbonic Anhydrase IX, OY-TES1, Sperm protein 17, LCK, high molecular weight melanoma-associated antigen (HMWMAA), AKAP-4, SSX2, XAGE 1, B7H3, Legumain, Tie 2, Page4, VEGFR2, MAD-CT-1, FAP, PDGFR-beta, MAD-CT-2, For-related antigen 1, TRP-1, CA-125, CA19-9, Calretinin, Epithelial membrane antigen (EMA), Epithelial tumor antigen (ETA), CD19, CD34, CD99, CD117, Chromogranin, Cytokeratin, Desmin, Glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, Myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), BAGE BAGE-1, CAGE, CTAGE, FATE, GAGE, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, HCA661, HOM-TES-85, MAGEA, MAGEB, MAGEC, NA88, NY-SAR-35, SPANXB1, SPA17, SSX, SYCP1, TPTE, Carbohydrate / ganglioside GM2 (oncofetal antigen-immunogenic-1 OFA-I-1), GM3, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA 50, CAM 43, CEA, EBNA, EF2, Epstein-Barr virus antigen, HLA-A2, HLA-A11, HSP70-2, KIAA0205, MUM-1, MUM-2, MUM-3, Myosin class I, GnTV, Herv-K-mel, LAGE-1, LAGE-2, (sperm protein) SP17, SCP-1, P15(58), Hom/Mel-40, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, TSP-180, P185erbB2, p180erbB-3, c-met, nm-23H1, TAG-72, TAG-72-4, CA-72-4, CAM 17.1, NuMa, 13-catenin, P16, TAGE, CT7, 43-9F, 5T4, 791Tgp72, 13HCG, BCA225, BTAA, CD68\KP1, CO-029, HTgp-175, M344, MG7-Ag, MOV18, NB\70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TLP, TPS, CD22, CD27, CD30, CD70, prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, integrin $\alpha v \beta 3$ (CD61), galactin, or Ral-B, CD123, CLL-1, CD38, CS-1, CD138, and ROR1.

[00137] In certain embodiments, described herein is a nucleic acid sequence comprising an arenavirus (*e.g.*, LCMV) genomic segment in which the ORF encoding the GP of the S genomic segment is substituted with a nucleotide sequence encoding one or more a tumor antigen, tumor associated antigen, or antigenic fragment thereof (*e.g.*, one or more of those listed in the above paragraph).

[00138] In another embodiment, provided herein is a cell wherein the cell comprises a nucleic acid or a vector system described above in this section. Cell lines derived from such cells, cultures comprising such cells, and methods of culturing such cells infected with nucleic

acids or vector systems are also provided herein. In certain embodiments, provided herein is a cell wherein the cell comprises a nucleic acid comprising the large genomic segment (L segment) of an infectious, replication-deficient arenavirus described herein, in which one ORF of the genomic segment is deleted or functionally inactivated, and the genomic segment comprises a nucleotide sequence encoding a tumor antigen, tumor associated antigen, or antigenic fragment thereof.

[00139] In other embodiments, provided herein is a cell wherein the cell comprises a nucleic acid sequence that comprises the short genomic segment (S segment) of an infectious, replication-deficient arenavirus described herein, in which one ORF of the genomic segment is deleted or functionally inactivated and wherein the short genomic segment comprises a nucleotide sequence encoding a tumor antigen, tumor associated antigen, or antigenic fragment thereof.

[00140] In another embodiment, provided herein is a cell wherein the cell comprises two nucleic acids or vector systems described herein. Cell lines derived from such cells, cultures comprising such cells, and methods of culturing such cells infected with nucleic acids or vector systems are also provided herein.

(e) Methods of Use

[00141] Vaccines have been successful for preventing and/or treating infectious diseases, such as those for polio virus and measles. However, therapeutic immunization in the setting of established, chronic disease, including cancer has been less successful. The ability to generate an arenavirus particle that is used in combination with a chemotherapeutic agent represents a new novel vaccine strategy.

[00142] In certain embodiments, provided herein are methods of treating a neoplastic disease in a subject. Such methods can include administering to a subject in need thereof an arenavirus particle provided herein and a chemotherapeutic agent provided herein. In certain embodiments, the arenavirus particle used in the methods is an infectious, replication-deficient arenavirus particle. Thus, in certain embodiments, the infectious, replication-deficient arenavirus particle used in the methods is engineered to contain a genome comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and the ability to amplify and express its genetic information in infected cells but unable to produce further infectious progeny particles in non-complementing cells.

[00143] In one embodiment, provided herein are methods of treating a neoplastic disease in a subject comprising administering to the subject one or more infectious, replication-deficient arenavirus particles expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof as provided herein or a composition thereof, and a chemotherapeutic agent provided herein. In a specific embodiment, a method for treating a neoplastic disease described herein comprises administering to a subject in need thereof a therapeutically effective amount of one or more infectious, replication-deficient arenavirus particles expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein or a composition thereof, and a chemotherapeutic agent provided herein. The subject can be a mammal, such as but not limited to a human, a mouse, a rat, a guinea pig, a domesticated animal, such as, but not limited to, a cow, a horse, a sheep, a pig, a goat, a cat, a dog, a hamster, a donkey. In a specific embodiment, the subject is a human.

[00144] In another embodiment, provided herein are methods for inducing an immune response against a neoplastic cell or tissue, such as a cancer cell or tumor, in a subject comprising administering to the subject an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein.

[00145] In another embodiment, the subjects to whom an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered have, are susceptible to, or are at risk for a neoplastic disease.

[00146] In another embodiment, the subjects to whom an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered have, are susceptible to, or are at risk for development of a neoplastic disease, such as cancer, or exhibit a pre-cancerous tissue lesion. In another specific embodiment, the subjects to whom infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered are diagnosed with a neoplastic disease, such as cancer, or exhibit a pre-cancerous tissue lesion.

[00147] In another embodiment, the subjects to whom an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered are suffering from, are susceptible to, or are at risk for, a neoplastic disease selected from, but not limited to, acute lymphoblastic leukemia; acute lymphoblastic lymphoma; acute lymphocytic leukaemia; acute myelogenous leukemia; acute myeloid leukemia (adult / childhood); adrenocortical carcinoma; AIDS-related cancers; AIDS-related lymphoma; anal cancer; appendix cancer; astrocytomas; atypical teratoid/rhabdoid tumor; basal-cell carcinoma; bile duct cancer, extrahepatic (cholangiocarcinoma); bladder cancer; bone osteosarcoma/malignant fibrous histiocytoma; brain cancer (adult / childhood); brain tumor, cerebellar astrocytoma (adult / childhood); brain tumor, cerebral astrocytoma/malignant glioma brain tumor; brain tumor, ependymoma; brain tumor, medulloblastoma; brain tumor, supratentorial primitive neuroectodermal tumors; brain tumor, visual pathway and hypothalamic glioma; brainstem glioma; breast cancer; bronchial adenomas/carcinoids; bronchial tumor; Burkitt lymphoma; cancer of childhood; carcinoid gastrointestinal tumor; carcinoid tumor; carcinoma of adult, unknown primary site; carcinoma of unknown primary; central nervous system embryonal tumor; central nervous system lymphoma, primary; cervical cancer; childhood adrenocortical carcinoma; childhood cancers; childhood cerebral astrocytoma; chordoma, childhood; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloid leukemia; chronic myeloproliferative disorders; colon cancer; colorectal cancer; craniopharyngioma; cutaneous T-cell lymphoma; desmoplastic small round cell tumor; emphysema; endometrial cancer; ependymoblastoma; ependymoma; esophageal cancer; ewing's sarcoma in the Ewing family of tumors; extracranial germ cell tumor; extragonadal germ cell tumor; extrahepatic bile duct cancer; gallbladder cancer; gastric (stomach) cancer; gastric carcinoid; gastrointestinal carcinoid tumor; gastrointestinal stromal tumor; germ cell tumor: extracranial, extragonadal, or ovarian gestational trophoblastic tumor; gestational trophoblastic tumor, unknown primary site; glioma; glioma of the brain stem; glioma, childhood visual pathway and hypothalamic; hairy cell leukemia; head and neck cancer; heart cancer; hepatocellular (liver) cancer; hodgkin lymphoma; hypopharyngeal cancer; hypothalamic and visual pathway glioma; intraocular melanoma; islet cell carcinoma (endocrine pancreas); Kaposi Sarcoma; kidney cancer (renal cell cancer); langerhans cell histiocytosis; laryngeal cancer; lip

and oral cavity cancer; liposarcoma; liver cancer (primary); lung cancer, non-small cell; lung cancer, small cell; lymphoma, primary central nervous system; macroglobulinemia, Waldenström; male breast cancer; malignant fibrous histiocytoma of bone/osteosarcoma; medulloblastoma; medulloepithelioma; melanoma; melanoma, intraocular (eye); merkel cell cancer; merkel cell skin carcinoma; mesothelioma; mesothelioma, adult malignant; metastatic squamous neck cancer with occult primary; mouth cancer; multiple endocrine neoplasia syndrome; multiple myeloma/plasma cell neoplasm; mycosis fungoides, myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; myelogenous leukemia, chronic; myeloid leukemia, adult acute; myeloid leukemia, childhood acute; myeloma, multiple (cancer of the bone-marrow); myeloproliferative disorders, chronic; nasal cavity and paranasal sinus cancer; nasopharyngeal carcinoma; neuroblastoma, non-small cell lung cancer; non-hodgkin lymphoma; oligodendroglioma; oral cancer; oral cavity cancer; oropharyngeal cancer; osteosarcoma/malignant fibrous histiocytoma of bone; ovarian cancer; ovarian epithelial cancer (surface epithelial-stromal tumor); ovarian germ cell tumor; ovarian low malignant potential tumor; pancreatic cancer; pancreatic cancer, islet cell; papillomatosis; paranasal sinus and nasal cavity cancer; parathyroid cancer; penile cancer; pharyngeal cancer; pheochromocytoma; pineal astrocytoma; pineal germinoma; pineal parenchymal tumors of intermediate differentiation; pineoblastoma and supratentorial primitive neuroectodermal tumors; pituitary tumor; pituitary adenoma; plasma cell neoplasia/multiple myeloma; pleuropulmonary blastoma; primary central nervous system lymphoma; prostate cancer; rectal cancer; renal cell carcinoma (kidney cancer); renal pelvis and ureter, transitional cell cancer; respiratory tract carcinoma involving the NUT gene on chromosome 15; retinoblastoma; rhabdomyosarcoma, childhood; salivary gland cancer; sarcoma, Ewing family of tumors; Sézary syndrome; skin cancer (melanoma); skin cancer (non-melanoma); small cell lung cancer; small intestine cancer soft tissue sarcoma; soft tissue sarcoma; spinal cord tumor; squamous cell carcinoma; squamous neck cancer with occult primary, metastatic; stomach (gastric) cancer; supratentorial primitive neuroectodermal tumor; T-cell lymphoma, cutaneous (Mycosis Fungoides and Sézary syndrome); testicular cancer; throat cancer; thymoma; thymoma and thymic carcinoma; thyroid cancer; thyroid cancer, childhood; transitional cell cancer of the renal pelvis and ureter; urethral cancer; uterine cancer, endometrial; uterine sarcoma; vaginal cancer; vulvar cancer; and Wilms Tumor.

[00148] In another embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject of any age group suffering from, are susceptible to, or are at risk for a neoplastic disease. In a specific embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject with a compromised immune system, a pregnant subject, a subject undergoing an organ or bone marrow transplant, a subject taking immunosuppressive drugs, a subject undergoing hemodialysis, a subject who has cancer, or a subject who is suffering from, are susceptible to, or are at risk for a neoplastic disease. In a more specific embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject who is a child of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 years of age suffering from, are susceptible to, or are at risk for a neoplastic disease. In yet another specific embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject who is an infant suffering from, is susceptible to, or is at risk for a neoplastic disease. In yet another specific embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject who is an infant of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months of age suffering from, is susceptible to, or is at risk for a neoplastic disease. In yet another specific embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to an elderly subject who is suffering from, is susceptible to, or is at risk for a neoplastic disease. In a more specific embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered

to a subject who is a senior subject of 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 years of age. Provided herein is a method for preventing a cancer in a subject susceptible to, or is at risk for a neoplastic disease.

[00149] In another embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to subjects with a heightened risk of cancer metastasis. In a specific embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to subjects in the neonatal period with a neonatal and therefore immature immune system.

[00150] In another embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject having grade 0 (*i.e.*, in situ neoplasm), grade 1, grade 2, grade 3 or grade 4 cancer or a subcategory thereof, such as grade 3A, 3B, or 3C, or an equivalent thereof.

[00151] In another embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject having cancer at a Tumor, Node, Metastasis (TNM) stage of any combination selected from Tumor T1, T2, T3, and T4, and Node N0, N1, N2, or N3, and Metastasis M0 and M1.

[00152] Successful treatment of a cancer patient can be assessed as prolongation of expected survival, induction of an anti-tumor immune response, or improvement of a particular characteristic of a cancer. Examples of characteristics of a cancer that might be improved include tumor size (*e.g.*, T0, T is, or T1-4), state of metastasis (*e.g.*, M0, M1), number of observable tumors, node involvement (*e.g.*, N0, N1-4, Nx), grade (*i.e.*, grades 1, 2, 3, or 4), stage (*e.g.*, 0, I, II, III, or IV), presence or concentration of certain markers on the cells or in bodily fluids (*e.g.*, AFP, B2M, beta-HCG, BTA, CA 15-3, CA 27.29, CA 125, CA 72.4, CA 19-9, calcitonin, CEA, chromgrainin A, EGFR, hormone receptors, HER2, HCG, immunoglobulins, NSE, NMP22, PSA, PAP, PSMA, S-100, TA-90, and thyroglobulin), and/or associated

pathologies (*e.g.*, ascites or edema) or symptoms (*e.g.*, cachexia, fever, anorexia, or pain). The improvement, if measureable by percent, can be at least 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, or 90% (*e.g.*, survival, or volume or linear dimensions of a tumor).

[00153] In another embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject having a dormant cancer (*e.g.*, the subject is in remission). Thus, provided herein is a method for preventing reactivation of a cancer. Also provided herein are methods for reducing the frequency of reoccurrence of a cancer.

[00154] In another embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject having a recurrent a cancer.

[00155] In another embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject with a genetic predisposition for a cancer. In another embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject with risk factors. Exemplary risk factors include, aging, tobacco, sun exposure, radiation exposure, chemical exposure, family history, alcohol, poor diet, lack of physical activity, or being overweight.

[00156] In another embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to subjects who suffer from one or more types of cancers. In other embodiments, any type of neoplastic disease, such as cancer, that is susceptible to treatment with the compositions described herein might be targeted.

[00157] In another embodiment, administering an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided or a composition thereof to subjects confer cell-mediated immunity (CMI)

against a neoplastic cell or tumor, such as a cancer cell or tumor. Without being bound by theory, in another embodiment, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided or a composition thereof infects and expresses antigens of interest in antigen presenting cells (APC) of the host (*e.g.*, macrophages) for direct presentation of antigens on Major Histocompatibility Complex (MHC) class I and II. In another embodiment, administering an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, to subjects induces plurifunctional IFN- γ and TNF- α co-producing cancer-specific CD4⁺ and CD8⁺ T cell responses (IFN- γ is produced by CD4⁺ and CD8⁺ T cells and TNF- α is produced by CD4⁺ T cells) of high magnitude to treat a neoplastic disease.

[00158] In another embodiment, administering an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein increases or improves one or more clinical outcome for cancer treatment. Non-limiting examples of such outcomes are overall survival, progression-free survival, time to progression, time to treatment failure, event-free survival, time to next treatment, overall response rate and duration of response. The increase or improvement in one or more of the clinical outcomes can be by at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or more, compared to a patient or group of patients having the same neoplastic disease in the absence of such treatment.

[00159] Changes in cell-mediated immunity (CMI) response function against a neoplastic cell or tumor, including a cancer cell or tumor, induced by administering an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided, or a composition thereof, in subjects can be measured by any assay known to the skilled artisan including, but not limited to flow cytometry (see, *e.g.*, Perfetto S.P. et al., Nat Rev Immun. 2004; 4(8):648-55), lymphocyte proliferation assays (see, *e.g.*, Bonilla F.A. et al., Ann Allergy Asthma Immunol. 2008; 101:101-4; and Hicks M.J. et al., Am J Clin Pathol. 1983; 80:159-63), assays to measure lymphocyte activation including determining changes in surface marker expression following activation of measurement of

cytokines of T lymphocytes (see, *e.g.*, Caruso A. et al., Cytometry. 1997;27:71-6), ELISPOT assays (see, *e.g.*, Czerkinsky C.C. et al., J Immunol Methods. 1983; 65:109-121; and Hutchings P.R. Et al., J Immunol Methods. 1989; 120:1-8), or Natural killer cell cytotoxicity assays (see, *e.g.*, Bonilla F.A. et al., Ann Allergy Asthma Immunol. 2005 May; 94(5 Suppl 1):S1-63).

[00160] Chemotherapeutic agents disclosed herein can be alkylating agents (*e.g.*, cyclophosphamide), platinum-based therapeutics, antimetabolites, topoisomerase inhibitors, cytotoxic antibiotics, intercalating agents, mitosis inhibitors, taxanes, or combinations of two or more thereof. In certain embodiments, the alkylating agent is a nitrogen mustard, a nitrosourea, an alkyl sulfonate, a non-classical alkylating agent, or a triazene. In certain embodiments, the chemotherapeutic agent comprises one or more of cyclophosphamide, thiotepa, mechlorethamine (chlormethine/mustine), uramustine, melphalan, chlorambucil, ifosfamide, chlornaphazine, cholophosphamide, estramustine, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, bendamustine, busulfan, improsulfan, piposulfan, carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine, streptozucin, cisplatin, carboplatin, nedaplatin, oxaliplatin, satraplatin, triplatin tetranitrate, procarbazine, altretamine, dacarbazine, mitozolomide, temozolomide, paclitaxel, docetaxel, vinblastine, vincristine, vinorelbine, cabazitaxel, dactinomycin (actinomycin D), calicheamicin, dynemicin, amsacrine, doxorubicin, daunorubicin, epirubicin, mitoxantrone, idarubicin, pirarubicin, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide, trimethylolomelamine, bullatacin, bullatacinone, camptothecin, topotecan, bryostatin, callystatin, CC-1065, adozelesin, carzelesin, bizelesin, cryptophycin, dolastatin, duocarmycin, KW-2189, CB1-TM1, eleutherobin, pancratistatin, sarcodictyin, spongistatin, clodronate, esperamicin, neocarzinostatin chromophore, aclacinomycin, anthramycin, azaserine, bleomycin, cactinomycin, carabycin, carminomycin, carzinophilin, chromomycinis, detorubicin, 6-diazo-5-oxo-L-norleucine, esorubicin, idarubicin, marcellomycin, mitomycin, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, methotrexate, 5-fluorouracil (5-FU), denopterin, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone, mitotane, trilostane, frolinic

acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elformithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansine, ansamitocins, mitoguazone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, PSK polysaccharide complex, razoxane, rhizoxin, sizofiran, spirogermanium, tenuazonic acid, triaziquone, 2,2',2''-trichlorotriethylamine; T-2 toxin, verracurin A, roridin A and anguidine, urethan, vindesine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside ("Ara-C"), etoposide (VP-16), vinorelbine, novantrone, teniposide, edatrexate, aminopterin, xeloda, ibandronate, irinotecan (e.g., CPT-11), topoisomerase inhibitor RFS 2000, difluoromethylornithine (DMFO), retinoic acid, capecitabine, plicomycin, gemcitabine, navelbine, transplatinum, and pharmaceutically acceptable salts, acids, or derivatives of any of the above. In specific embodiments, the chemotherapeutic agent comprises cyclophosphamide. In certain embodiments, the nitrogen mustard is mechlorethamine, cyclophosphamide, melphalan, chlorambucil, ifosfamide, or busulfan. In certain embodiments, the chemotherapeutic agent alkylates DNA. In certain embodiments, the chemotherapeutic agent alkylates DNA, resulting in the formation of interstrand cross-links ("ICLs").

[00161] In certain embodiments, chemotherapeutic agents described herein are used in combination with an immune checkpoint inhibitor that inhibits, decreases or interferes with the activity of a negative checkpoint regulator. In certain embodiments, the negative checkpoint regulator is selected from the group consisting of Cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD80, CD86, Programmed cell death 1 (PD-1), Programmed cell death ligand 1 (PD-L1), Programmed cell death ligand 2 (PD-L2), Lymphocyte activation gene-3 (LAG-3; also known as CD223), Galectin-3, B and T lymphocyte attenuator (BTLA), T-cell membrane protein 3 (TIM3), Galectin-9 (GAL9), B7-H1, B7-H3, B7-H4, T-Cell immunoreceptor with Ig and ITIM domains (TIGIT/Vstm3/WUCAM/VSIG9), V-domain Ig suppressor of T-Cell activation (VISTA), Glucocorticoid-induced tumor necrosis factor receptor-related (GITR) protein, Herpes Virus Entry Mediator (HVEM), OX40, CD27, CD28, CD137. CGEN-15001T, CGEN-15022, CGEN-15027, CGEN-15049, CGEN-15052, and CGEN-15092. In certain embodiments, the immune checkpoint inhibitor is an anti-PD-1 antibody.

[00162] In certain embodiments, an infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is preferably administered in multiple injections (*e.g.*, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 25, 30, 40, 45, or 50 injections) or by continuous infusion (*e.g.*, using a pump) at multiple sites (*e.g.*, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, or 14 sites). In certain embodiments, the infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, is administered in two or more separate injections over a 6-month period, a 12-month period, a 24-month period, or a 48-month period. In certain embodiments, the infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, is administered with a first dose at an elected date, a second dose at least 2 months after the first dose, and a third dose 6 months after the first dose.

[00163] In one example, cutaneous injections are performed at multiple body sites to reduce extent of local skin reactions. On a given vaccination day, the patient receives the assigned total dose administered from one syringe in 3 to 5 separate intradermal injections of the dose (*e.g.*, at least 0.4 ml, 0.2 ml, or 0.1 ml) each in an extremity spaced at least about 5 cm (*e.g.*, at least 4.5, 5, 6, 7, 8, 9, or cm) at needle entry from the nearest neighboring injection. On subsequent vaccination days, the injection sites are rotated to different limbs in a clockwise or counter-clockwise manner.

[00164] In certain embodiments, the methods further comprise co-administration of the arenavirus particle provided herein and a chemotherapeutic agent. In certain embodiments, the co-administration is simultaneous. In another embodiment, the arenavirus particle is administered prior to administration of the chemotherapeutic agent. In other embodiments, the arenavirus particle is administered after administration of the chemotherapeutic agent. In certain embodiments, the interval between administration of the arenavirus particle and the chemotherapeutic agent is about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, or about 12 hours. In certain embodiments, the interval between administration of the arenavirus particle and the chemotherapeutic agent is about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 8 days, about 9 days, about 10

days, about 11 days, about 12 days, about 13 days, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks. In certain embodiments, the interval between administration of the arenavirus particle and the chemotherapeutic agent is about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, or about 6 months. In some embodiments, the method further includes administering at least one additional therapy.

[00165] In another embodiment, two infectious, replication-deficient arenavirus particles are administered in a treatment regime at molar ratios ranging from about 1:1 to 1:1000, in particular including: 1:1 ratio, 1:2 ratio, 1:5 ratio, 1:10 ratio, 1:20 ratio, 1:50 ratio, 1:100 ratio, 1:200 ratio, 1:300 ratio, 1:400 ratio, 1:500 ratio, 1:600 ratio, 1:700 ratio, 1:800 ratio, 1:900 ratio, 1:1000 ratio.

[00166] In certain embodiments, provided herein is a method of treating neoplastic disease wherein a first infectious, replication-deficient arenavirus particle is administered first as a “prime,” and a second infectious, replication-deficient arenavirus particle is administered as a “boost.” The first and the second infectious, replication-deficient arenavirus particles can express the same or different tumor antigens, tumor associated antigens or antigenic fragments thereof. Alternatively, or additionally, some certain embodiments, the “prime” and “boost” administration are performed with an infectious, replication-deficient arenavirus particle derived from different species. In certain specific embodiments, the “prime” administration is performed with an infectious, replication-deficient arenavirus particle derived from LCMV, and the “boost” is performed with an infectious, replication-deficient arenavirus particle derived from Junin virus. In certain specific embodiments, the “prime” administration is performed with an infectious, replication-deficient arenavirus particle derived from Junin virus, and the “boost” is performed with an infectious, replication-deficient arenavirus particle derived from LCMV. In certain embodiments, the “prime” administration is performed with an arenavirus particle derived from Pichinde virus, and the “boost” is performed with an arenavirus particle derived from LCMV. In certain embodiments, the “prime” administration is performed with an arenavirus particle derived from Pichinde virus, and the “boost” is performed with an arenavirus particle derived from Junin virus. In certain embodiments, the “prime” administration is performed with an arenavirus particle derived from LCMV, and the “boost” is performed with an arenavirus particle derived from Pichinde virus. In certain embodiments, the “prime”

administration is performed with an arenavirus particle derived from Junin virus, and the “boost” is performed with an arenavirus particle derived from Pichinde virus. In certain embodiments, the “prime” administration and/or the “boost” administration are performed in combination with the administration of an immunomodulatory peptide, polypeptide, or protein. In certain embodiments, the “prime” administration and/or the “boost” administration are performed in combination with the administration of a chemotherapeutic agent.

[00167] In certain embodiments, administering a first infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof, followed by administering a second infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof results in a greater antigen specific CD8⁺ T cell response than administering a single infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof. In certain embodiments, the antigen specific CD8⁺ T cell count increases by 50%, 100%, 150% or 200% after the second administration compared to the first administration. In certain embodiments, administering a third infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof results in a greater antigen specific CD8⁺ T cell response than administering two consecutive infectious, replication-deficient arenavirus particles expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof. In certain embodiments, the antigen specific CD8⁺ T cell count increases by about 50%, about 100%, about 150%, about 200% or about 250% after the third administration compared to the first administration.

[00168] In certain embodiments, provided herein are methods for treating a neoplastic disease comprising administering two or more arenavirus particles, wherein the two or more arenavirus particles are homologous, and wherein the time interval between each administration is about 1 week, about 2 weeks, about 3 week, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about 12 months, about 18 months, or about 24 months.

[00169] In certain embodiments, administering a first infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof and a second, heterologous, infectious, replication-deficient arenavirus particle

expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof elicits a greater CD8⁺ T cell response than administering a first infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof and a second, homologous, infectious, replication-deficient arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof.

(f) Compositions, Administration and Dosage

[00170] In certain embodiments, vaccines, immunogenic compositions (*e.g.*, vaccine formulations), and pharmaceutical compositions comprising an arenavirus particle provided herein, can be used with the methods and compositions provided herein, such as combinations with a chemotherapeutic agent provided herein. Such vaccines, immunogenic compositions and pharmaceutical compositions can be formulated according to standard procedures in the art.

[00171] In another embodiment, provided herein are compositions comprising an infectious, replication-deficient arenavirus particle described herein, and, in certain embodiments, a chemotherapeutic agent provided herein. Such compositions can be used in methods of treating a neoplastic disease. In another specific embodiment, the immunogenic compositions provided herein can be used to induce an immune response in a host to whom the composition is administered. The immunogenic compositions described herein can be used as vaccines and can accordingly be formulated as pharmaceutical compositions. In a specific embodiment, the immunogenic compositions described herein are used in the treatment of a neoplastic disease a subject (*e.g.*, human subject). In other embodiments, the vaccine, immunogenic composition or pharmaceutical composition are suitable for veterinary and/or human administration.

[00172] In certain embodiments, provided herein are immunogenic compositions comprising an arenavirus particle (or a combination of different arenavirus particles) as described herein. In certain embodiments, such an immunogenic composition further comprises a pharmaceutically acceptable excipient. In certain embodiments, such an immunogenic composition further comprises an adjuvant. The adjuvant for administration in combination with a composition described herein may be administered before, concomitantly with, or after administration of said composition. In some embodiments, the term “adjuvant” refers to a compound that when administered in conjunction with or as part of a composition described herein augments, enhances and/or boosts the immune response to an infectious, replication-

deficient arenavirus particle, but when the compound is administered alone does not generate an immune response to the infectious, replication-deficient arenavirus particle. In some embodiments, the adjuvant generates an immune response to the infectious, replication-deficient arenavirus particle and does not produce an allergy or other adverse reaction. Adjuvants can enhance an immune response by several mechanisms including, *e.g.*, lymphocyte recruitment, stimulation of B and/or T cells, and stimulation of macrophages. When a vaccine or immunogenic composition of the invention comprises adjuvants or is administered together with one or more adjuvants, the adjuvants that can be used include, but are not limited to, mineral salt adjuvants or mineral salt gel adjuvants, particulate adjuvants, microparticulate adjuvants, mucosal adjuvants, and immunostimulatory adjuvants. Examples of adjuvants include, but are not limited to, aluminum salts (alum) (such as aluminum hydroxide, aluminum phosphate, and aluminum sulfate), 3 De-O-acylated monophosphoryl lipid A (MPL) (see GB 2220211), MF59 (Novartis), AS03 (GlaxoSmithKline), AS04 (GlaxoSmithKline), polysorbate 80 (Tween 80; ICL Americas, Inc.), imidazopyridine compounds (see International Application No. PCT/US2007/064857, published as International Publication No. WO2007/109812), imidazoquinoxaline compounds (see International Application No. PCT/US2007/064858, published as International Publication No. WO2007/109813) and saponins, such as QS21 (see Kensil et al., in *Vaccine Design: The Subunit and Adjuvant Approach* (eds. Powell & Newman, Plenum Press, NY, 1995); U.S. Pat. No. 5,057,540). In some embodiments, the adjuvant is Freund's adjuvant (complete or incomplete). Other adjuvants are oil in water emulsions (such as squalene or peanut oil), optionally in combination with immune stimulants, such as monophosphoryl lipid A (see Stoute et al., *N. Engl. J. Med.* 336, 86-91 (1997)).

[00173] The compositions comprise the infectious, replication-deficient arenavirus particles described herein alone or together with a pharmaceutically acceptable carrier and/or a chemotherapeutic agent. Suspensions or dispersions of genetically engineered arenavirus particles, especially isotonic aqueous suspensions or dispersions, can be used. The pharmaceutical compositions may be sterilized and/or may comprise excipients, *e.g.*, preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers and are prepared in a manner known per se, for example by means of conventional dispersing and suspending processes. In certain embodiments, such dispersions or suspensions may comprise viscosity-regulating agents. The suspensions or

dispersions are kept at temperatures around 2-8°C, or preferentially for longer storage may be frozen and then thawed shortly before use. For injection, the vaccine or immunogenic preparations may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[00174] In certain embodiments, the compositions described herein additionally comprise a preservative, *e.g.*, the mercury derivative thimerosal. In a specific embodiment, the pharmaceutical compositions described herein comprise 0.001% to 0.01% thimerosal. In other embodiments, the pharmaceutical compositions described herein do not comprise a preservative.

[00175] The pharmaceutical compositions comprise from about 10^3 to about 10^{11} focus forming units of the genetically engineered arenavirus particles. Unit dose forms for parenteral administration are, for example, ampoules or vials, *e.g.*, vials containing from about 10^3 to 10^{10} focus forming units or 10^5 to 10^{15} physical particles of genetically engineered arenavirus particles.

[00176] In another embodiment, a vaccine or immunogenic composition provided herein is administered to a subject by, including but not limited to, oral, intradermal, intramuscular, intraperitoneal, intravenous, topical, subcutaneous, percutaneous, intranasal and inhalation routes, and via scarification (scratching through the top layers of skin, *e.g.*, using a bifurcated needle). Specifically, subcutaneous, intramuscular or intravenous routes can be used.

[00177] For administration intranasally or by inhalation, the preparation for use according to the present invention can be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflators may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[00178] The dosage of the active ingredient depends upon the type of vaccination and upon the subject, and their age, weight, individual condition, the individual pharmacokinetic data, and the mode of administration.

[00179] In certain embodiments, the compositions can be administered to the patient in a single dosage comprising a therapeutically effective amount of the arenavirus particle and/or a therapeutically effective amount of a chemotherapeutic agent. In some embodiments, the arenavirus particle can be administered to the patient in a single dose comprising an arenavirus particle and a chemotherapeutic agent, each in a therapeutically effective amount.

[00180] In certain embodiments, the composition is administered to the patient as a single dose followed by a second dose three to six weeks later. In accordance with these embodiments, the booster inoculations may be administered to the subjects at six to twelve month intervals following the second inoculation. In certain embodiments, the booster inoculations may utilize a different arenavirus particle or composition thereof. In some embodiments, the administration of the same composition as described herein may be repeated and separated by at least 1 day, 2 days, 3 days, 4 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or at least 6 months.

[00181] Also provided are processes and uses of an arenavirus particle and a chemotherapeutic agent for the manufacture of vaccines in the form of pharmaceutical preparations, which comprise the arenavirus particle and the chemotherapeutic agent as an active ingredient. Still further provided is a combination of an arenavirus particle provided herein and a chemotherapeutic agent provided herein for use in the treatment of a neoplastic disease described herein. In certain embodiments, the combination is in the same pharmaceutical composition. In certain embodiments, the combination is not in the same pharmaceutical composition, such as when the arenavirus particle and the chemotherapeutic agent are to be separately administered. The pharmaceutical compositions of the present application are prepared in a manner known per se, for example by means of conventional mixing and/or dispersing processes.

[00182] Also provided herein are kits that can be used to perform the methods described herein. In certain embodiments, the kit provided herein can include one or more containers. These containers can hold for storage the compositions (*e.g.*, pharmaceutical, immunogenic or vaccine composition) provided herein. Also included in the kit are instructions for use. These instructions describe, in sufficient detail, a treatment protocol for using the compositions contained therein. For example, the instructions can include dosing and administration instructions as provided herein for the methods of treating a neoplastic disease.

[00183] In certain embodiments, a kit provided herein includes containers that each contains the active ingredients for performing the methods described herein. Thus, in certain embodiments, the kit provided herein includes two or more containers and instructions for use, wherein one of the containers comprises an infectious, replication-deficient arenavirus particle provided herein and another container that comprises a chemotherapeutic agent provided herein.

[00184] In a specific embodiment, a kit provided herein includes two or more containers and instructions for use, wherein one of the containers comprises an infectious, replication-deficient arenavirus particle provided herein and another container that comprises a chemotherapeutic agent provided herein.

(g) Assays

[00185] **Assay for Measuring Arenavirus Vector Infectivity** Any assay known to the skilled artisan can be used for measuring the infectivity of an arenavirus vector preparation. For example, determination of the virus/vector titer can be done by a “focus forming unit assay” (FFU assay). In brief, complementing cells, *e.g.* HEK 293 cells expressing LCMV GP protein, are plated and inoculated with different dilutions of a virus/vector sample. After an incubation period, to allow cells to form a monolayer and virus to attach to cells, the monolayer is covered with Methylcellulose. When the plates are further incubated, the original infected cells release viral progeny. Due to the Methylcellulose overlay the spread of the new viruses is restricted to neighboring cells. Consequently, each infectious particle produces a circular zone of infected cells called a Focus. Such Foci can be made visible and by that countable using antibodies against LCMV- NP and a HRP-based color reaction. The titer of a virus / vector can be calculated in focus-forming units per milliliter (FFU/mL).

[00186] To determine the infectious titer (FFU/mL) of transgene-carrying vectors this assay is modified by the use of the respective transgene-specific antibody instead of anti-LCMV- NP antibody.

[00187] **Serum ELISA** Determination of the humoral immune response upon vaccination of animals (*e.g.* mice, guinea pigs) can be done by antigen-specific serum ELISAs (enzyme-linked immunosorbent assays). In brief, plates are coated with antigen (*e.g.* recombinant protein), blocked to avoid unspecific binding of antibodies and incubated with serial dilutions of sera. After incubation, bound serum-antibodies can be detected, *e.g.*, using an enzyme-coupled anti-species (*e.g.* mouse, guinea pig)-specific antibody (detecting total IgG or IgG subclasses)

and subsequent color reaction. Antibody titers can be determined as, *e.g.*, endpoint geometric mean titer.

[00188] Immunocapture ELISA (IC-ELISA) may also be performed (*see* Shanmugham et al., 2010, Clin. Vaccine Immunol. 17(8):1252-1260), wherein the capture agents are cross-linked to beads.

[00189] Immunocapture ELISA (IC-ELISA) may also be performed (*see* Shanmugham et al., 2010, Clin. Vaccine Immunol. 17(8):1252-1260), wherein the capture agents are cross-linked to beads.

[00190] Neutralizing Assay in ARPE-19 cells Determination of the neutralizing activity of induced antibodies in sera is performed with the following cell assay using ARPE-19 cells from ATCC and a GFP-tagged virus. In addition supplemental serum as a source of exogenous complement is used. The assay is started with seeding of 6.5×10^3 cells/well (50 μ l/well) in a 384 well plate one or two days before using for neutralization. The neutralization is done in 96-well sterile tissue culture plates without cells for 1h at 37°C. After the neutralization incubation step the mixture is added to the cells and incubated for additional 4 days for GFP-detection with a plate reader. A positive neutralizing human sera is used as assay positive control on each plate to check the reliability of all results. Titers (EC50) are determined using a 4 parameter logistic curve fitting. As additional testing the wells are checked with a fluorescence microscope.

[00191] Plaque Reduction Assay In brief, plaque reduction (neutralization) assays for LCMV can be performed by use of a replication-deficient LCMV that is tagged with green fluorescent protein, 5% rabbit serum may be used as a source of exogenous complement, and plaques can be enumerated by fluorescence microscopy. Neutralization titers may be defined as the highest dilution of serum that results in a 50%, 75%, 90% or 95% reduction in plaques, compared with that in control (pre-immune) serum samples.

[00192] Neutralization Assay in guinea pig lung fibroblast (GPL) cells In brief, serial dilutions of test and control (pre-vaccination) sera were prepared in GPL complete media with supplemental rabbit serum (1%) as a source of exogenous complement. The dilution series spanned 1:40 through 1:5120. Serum dilutions were incubated with eGFP tagged virus (100-200 pfu per well) for 30 min at 37°C, and then transferred to 12-well plates containing confluent GPL cells. Samples were processed in triplicate. After 2 hours incubation at 37°C the cells were washed with PBS, re-fed with GPL complete media and incubated at 37°C / 5% CO₂ for 5 days.

Plaques were visualized by fluorescence microscopy, counted, and compared to control wells. That serum dilution resulting in a 50% reduction in plaque number compared to controls was designated as the neutralizing titer.

[00193] qPCR LCMV RNA genomes are isolated using QIAamp Viral RNA mini Kit (QIAGEN), according to the protocol provided by the manufacturer. LCMV RNA genome equivalents are detected by quantitative PCR carried out on an StepOnePlus Real Time PCR System (Applied Biosystems) with SuperScript® III Platinum® One-Step qRT-PCR Kit (Invitrogen) and primers and probes (FAM reporter and NFQ-MGB Quencher) specific for part of the LCMV NP coding region. The temperature profile of the reaction is : 30 min at 60°C, 2 min at 95°C, followed by 45 cycles of 15 s at 95°C, 30 s at 56°C. RNA is quantified by comparison of the sample results to a standard curve prepared from a log10 dilution series of a spectrophotometrically quantified, in vitro-transcribed RNA fragment, corresponding to a fragment of the LCMV NP coding sequence containing the primer and probe binding sites.

[00194] Neutralization Assay in guinea pig lung fibroblast (GPL) cells In brief, serial dilutions of test and control (pre-vaccination) sera were prepared in GPL complete media with supplemental rabbit serum (1%) as a source of exogenous complement. The dilution series spanned 1:40 through 1:5120. Serum dilutions were incubated with eGFP tagged virus (100-200 pfu per well) for 30 min at 37°C, and then transferred to 12-well plates containing confluent GPL cells. Samples were processed in triplicate. After 2 hours incubation at 37°C the cells were washed with PBS, re-fed with GPL complete media and incubated at 37°C / 5% CO₂ for 5 days. Plaques were visualized by fluorescence microscopy, counted, and compared to control wells. That serum dilution resulting in a 50% reduction in plaque number compared to controls was designated as the neutralizing titer.

[00195] Western Blotting Infected cells grown in tissue culture flasks or in suspension are lysed at indicated timepoints post infection using RIPA buffer (Thermo Scientific) or used directly without cell-lysis. Samples are heated to 99°C for 10 minutes with reducing agent and NuPage LDS Sample buffer (NOVEX) and chilled to room temperature before loading on 4-12% SDS-gels for electrophoresis. Proteins are blotted onto membranes using Invitrogens iBlot Gel transfer Device and visualized by Ponceau staining. Finally, the preparations are probed with an primary antibodies directed against proteins of interest and alkaline phosphatase

conjugated secondary antibodies followed by staining with 1-Step NBT/BCIP solution (INVITROGEN).

[00196] MHC-Peptide Multimer Staining Assay for Detection of Antigen-Specific CD8+ T-cell proliferation Any assay known to the skilled artisan can be used to test antigen-specific CD8+ T-cell responses. For example, the MHC-peptide tetramer staining assay can be used (see, *e.g.*, Altman J.D. et al., *Science*. 1996; 274:94-96; and Murali-Krishna K. et al., *Immunity*. 1998; 8:177-187). Briefly, the assay comprises the following steps, a tetramer assay is used to detect the presence of antigen specific T-cells. In order for a T-cell to detect the peptide to which it is specific, it must both recognize the peptide and the tetramer of MHC molecules custom made for an antigen specific T-cell (typically fluorescently labeled). The tetramer is then detected by flow cytometry via the fluorescent label.

[00197] ELISPOT Assay for Detection of Antigen-Specific CD4+ T-cell Proliferation Any assay known to the skilled artisan can be used to test antigen-specific CD4+ T-cell responses. For example, the ELISPOT assay can be used (see, *e.g.*, Czerkinsky C.C. et al., *J Immunol Methods*. 1983; 65:109-121; and Hutchings P.R. Et al., *J Immunol Methods*. 1989; 120:1-8). Briefly, the assay comprises the following steps: An immunospot plate is coated with an anti-cytokine antibody. Cells are incubated in the immunospot plate. Cells secrete cytokines and are then washed off. Plates are then coated with a second biotinylated-anticytokine antibody and visualized with an avidin-HRP system.

[00198] Intracellular Cytokine Assay for Detection of Functionality of CD8+ and CD4+ T-cell Responses Any assay known to the skilled artisan can be used to test the functionality of CD8+ and CD4+ T cell responses. For example, the intracellular cytokine assay combined with flow cytometry can be used (see, *e.g.*, Suni M.A. et al., *J Immunol Methods*. 1998; 212:89-98; Nomura L.E. et al., *Cytometry*. 2000; 40:60-68; and Ghanekar S.A. et al., *Clinical and Diagnostic Laboratory Immunology*. 2001; 8:628-63). Briefly, the assay comprises the following steps: activation of cells via specific peptides or protein, an inhibition of protein transport (*e.g.*, brefeldin A) is added to retain the cytokines within the cell. After washing, antibodies to other cellular markers can be added to the cells. Cells are then fixed and permeabilized. The anti-cytokine antibody is added and the cells can be analyzed by flow cytometry.

[00199] Assay for Confirming Replication-Deficiency of Viral Vectors Any assay known to the skilled artisan that determines concentration of infectious and replication-competent virus particles can also be used as a to measure replication-deficient viral particles in a sample. For example, FFU assays with non-complementing cells can be used for this purpose.

[00200] Furthermore, plaque-based assays are the standard method used to determine virus concentration in terms of plaque forming units (PFU) in a virus sample. Specifically, a confluent monolayer of non-complementing host cells is infected with the virus at varying dilutions and covered with a semi-solid medium, such as agar to prevent the virus infection from spreading indiscriminately. A viral plaque is formed when a virus successfully infects and replicates itself in a cell within the fixed cell monolayer (see, *e.g.*, Kaufmann, S.H.; Kabelitz, D. (2002). *Methods in Microbiology Vol.32:Immunology of Infection*. Academic Press. ISBN 0-12-521532-0). Plaque formation can take 3 – 14 days, depending on the virus being analyzed. Plaques are generally counted manually and the results, in combination with the dilution factor used to prepare the plate, are used to calculate the number of plaque forming units per sample unit volume (PFU/mL). The PFU/mL result represents the number of infective replication-competent particles within the sample.

[00201] Assay for Expression of Viral Antigen Any assay known to the skilled artisan can be used for measuring expression of viral antigens. For example, FFU assays can be performed. For detection, mono- or polyclonal antibody preparation(s) against respective viral antigens are used (transgene-specific FFU).

[00202] Animal Models The safety, tolerance and immunogenic effectiveness of vaccines comprising of an infectious, replication-deficient arenavirus expressing a tumor antigen, tumor associate antigen or antigenic fragment thereof described herein or a composition thereof can be tested in animals models. In certain embodiments, the animal models that can be used to test the safety, tolerance and immunogenic effectiveness of the vaccines and compositions thereof used herein include mouse, guinea pig, rat, monkey, and chimpanzee. In a preferred embodiment, the animal models that can be used to test the safety, tolerance and immunogenic effectiveness of the vaccines and compositions thereof used herein include mouse.

[00203] Chemotherapeutic Agent Assays

[00204] A number of assays have been devised that are capable of assessing properties of proposed chemotherapeutic agents. Tumor models that can be used to test the methods and

compositions disclosed herein include Colon26 (CT26), MC38 (mouse colon adenocarcinoma), B16F10 (B16), Lewis Lung (LLC), Madison109 (Mad 109), EMT-6 (murine breast cancer), 4T1 (4T1) (murine breast cancer), Hgcmel3 (murine melanoma), HgfcxCDK4^{R24C/R24C} (murine melanoma), and (RENCA) (murine renal cancer).

[00205] In certain embodiments, in these model systems, “transplantable tumors” can be generated by subcutaneous (*e.g.*, CT26, 4T1, MAD109, RENCA, LLC, or B16) or intracerebral (*e.g.*, GL261, ONC26M4) inoculation of tumor cell lines into rodents, for example in adult female mice. Tumors can be developed over pre-determined time intervals, for example several days. These tumors are grown in syngeneic, immunocompetent rodent, *e.g.*, mouse, strains. For example CT26, 4T1, MAD109, and RENCA can be grown in BALB/c mice, LLC, B16, and GL261 can be grown in C57BL/6 mice, and ONC26M4 can be grown in FVBN mice.

“Spontaneous tumors” can be generated by intracerebral injection of DNA plasmids encoding a number (*e.g.*, one, two, three or more) of oncogenes and encoding one or more reporter, *e.g.*, firefly luciferase reporter, into neonatal C57BL/6 or FVBN mice to transform endogenous brain cells. Growth of gliomas can be monitored by techniques known in the art, *e.g.*, bioluminescence imaging. Growth of subcutaneous tumors can be monitored by techniques known in the art, *e.g.*, caliper measurements in three dimensions at specified time intervals.

5.2 Tri-Segmented Arenavirus Particles

[00206] In certain embodiments, tri-segmented arenavirus particles comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof in combination with a chemotherapeutic agent, can be used as immunotherapies for treating a neoplastic disease, such as cancer. The term “neoplastic” or “neoplasm” refers to an abnormal new growth of cells or tissue. This abnormal new growth can form a mass, also known as a tumor or neoplasia. A neoplasm includes a benign neoplasm, an in situ neoplasm, a malignant neoplasm, and a neoplasm of uncertain or unknown behavior. In certain embodiments, the neoplastic disease treated using the methods and compositions described herein is cancer.

[00207] Provided herein are combination treatments for the treatment and/or prevention of a neoplastic disease, such as cancer. Specifically, such combination treatments comprise administering arenavirus particles or viral vectors that comprise a nucleotide sequence encoding one or more tumor antigens, tumor associated antigens or antigenic fragments thereof, in

combination with one or more chemotherapeutic agents. These genetically modified viruses can be administered to a subject for the treatment of a neoplastic disease, such as cancer. Detailed descriptions of the arenaviruses provided herein, including the nucleotide sequences encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof can be found in Sections 5.2.(a), 5.2.(b), and 5.2.(c). Arenaviruses comprising an open reading frame at a non-natural position are described in Section 5.2.(a). Tri-segmented arenaviruses are described in Section 5.2.(b). Tumor antigens that can be used with the present methods and compositions can be found in Section 5.2.(c). Additionally, methods for generation of arenavirus particles or viral vectors for use in the methods and compositions described herein are described in more detail in Section 5.2. (d).

[00208] In addition to administering arenavirus particles or viral vectors to a subject, the immunotherapies for treating a neoplastic disease provided herein can include a chemotherapeutic agent. “Chemotherapeutic agents” are cytotoxic anti-cancer agents, and can be categorized by their mode of activity within a cell, for example, at what stage they affect the cell cycle (*e.g.*, a mitosis inhibitor). Alternatively, chemotherapeutic agents can be characterized based on ability to cross-link DNA, to intercalate into DNA, or to induce chromosomal aberrations by affecting nucleic acid synthesis (*e.g.*, alkylating agents), among other mechanisms of action. Chemotherapeutic agents can also be characterized based on chemical components or structure (*e.g.*, platinum-based therapeutics). Thus, in certain embodiments, provided herein are methods and compositions for treating a neoplastic disease using an arenavirus particle or viral vector comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof and a chemotherapeutic agent. Thus, in certain embodiments, provided herein are methods for treating a neoplastic disease using an arenavirus particle or viral vector comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof, and a chemotherapeutic agent. Also, in certain embodiments, provided herein are compositions comprising an arenavirus particle or viral vector comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof, and a chemotherapeutic agent. In certain embodiments, the arenavirus particle or viral vector provided herein is engineered to contain an arenavirus genomic segment having a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof and at least one arenavirus open reading frame (“ORF”) in a position other than the wild-

type position of the ORF. In certain embodiments, the arenavirus particle or viral vector provided herein is an infectious, replication deficient arenavirus particle or viral vector. In other embodiments, the arenavirus particle provided herein is a tri-segmented arenavirus particle or viral vector, which can be replication-deficient or replication-competent. In still other embodiments, the tri-segmented arenavirus particle or viral vector provided herein, when propagated, does not result in a replication-competent bi-segmented viral particle. Methods and compositions for using an arenavirus particle or viral vector and a chemotherapeutic agent provided herein are described in more detail in Sections 5.2.(f) and 5.2.(g).

[00209] In addition to administering arenavirus particles or viral vectors to a subject in combination with a chemotherapeutic agent, the immunotherapies for treating a neoplastic disease provided herein can also include an immune checkpoint modulator. The term “immune checkpoint modulator” (also referred to as “checkpoint modulator” or as “checkpoint regulator”) refers to a molecule or to a compound that modulates (*e.g.*, totally or partially reduces, inhibits, interferes with, activates, stimulates, increases, reinforces or supports) the function of one or more checkpoint molecules. Thus, an immune checkpoint modulator may be an immune checkpoint inhibitor or an immune checkpoint activator.

[00210] An “immune checkpoint inhibitor” refers to a molecule that inhibits, decreases or interferes with the activity of a negative checkpoint regulator. In certain embodiments, immune checkpoint inhibitors for use with the methods and compositions disclosed herein can inhibit the activity of a negative checkpoint regulator directly, or decrease the expression of a negative checkpoint regulator, or interfere with the interaction of a negative checkpoint regulator and a binding partner (*e.g.*, a ligand). Immune checkpoint inhibitors for use with the methods and compositions disclosed herein include a protein, a polypeptide, a peptide, an antisense oligonucleotide, an antibody, an antibody fragment, or an inhibitory RNA molecule that targets the expression of a negative checkpoint regulator.

[00211] A “negative checkpoint regulator” refers to a molecule that down-regulates immune responses (*e.g.*, T-cell activation) by delivery of a negative signal to T-cells following their engagement by ligands or counter-receptors. Exemplary functions of a negative-checkpoint regulator are to prevent out-of-proportion immune activation, minimize collateral damage, and/or maintain peripheral self-tolerance. In certain embodiments, a negative checkpoint regulator is a ligand or receptor expressed by an antigen presenting cell. In certain embodiments, a negative

checkpoint regulator is a ligand or receptor expressed by a T-cell. In certain embodiments, a negative checkpoint regulator is a ligand or receptor expressed by both an antigen presenting cell and a T-cell.

(a) Arenaviruses with an Open Reading Frame in a Non-natural Position

[00212] In certain embodiments, arenaviruses with rearrangements of their ORFs and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein can be used with the methods and compositions provided herein, such as combinations with a chemotherapeutic agent. In certain embodiments, such arenaviruses are replication-competent and infectious. Thus, in certain embodiments, provided herein is an arenavirus genomic segment, wherein the arenavirus genomic segment is engineered to carry an arenavirus ORF in a position other than the position in which the respective gene is found in viruses isolated from the wild, such as LCMV-MP (referred to herein as “wild-type position”) of the ORF (*i.e.*, a non-natural position) and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein.

[00213] The wild-type arenavirus genomic segments and ORFs are known in the art. In particular, the arenavirus genome consists of an S segment and an L segment. The S segment carries the ORFs encoding the GP and the NP. The L segment encodes the L protein and the Z protein. Both segments are flanked by the respective 5' and 3' UTRs.

[00214] In certain embodiments, an arenavirus genomic segment can be engineered to carry two or more arenavirus ORFs in a position other than the wild-type position. In other embodiments, the arenavirus genomic segment can be engineered to carry two arenavirus ORFs, or three arenavirus ORFs, or four arenavirus ORFs in a position other than the wild-type position.

[00215] In certain embodiments, an arenavirus genomic segment provided herein can be:

- (xix) an arenavirus S segment, wherein the ORF encoding the NP is under control of an arenavirus 5' UTR;
- (xx) an arenavirus S segment, wherein the ORF encoding the Z protein is under control of an arenavirus 5' UTR;
- (xxi) an arenavirus S segment, wherein the ORF encoding the L protein is under control of an arenavirus 5' UTR;

- (xxii) an arenavirus S segment, wherein the ORF encoding the GP is under control of an arenavirus 3' UTR;
- (xxiii) an arenavirus S segment, wherein the ORF encoding the L protein is under control of an arenavirus 3' UTR;
- (xxiv) an arenavirus S segment, wherein the ORF encoding the Z protein is under control of an arenavirus 3' UTR;
- (xxv) an arenavirus L segment, wherein the ORF encoding the GP is under control of an arenavirus 5' UTR;
- (xxvi) an arenavirus L segment, wherein the ORF encoding the NP is under control of an arenavirus 5' UTR;
- (xxvii) an arenavirus L segment, wherein the ORF encoding the L protein is under control of an arenavirus 5' UTR;
- (xxviii) an arenavirus L segment, wherein the ORF encoding the GP is under control of an arenavirus 3' UTR;
- (xxix) an arenavirus L segment, wherein the ORF encoding the NP is under control of an arenavirus 3' UTR; and
- (xxx) an arenavirus L segment, wherein the ORF encoding the Z protein is under control of an arenavirus 3' UTR.

[00216] In certain embodiments, the ORF that is in the non-natural position of the arenavirus genomic segment described herein can be under the control of an arenavirus 3' UTR or an arenavirus 5' UTR. In more specific embodiments, the arenavirus 3' UTR is the 3' UTR of the arenavirus S segment. In another specific embodiment, the arenavirus 3' UTR is the 3' UTR of the arenavirus L segment. In more specific embodiments, the arenavirus 5' UTR is the 5' UTR of the arenavirus S segment. In other specific embodiments, the 5' UTR is the 5' UTR of the L segment.

[00217] In other embodiments, the ORF that is in the non-natural position of the arenavirus genomic segment described herein can be under the control of the arenavirus conserved terminal sequence element (the 5'- and 3'-terminal 19-20-nt regions) (see *e.g.*, Perez & de la Torre, 2003, J Virol. 77(2): 1184–1194).

[00218] In certain embodiments, the ORF that is in the non-natural position of the arenavirus genomic segment can be under the control of the promoter element of the 5' UTR (see

e.g., Albarino *et al.*, 2011, J Virol., 85(8):4020-4). In another embodiment, the ORF that is in the non-natural position of the arenavirus genomic segment can be under the control of the promoter element of the 3' UTR (see *e.g.*, Albarino *et al.*, 2011, J Virol., 85(8):4020-4). In more specific embodiments, the promoter element of the 5' UTR is the 5' UTR promoter element of the S segment or the L segment. In another specific embodiment, the promoter element of the 3' UTR is the 3' UTR the promoter element of the S segment or the L segment.

[00219] In certain embodiments, the ORF that is in the non-natural position of the arenavirus genomic segment can be under the control of a truncated arenavirus 3' UTR or a truncated arenavirus 5' UTR (see *e.g.*, Perez & de la Torre, 2003, J Virol. 77(2): 1184–1194; Albarino *et al.*, 2011, J Virol., 85(8):4020-4). In more specific embodiments, the truncated 3' UTR is the 3' UTR of the arenavirus S segment or L segment. In more specific embodiments, the truncated 5' UTR is the 5' UTR of the arenavirus S segment or L segment.

[00220] Also provided herein, is an arenavirus particle comprising a first genomic segment that has been engineered to carry an ORF in a position other than the wild-type position of the ORF and a second arenavirus genomic segment so that the arenavirus particle comprises an S segment and an L segment. In specific embodiments, the ORF in a position other than the wild-type position of the ORF is one of the arenavirus ORFs.

[00221] In certain specific embodiments, the arenavirus particle can comprise a full complement of all four arenavirus ORFs. In specific embodiments, the second arenavirus genomic segment has been engineered to carry an ORF in a position other than the wild-type position of the ORF. In another specific embodiment, the second arenavirus genomic segment can be the wild-type genomic segment (*i.e.*, comprises the ORFs on the segment in the wild-type position).

[00222] In certain embodiments, the first arenavirus genomic segment is an L segment and the second arenavirus genomic segment is an S segment. In other embodiments, the first arenavirus genomic segment is an S segment and the second arenavirus genomic segment is an L segment.

[00223] Non-limiting examples of the arenavirus particle comprising a genomic segment with an ORF in a position other than the wild-type position of the ORF and a second genomic segment are illustrated in Table 1.

Table 1

Arenavirus particle

*Position 1 is under the control of an arenavirus S segment 5' UTR; Position 2 is under the control of an arenavirus S segment 3' UTR; Position 3 is under the control of an arenavirus L segment 5' UTR; Position 4 is under the control of an arenavirus L segment 3' UTR.

Position 1	Position 2	Position 3	Position 4
GP	NP	L	Z
GP	Z	L	NP
GP	Z	NP	L
GP	L	NP	Z
GP	L	Z	NP
NP	GP	L	Z
NP	GP	Z	L
NP	L	GP	Z
NP	L	Z	GP
NP	Z	GP	L
NP	Z	L	GP
Z	GP	L	NP
Z	GP	NP	L
Z	NP	GP	L
Z	NP	L	GP
Z	L	NP	GP
Z	L	GP	NP
L	NP	GP	Z
L	NP	Z	GP
L	GP	Z	NP
L	GP	NP	Z
L	Z	NP	GP
L	Z	GP	NP

[00224] Also provided herein, is a cDNA of the arenavirus genomic segment engineered to carry an ORF in a position other than the wild-type position of the ORF and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In more specific embodiments, provided herein is a cDNA or a set of cDNAs of an arenavirus genome as set forth in Table 1.

[00225] In certain embodiments, a cDNA of the arenavirus genomic segment that is engineered to carry an ORF in a position other than the wild-type position of the ORF is part of or incorporated into a DNA expression vector. In a specific embodiment, a cDNA of the

arenavirus genomic segment that is engineered to carry an ORF in a position other than the wild-type position of the ORF is part of or incorporated into a DNA expression vector that facilitates production of an arenavirus genomic segment as described herein. In another embodiment, a cDNA described herein can be incorporated into a plasmid. More detailed description of the cDNAs or nucleic acids and expression systems are provided in Section 5.2.(e). Techniques for the production of a cDNA are routine and conventional techniques of molecular biology and DNA manipulation and production. Any cloning technique known to the skilled artisan can be used. Such as techniques are well known and are available to the skilled artisan in laboratory manuals such as, Sambrook and Russell, *Molecular Cloning: A laboratory Manual*, 3rd edition, Cold Spring Harbor Laboratory N.Y. (2001).

[00226] In certain embodiments, the cDNA of the arenavirus genomic segment that is engineered to carry an ORF in a position other than the wild-type position of the ORF and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein is introduced (*e.g.*, transfected) into a host cell. Thus, in some embodiments provided herein, is a host cell comprising a cDNA of the arenavirus genomic segment that is engineered to carry an ORF in a position other than the wild-type position of the ORF (*i.e.*, a cDNA of the genomic segment) and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In other embodiments, the cDNA described herein is part of or can be incorporated into a DNA expression vector and introduced into a host cell. Thus, in some embodiments provided herein is a host cell comprising a cDNA described herein that is incorporated into a vector. In other embodiments, the arenavirus genomic segment described herein is introduced into a host cell.

[00227] In certain embodiments, described herein is a method of producing the arenavirus genomic segment comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, wherein the method comprises transcribing the cDNA of the arenavirus genomic segment. In certain embodiments, a viral polymerase protein can be present during transcription of the arenavirus genomic segment *in vitro* or *in vivo*.

[00228] In certain embodiments transcription of the arenavirus genomic segment is performed using a bi-directional promoter. In other embodiments, transcription of the arenavirus genomic segment is performed using a bi-directional expression cassette (see *e.g.*, Ortiz-Riaño *et*

al., 2013, J Gen Virol., 94(Pt 6): 1175–1188). In more specific embodiments the bi-directional expression cassette comprises both a polymerase I and a polymerase II promoter reading from opposite sides into the two termini of the inserted arenavirus genomic segment, respectively. In yet more specific embodiments the bi-directional expression cassette with pol-I and pol-II promoters read from opposite sides into the L segment and S segment

[00229] In other embodiments, transcription of the cDNA of the arenavirus genomic segment described herein comprises a promoter. Specific examples of promoters include an RNA polymerase I promoter, an RNA polymerase II promoter, an RNA polymerase III promoter, a T7 promoter, an SP6 promoter or a T3 promoter.

[00230] In certain embodiments, the method of producing the arenavirus genomic segment can further comprise introducing into a host cell the cDNA of the arenavirus genomic segment comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In certain embodiments, the method of producing the arenavirus genomic segment can further comprise introducing into a host cell the cDNA of the arenavirus genomic segment comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, wherein the host cell expresses all other components for production of the arenavirus genomic segment; and purifying the arenavirus genomic segment from the supernatant of the host cell. Such methods are well-known to those skilled in the art.

[00231] Provided herein are cell lines, cultures and methods of culturing cells infected with nucleic acids, vectors, and compositions provided herein. More detailed description of nucleic acids, vector systems and cell lines described herein is provided in Section 5.2.(e).

[00232] In certain embodiments, the arenavirus particle as described herein results in an infectious and replication competent arenavirus particle. In specific embodiments, the arenavirus particle described herein is attenuated. In a particular embodiment, the arenavirus particle is attenuated such that the virus remains, at least partially, able to spread and can replicate *in vivo*, but can only generate low viral loads resulting in subclinical levels of infection that are non-pathogenic. Such attenuated viruses can be used as an immunogenic composition. Provided herein, are immunogenic compositions that comprise an arenavirus with an ORF in a non-natural position as described in Section (g).

(i) Replication-Defective Arenavirus Particle with an Open Reading Frame in a Non-natural Position

[00233] In certain embodiments, provided herein is an arenavirus particle in which (i) an ORF is in a position other than the wild-type position of the ORF; and (ii) an ORF encoding GP, NP, Z protein, and L protein has been removed or functionally inactivated such that the resulting virus cannot produce further infectious progeny virus particles. An arenavirus particle comprising a genetically modified genome in which one or more ORFs has been deleted or functionally inactivated can be produced in complementing cells (*i.e.*, cells that express the arenavirus ORF that has been deleted or functionally inactivated). The genetic material of the resulting arenavirus particle can be transferred upon infection of a host cell into the host cell, wherein the genetic material can be expressed and amplified. In addition, the genome of the genetically modified arenavirus particle described herein can encode a heterologous ORF from an organism other than an arenavirus particle.

[00234] In certain embodiments, an ORF of the arenavirus is deleted or functionally inactivated and replaced with a nucleotide sequence encoding a tumor antigen or tumor associated antigen as described herein. In a specific embodiment, the ORF that encodes the glycoprotein GP of the arenavirus is deleted or functionally inactivated. In certain embodiments, functional inactivation of a gene eliminates any translation product. In certain embodiments, functional inactivation refers to a genetic alteration that allows some translation, the translation product, however, is not longer functional and cannot replace the wild type protein.

[00235] In certain embodiments, at least one of the four ORFs encoding GP, NP, Z protein, and L protein is removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In another embodiment, at least one ORF, at least two ORFs, at least three ORFs, or at least four ORFs encoding GP, NP, Z protein and L protein can be removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In specific embodiments, only one of the four ORFs encoding GP, NP, Z protein, and L protein is removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In more specific embodiments, the ORF that encodes GP of the arenavirus genomic segment is removed. In another specific embodiment, the ORF that encodes the NP of the arenavirus genomic

segment is removed. In more specific embodiments, the ORF that encodes the Z protein of the arenavirus genomic segment is removed. In yet another specific embodiment, the ORF encoding the L protein is removed.

[00236] Thus, in certain embodiments, the arenavirus particle provided herein comprises a genomic segment that (i) is engineered to carry an ORF in a non-natural position; (ii) an ORF encoding GP, NP, Z protein, or L protein is removed; (iii) the ORF that is removed is replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein.

[00237] In certain embodiments, the fragment of the tumor antigen or tumor associated antigen is antigenic when it is capable of (i) eliciting an antibody immune response in a host (*e.g.*, mouse, rabbit, goat, donkey or human) wherein the resulting antibodies bind specifically to an immunogenic protein expressed in or on a neoplastic cell (*e.g.*, a cancer cell); and/or (ii) eliciting a specific T cell immune response.

[00238] In certain embodiments, the nucleotide sequence encoding an antigenic fragment provided herein is 8 to 100 nucleotides in length, 15 to 100 nucleotides in length, 25 to 100 nucleotides in length, 50 to 200 nucleotide in length, 50 to 400 nucleotide in length, 200 to 500 nucleotide in length, or 400 to 600 nucleotides in length, 500 to 800 nucleotide in length. In other embodiments, the nucleotide sequence encoding an antigenic fragment provided herein is 750 to 900 nucleotides in length, 800 to 100 nucleotides in length, 850 to 1000 nucleotides in length, 900 to 1200 nucleotides in length, 1000 to 1200 nucleotides in length, 1000 to 1500 nucleotides or 10 to 1500 nucleotides in length, 1500 to 2000 nucleotides in length, 1700 to 2000 nucleotides in length, 2000 to 2300 nucleotides in length, 2200 to 2500 nucleotides in length, 2500 to 3000 nucleotides in length, 3000 to 3200 nucleotides in length, 3000 to 3500 nucleotides in length, 3200 to 3600 nucleotides in length, 3300 to 3800 nucleotides in length, 4000 nucleotides to 4400 nucleotides in length, 4200 to 4700 nucleotides in length, 4800 to 5000 nucleotides in length, 5000 to 5200 nucleotides in length, 5200 to 5500 nucleotides in length, 5500 to 5800 nucleotides in length, 5800 to 6000 nucleotides in length, 6000 to 6400 nucleotides in length, 6200 to 6800 nucleotides in length, 6600 to 7000 nucleotides in length, 7000 to 7200 nucleotides in lengths, 7200 to 7500 nucleotides in length, or 7500 nucleotides in length. In some embodiments, the nucleotide sequence encodes a peptide or polypeptide that is 5 to 10 amino acids in length, 10 to 25 amino acids in length, 25 to 50 amino acids in length, 50 to 100

amino acids in length, 100 to 150 amino acids in length, 150 to 200 amino acids in length, 200 to 250 amino acids in length, 250 to 300 amino acids in length, 300 to 400 amino acids in length, 400 to 500 amino acids in length, 500 to 750 amino acids in length, 750 to 1000 amino acids in length, 1000 to 1250 amino acids in length, 1250 to 1500 amino acids in length, 1500 to 1750 amino acids in length, 1750 to 2000 amino acids in length, 2000 to 2500 amino acids in length, or more than 2500 or more amino acids in length. In some embodiments, the nucleotide sequence encodes a polypeptide that does not exceed 2500 amino acids in length. In specific embodiments the nucleotide sequence does not contain a stop codon. In certain embodiments, the nucleotide sequence is codon-optimized. In certain embodiments the nucleotide composition, nucleotide pair composition or both can be optimized. Techniques for such optimizations are known in the art and can be applied to optimize a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein.

[00239] In certain embodiments, the growth and infectivity of the arenavirus particle is not affected by the nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein.

[00240] Techniques known to one skilled in the art may be used to produce an arenavirus particle comprising an arenavirus genomic segment engineered to carry an arenavirus ORF in a position other than the wild-type position and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. For example, reverse genetics techniques may be used to generate such arenavirus particle. In other embodiments, the replication-defective arenavirus particle (*i.e.*, the arenavirus genomic segment engineered to carry an arenavirus ORF in a position other than the wild-type position, wherein an ORF encoding GP, NP, Z protein, L protein, has been deleted) can be produced in a complementing cell.

[00241] In certain embodiments, an arenavirus particle or arenavirus genomic segment provided herein comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof as provided herein further comprises at least one nucleotide sequence encoding at least one immunomodulatory peptide, polypeptide or protein. In certain embodiments, the immunomodulatory peptide, polypeptide or protein is Calreticulin (CRT), or a fragment thereof; Ubiquitin or a fragment thereof; Granulocyte-Macrophage Colony-Stimulating

Factor (GM-CSF), or a fragment thereof; Invariant chain (CD74) or an antigenic fragment thereof; Mycobacterium tuberculosis Heat shock protein 70 or an antigenic fragment thereof; Herpes simplex virus 1 protein VP22 or an antigenic fragment thereof; CD40 ligand or an antigenic fragment thereof; or Fms-related tyrosine kinase 3 (Flt3) ligand or an antigenic fragment thereof.

[00242] In certain embodiments, the arenavirus genomic segment or the arenavirus particle used according to the present application can be Old World viruses, for example Lassa virus, Lymphocytic choriomeningitis virus (LCMV), Mobala virus, Mopeia virus, or Ippy virus, or New World viruses, for example Amapari virus, Flexal virus, Guanarito virus, Junin virus, Latino virus, Machupo virus, Oliveros virus, Parana virus, Pichinde virus, Pirital virus, Sabia virus, Tacaribe virus, Tamiami virus, Bear Canyon virus, or Whitewater Arroyo virus.

[00243] In certain embodiments, the arenavirus particle as described herein is suitable for use as a vaccine and methods of using such arenavirus particle in a vaccination and treatment for a neoplastic disease, for example, cancer, is provided. More detailed description of the methods of using the arenavirus particle described herein is provided in Section 5.2.(f)

[00244] In certain embodiments, the arenavirus particle as described herein is suitable for use as a pharmaceutical composition and methods of using such arenavirus particle in a vaccination and treatment for a neoplastic disease, for example, cancer, is provided. More detailed description of the methods of using the arenavirus particle described herein is provided in Section 5.2.(g).

(b) Tri-segmented Arenavirus Particle

[00245] In certain embodiments, tri-segmented arenavirus particles with rearrangements of their ORFs and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein can be used with the methods and compositions provided herein, such as combinations with a chemotherapeutic agent. In one aspect, provided herein is a tri-segmented arenavirus particle comprising one L segment and two S segments or two L segments and one S segment. In certain embodiments, the tri-segmented arenavirus particle does not recombine into a replication competent bi-segmented arenavirus particle. More specifically, in certain embodiments, two of the genomic segments (*e.g.*, the two S segments or the two L segments, respectively) cannot recombine in a way to yield a single viral segment that could replace the two parent segments. In specific embodiments, the tri-segmented arenavirus

particle comprises an ORF in a position other than the wild-type position of the ORF and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In yet another specific embodiment, the tri-segmented arenavirus particle comprises all four arenavirus ORFs. Thus, in certain embodiments, the tri-segmented arenavirus particle is replication competent and infectious. In other embodiments, the tri-segmented arenavirus particle lacks one of the four arenavirus ORFs. Thus, in certain embodiments, the tri-segmented arenavirus particle is infectious but unable to produce further infectious progeny in non-complementing cells.

[00246] In certain embodiments, the ORF encoding GP, NP, Z protein, or the L protein of the tri-segmented arenavirus particle described herein can be under the control of an arenavirus 3' UTR or an arenavirus 5' UTR. In more specific embodiments, the tri-segmented arenavirus 3' UTR is the 3' UTR of an arenavirus S segment(s). In another specific embodiment, the tri-segmented arenavirus 3' UTR is the 3' UTR of a tri-segmented arenavirus L segment(s). In more specific embodiments, the tri-segmented arenavirus 5' UTR is the 5' UTR of an arenavirus S segment(s). In other specific embodiments, the 5' UTR is the 5' UTR of the L segment(s).

[00247] In other embodiments, the ORF encoding GP, NP, Z protein, or the L protein of tri-segmented arenavirus particle described herein can be under the control of the arenavirus conserved terminal sequence element (the 5'- and 3'-terminal 19-20-nt regions) (see *e.g.*, Perez & de la Torre, 2003, J Virol. 77(2): 1184–1194).

[00248] In certain embodiments, the ORF encoding GP, NP, Z protein or the L protein of the tri-segmented arenavirus particle can be under the control of the promoter element of the 5' UTR (see *e.g.*, Albarino *et al.*, 2011, J Virol., 85(8):4020-4). In another embodiment, the ORF encoding GP, NP Z protein, L protein of the tri-segmented arenavirus particle can be under the control of the promoter element of the 3' UTR (see *e.g.*, Albarino *et al.*, 2011, J Virol., 85(8):4020-4). In more specific embodiments, the promoter element of the 5' UTR is the 5' UTR promoter element of the S segment(s) or the L segment(s). In another specific embodiment, the promoter element of the 3' UTR is the 3' UTR the promoter element of the S segment(s) or the L segment(s).

[00249] In certain embodiments, the ORF that encoding GP, NP, Z protein or the L protein of the tri-segmented arenavirus particle can be under the control of a truncated arenavirus 3' UTR or a truncated arenavirus 5' UTR (see *e.g.*, Perez & de la Torre, 2003, J Virol. 77(2):

1184–1194; Albarino *et al.*, 2011, J Virol., 85(8):4020-4). In more specific embodiments, the truncated 3' UTR is the 3' UTR of the arenavirus S segment or L segment. In more specific embodiments, the truncated 5' UTR is the 5' UTR of the arenavirus S segment(s) or L segment(s).

[00250] Also provided herein, is a cDNA of the tri-segmented arenavirus particle comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In more specific embodiments, provided herein is a DNA nucleotide sequence or a set of DNA nucleotide sequences encoding a tri-segmented arenavirus particle as set forth in Table 2 or Table 3.

[00251] In certain embodiments, the nucleic acids encoding the tri-segmented arenavirus genome are part of or incorporated into one or more DNA expression vectors. In a specific embodiment, nucleic acids encoding the genome of the tri-segmented arenavirus particle are part of or incorporated into one or more DNA expression vectors that facilitate production of a tri-segmented arenavirus particle as described herein. In another embodiment, a cDNA described herein can be incorporated into a plasmid. More detailed description of the cDNAs and expression systems are provided in Section 5.2.(e). Techniques for the production of a cDNA routine and conventional techniques of molecular biology and DNA manipulation and production. Any cloning technique known to the skilled artisan can be used. Such techniques are well known and are available to the skilled artisan in laboratory manuals such as, Sambrook and Russell, *Molecular Cloning: A laboratory Manual*, 3rd edition, Cold Spring Harbor Laboratory N.Y. (2001).

[00252] In certain embodiments, the cDNA of the tri-segmented arenavirus comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein is introduced (*e.g.*, transfected) into a host cell. Thus, in some embodiments provided herein, is a host cell comprising a cDNA of the tri-segmented arenavirus particle (*i.e.*, a cDNA of the genomic segments of the tri-segmented arenavirus particle) and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In other embodiments, the cDNA described herein that is part of or can be incorporated into a DNA expression vector and introduced into a host cell. Thus, in some embodiments provided herein is a host cell comprising a cDNA described herein that is incorporated into a vector. In other embodiments, the tri-segmented arenavirus genomic

segments (*i.e.*, the L segment and/or S segment or segments) described herein is introduced into a host cell.

[00253] In certain embodiments, described herein is a method of producing the tri-segmented arenavirus particle, wherein the method comprises transcribing the cDNA of the tri-segmented arenavirus particle comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In certain embodiments, a viral polymerase protein can be present during transcription of the tri-segmented arenavirus particle *in vitro* or *in vivo*. In certain embodiments, transcription of the arenavirus genomic segment is performed using a bi-directional promoter.

[00254] In other embodiments, transcription of the arenavirus genomic segment is performed using a bi-directional expression cassette (see *e.g.*, Ortiz-Riaño *et al.*, 2013, J Gen Virol., 94(Pt 6): 1175–1188). In more specific embodiments the bi-directional expression cassette comprises both a polymerase I and a polymerase II promoter reading from opposite sides into the two termini of the inserted arenavirus genomic segment, respectively.

[00255] In other embodiments, transcription of the cDNA of the arenavirus genomic segment described herein comprises a promoter. Specific examples of promoters include an RNA polymerase I promoter, an RNA polymerase II promoter, an RNA polymerase III promoter, a T7 promoter, an SP6 promoter or a T3 promoter.

[00256] In certain embodiments, the method of producing the tri-segmented arenavirus particle can further comprise introducing into a host cell the cDNA of the tri-segmented arenavirus particle comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In certain embodiments, the method of producing the tri-segmented arenavirus particle can further comprise introducing into a host cell the cDNA of the tri-segmented arenavirus particle that comprises a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, wherein the host cell expresses all other components for production of the tri-segmented arenavirus particle; and purifying the tri-segmented arenavirus particle from the supernatant of the host cell. Such methods are well-known to those skilled in the art.

[00257] Provided herein are cell lines, cultures and methods of culturing cells infected with nucleic acids, vectors, and compositions provided herein. More detailed description of nucleic acids, vector systems and cell lines described herein is provided in Section 5.2.(e).

[00258] In certain embodiments, the tri-segmented arenavirus particle as described herein results in a infectious and replication competent arenavirus particle. In specific embodiments, the arenavirus particle described herein is attenuated. In a particular embodiment, the tri-segmented arenavirus particle is attenuated such that the virus remains, at least partially, replication-competent and can replicate *in vivo*, but can only generate low viral loads resulting in subclinical levels of infection that are non-pathogenic. Such attenuated viruses can be used as an immunogenic composition.

[00259] In certain embodiments, the tri-segmented arenavirus particle has the same tropism as the bi-segmented arenavirus particle.

[00260] Also provided herein, are compositions that comprise the tri-segmented arenavirus particle as described in Section 5.2.(g).

- (i) Tri-segmented Arenavirus Particle comprising one L segment and two S segments

[00261] Provided herein is a tri-segmented arenavirus particle that is replication competent. In certain specific embodiments, provided herein is a tri-segmented arenavirus particle that is replication defective. Tri-segmented arenavirus particles provided herein may be generated as described in International Publication No.: WO 2016/075250 A1 and International Patent Application No. PCT/EP2017/061865, which are herein incorporated in their entireties.

[00262] In one aspect, provided herein is a tri-segmented arenavirus particle comprising one L segment and two S segments. In certain embodiments, propagation of the tri-segmented arenavirus particle comprising one L segment and two S segments does not result in a replication-competent bi-segmented viral particle. In specific embodiments, propagation of the tri-segmented arenavirus particle comprising one L segment and two S segments does not result in a replication-competent bi-segmented viral particle after at least 10 days, at least 20 days, at least 30 days, at least 40 days, at least 50 days, at least 60 days, at least 70 days, at least 80 days, at least 90 days, or at least 100 days of persistent infection in mice lacking type I interferon receptor, type II interferon receptor and recombination activating gene (RAG1), and having been infected with 10^4 PFU of the tri-segmented arenavirus particle (see Section 5.2.(h)(vii)). In other embodiments, propagation of the tri-segmented arenavirus particle comprising one L segment and two S segments does not result in a replication-competent bi-segmented viral particle after at

least 10 passages, at least 20 passages, at least 30 passages, at least 40 passages, or at least 50 passages.

[00263] The tri-segmented arenavirus particle with all viral genes in their respective wild-type position is known in the art (*e.g.*, Emonet *et al.*, 2011 J. Virol., 85(4):1473; Popkin *et al.*, 2011, J. Virol., 85(15):7928). In particular, the tri-segmented arenavirus genome consists of one L segment and two S segments, in which a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein is inserted into one position on each S segment. More specifically, one S segment encodes GP and a tumor antigen, tumor associated antigen or an antigenic fragment thereof, respectively. The other S segment encodes a tumor antigen, a tumor associated antigen or an antigenic fragment thereof and NP, respectively. The L segment encodes the L protein and Z protein. All segments are flanked by the respective 5' and 3' UTRs.

[00264] In certain embodiments, inter-segmental recombination of the two S segments of the tri-segmented arenavirus particle, provided herein, that unities the two arenaviral ORFs on one instead of two separate segments results in a non functional promoter (*i.e.*, a genomic segment of the structure: 5' UTR-----5' UTR or a 3' UTR-----3' UTR), wherein each UTR forming one end of the genome is an inverted repeat sequence of the other end of the same genome.

[00265] In certain embodiments, the tri-segmented arenavirus particle comprising one L segment and two S segments has been engineered to carry an arenavirus ORF in a position other than the wild-type position of the ORF and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In other embodiments, the tri-segmented arenavirus particle comprising one L segment and two S segments has been engineered to carry two arenavirus ORFs, or three arenavirus ORFs, or four arenavirus ORFs, or five arenavirus ORFs, or six arenavirus ORFs in a position other than the wild-type position. In specific embodiments, the tri-segmented arenavirus particle comprising one L segment and two S segments comprises a full complement of all four arenavirus ORFs. Thus, in some embodiments, the tri-segmented arenavirus particle is an infectious and replication competent tri-segmented arenavirus particle. In specific embodiments, the two S segments of the tri-segmented arenavirus particle have been engineered to carry one of their ORFs in a position other than the wild-type position. In more specific embodiments, the two S segments comprise a

full complement of the S segment ORF's. In certain specific embodiments, the L segment has been engineered to carry an ORF in a position other than the wild-type position or the L segment can be the wild-type genomic segment.

[00266] In certain embodiments, one of the two S segments can be:

- (i) an arenavirus S segment, wherein the ORF encoding the Z protein is under control of an arenavirus 5' UTR;
- (ii) an arenavirus S segment, wherein the ORF encoding the L protein is under control of an arenavirus 5' UTR;
- (iii) an arenavirus S segment, wherein the ORF encoding the NP is under control of an arenavirus 5' UTR;
- (iv) an arenavirus S segment, wherein the ORF encoding the GP is under control of an arenavirus 3' UTR;
- (v) an arenavirus S segment, wherein the ORF encoding the L is under control of an arenavirus 3' UTR; and
- (vi) an arenavirus S segment, wherein the ORF encoding the Z protein is under control of an arenavirus 3' UTR.

[00267] In certain embodiments, the tri-segmented arenavirus particle comprising one L segment and two S segments can comprise a duplicate ORF (*i.e.*, two wild-type S segment ORFs *e.g.*, GP or NP). In specific embodiments, the tri-segmented arenavirus particle comprising one L segment and two S segments can comprise one duplicate ORF (*e.g.*, (GP, GP)) or two duplicate ORFs (*e.g.*, (GP, GP) and (NP, NP)).

[00268] Table 2A, below, is an illustration of the genome organization of a tri-segmented arenavirus particle comprising one L segment and two S segments, wherein intersegmental recombination of the two S segments in the tri-segmented arenavirus genome does not result in a replication-competent bi-segmented viral particle and abrogates arenaviral promoter activity (*i.e.*, the resulting recombined S segment is made up of two 3'UTRs instead of a 3' UTR and a 5' UTR).

Table 2A

Tri-segmented arenavirus particle comprising one L segment and two S segments

Position 1 is under the control of an arenavirus S segment 5' UTR; Position 2 is under the control of an arenavirus S segment 3' UTR; Position 3 is under the control of an arenavirus S segment 5' UTR; Position

4 under the control of an arenavirus S segment 3' UTR; Position 5 is under the control of an arenavirus L segment 5' UTR; Position 6 is under the control of an arenavirus L segment 3' UTR.

*ORF indicates that a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein has been inserted.

Position 1	Position 2	Position 3	Position 4	Position 5	Position 6
*ORF	GP	*ORF	NP	Z	L
*ORF	NP	*ORF	GP	Z	L
*ORF	NP	*ORF	GP	L	Z
*ORF	NP	*ORF	Z	L	GP
*ORF	NP	Z	GP	*ORF	Z
*ORF	NP	Z	GP	Z	*ORF
*ORF	NP	*ORF	L	Z	GP
*ORF	L	*ORF	NP	Z	GP
*ORF	L	Z	NP	*ORF	GP
*ORF	L	*ORF	GP	Z	NP
*ORF	L	Z	GP	*ORF	NP
*ORF	Z	L	NP	*ORF	GP
*ORF	Z	*ORF	GP	L	NP
*ORF	Z	L	GP	*ORF	NP
L	GP	*ORF	NP	*ORF	Z
L	GP	*ORF	*ORF	Z	NP
L	GP	*ORF	Z	*ORF	NP
L	*ORF	Z	GP	*ORF	NP
L	GP	*ORF	NP	*ORF	Z
L	GP	*ORF	Z	*ORF	NP
L	GP	Z	NP	*ORF	*ORF
L	GP	Z	NP	*ORF	*ORF
L	*ORF	Z	NP	*ORF	GP
L	NP	*ORF	Z	*ORF	GP
L	NP	Z	*ORF	GP	*ORF
L	*ORF	Z	*ORF	GP	NP
L	NP	Z	GP	*ORF	*ORF
L	NP	*ORF	Z	*ORF	GP
L	*ORF	Z	NP	*ORF	GP
L	Z	*ORF	GP	*ORF	NP
L	Z	*ORF	NP	*ORF	GP
Z	GP	*ORF	NP	*ORF	L
Z	GP	*ORF	*ORF	L	NP
Z	GP	*ORF	L	*ORF	NP
Z	*ORF	L	GP	*ORF	NP
Z	GP	*ORF	NP	*ORF	L
Z	GP	*ORF	L	*ORF	NP
Z	GP	L	NP	*ORF	*ORF

Position 1	Position 2	Position 3	Position 4	Position 5	Position 6
Z	GP	L	NP	*ORF	*ORF
Z	*ORF	L	NP	*ORF	GP
Z	NP	*ORF	*ORF	L	GP
Z	NP	*ORF	GP	*ORF	L
Z	NP	*ORF	*ORF	L	GP
Z	NP	*ORF	L	*ORF	GP
Z	NP	L	GP	*ORF	*ORF
Z	*ORF	L	GP	*ORF	NP
Z	NP	*ORF	GP	*ORF	L
Z	NP	*ORF	L	*ORF	GP
Z	*ORF	L	NP	*ORF	GP
Z	L	*ORF	GP	*ORF	NP

[00269] In certain embodiments, the IGR between position one and position two can be an arenavirus S segment or L segment IGR; the IGR between position two and three can be an arenavirus S segment or L segment IGR; and the IGR between the position five and six can be an arenavirus L segment IGR. In a specific embodiment, the IGR between position one and position two can be an arenavirus S segment IGR; the IGR between position two and three can be an arenavirus S segment IGR; and the IGR between the position five and six can be an arenavirus L segment IGR. In certain embodiments, other combinations are also possible. For example, a tri-segmented arenavirus particle comprising one L segment and two S segments, wherein intersegmental recombination of the two S segments in the tri-segmented arenavirus genome does not result in a replication-competent bi-segmented viral particle and abrogates arenaviral promoter activity (*i.e.*, the resulting recombined S segment is made up of two 5'UTRs instead of a 3' UTR and a 5' UTR).

[00270] In certain embodiments, intersegmental recombination of an S segment and an L segment in the tri-segmented arenavirus particle comprising one L segment and two S segments, restores a functional segment with two viral genes on only one segment instead of two separate segments. In other embodiments, intersegmental recombination of an S segment and an L segment in the tri-segmented arenavirus particle comprising one L segment and two S segments does not result in a replication-competent bi-segmented viral particle.

[00271] Table 2B, below, is an illustration of the genome organization of a tri-segmented arenavirus particle comprising one L segment and two S segments, wherein intersegmental recombination of an S segment and an L segment in the tri-segmented arenavirus genome does

not result in a replication-competent bi-segmented viral particle and abrogates arenaviral promoter activity (*i.e.*, the resulting recombined S segment is made up of two 3'UTRs instead of a 3' UTR and a 5' UTR).

Table 2B

Tri-segmented arenavirus particle comprising one L segment and two S segments
Position 1 is under the control of an arenavirus S segment 5' UTR; Position 2 is under the control of an arenavirus S segment 3' UTR; Position 3 is under the control of an arenavirus S segment 5' UTR; Position 4 under the control of an arenavirus S segment 3' UTR; Position 5 is under the control of an arenavirus L segment 5' UTR; Position 6 is under the control of an arenavirus L segment 3' UTR.

*ORF indicates that a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein has been inserted.

Position 1	Position 2	Position 3	Position 4	Position 5	Position 6
L	GP	*ORF	NP	Z	*ORF
L	GP	Z	*ORF	*ORF	NP
L	GP	*ORF	NP	Z	*ORF
L	GP	Z	*ORF	*ORF	NP
L	NP	*ORF	GP	Z	*ORF
L	NP	Z	*ORF	*ORF	GP
L	NP	*ORF	GP	Z	*ORF
L	NP	Z	*ORF	*ORF	GP
Z	GP	*ORF	NP	L	*ORF
Z	GP	L	*ORF	*ORF	NP
Z	GP	*ORF	NP	L	*ORF
Z	NP	L	*ORF	*ORF	GP
Z	NP	*ORF	GP	L	*ORF
Z	NP	L	*ORF	*ORF	GP

[00272] In certain embodiments, the IGR between position one and position two can be an arenavirus S segment or L segment IGR; the IGR between position two and three can be an arenavirus S segment or L segment IGR; and the IGR between the position five and six can be an arenavirus L segment IGR. In a specific embodiment, the IGR between position one and position two can be an arenavirus S segment IGR; the IGR between position two and three can be an arenavirus S segment IGR; and the IGR between the position five and six can be an arenavirus L segment IGR. In certain embodiments, other combinations are also possible. For example, a tri-segmented arenavirus particle comprising one L segment and two S segments,

wherein intersegmental recombination of the two S segments in the tri-segmented arenavirus genome does not result in a replication-competent bi-segmented viral particle and abrogates arenaviral promoter activity (*i.e.*, the resulting recombined S segment is made up of two 5'UTRs instead of a 3' UTR and a 5' UTR).

[00273] In certain embodiments, one of skill in the art could construct an arenavirus genome with an organization as illustrated in Table 2A or 2B and as described herein, and then use an assay as described in Section 5.2.(h) to determine whether the tri-segmented arenavirus particle is genetically stable, *i.e.*, does not result in a replication-competent bi-segmented viral particle as discussed herein.

(ii) Tri-segmented Arenavirus Particle comprising two L segments and one S segment

[00274] Provided herein is a tri-segmented arenavirus particle that is replication competent. In certain specific embodiments, provided herein is a tri-segmented arenavirus particle that is replication defective. Tri-segmented arenavirus particles provided herein may be generated as described in International Publication No.: WO 2016/075250 A1 and International Patent Application No. PCT/EP2017/061865, which are herein incorporated in their entireties.

[00275] In one aspect, provided herein is a tri-segmented arenavirus particle comprising two L segments and one S segment. In certain embodiments, propagation of the tri-segmented arenavirus particle comprising two L segments and one S segment does not result in a replication-competent bi-segmented viral particle. In specific embodiments, propagation of the tri-segmented arenavirus particle comprising two L segments and one S segment does not result in a replication-competent bi-segmented viral particle after at least 10 days, at least 20 days, at least 30 days, at least 40 days, or at least 50 days, at least 60 days, at least 70 days, at least 80 days, at least 90 days, at least 100 days of persistent in mice lacking type I interferon receptor, type II interferon receptor and recombination activating gene (RAG1), and having been infected with 10^4 PFU of the tri-segmented arenavirus particle (see Section 5.2.(h)(vii)). In other embodiments, propagation of the tri-segmented arenavirus particle comprising two L segments and one S segment does not result in a replication-competent bi-segmented viral particle after at least 10 passages, 20 passages, 30 passages, 40 passages, or 50 passages.

[00276] In certain embodiments, inter-segmental recombination of the two L segments of the tri-segmented arenavirus particle, provided herein, that unities the two arenaviral ORFs on

one instead of two separate segments results in a non functional promoter (*i.e.*, a genomic segment of the structure: 5' UTR-----5' UTR or a 3' UTR-----3' UTR), wherein each UTR forming one end of the genome is an inverted repeat sequence of the other end of the same genome.

[00277] In certain embodiments, the tri-segmented arenavirus particle comprising two L segments and one S segment has been engineered to carry an arenavirus ORF in a position other than the wild-type position of the ORF and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In other embodiments, the tri-segmented arenavirus particle comprising two L segments and one S segment has been engineered to carry two arenavirus ORFs, or three arenavirus ORFs, or four arenavirus ORFs, or five arenavirus ORFs, or six arenavirus ORFs in a position other than the wild-type position. In specific embodiments, the tri-segmented arenavirus particle comprising two L segments and one S segment comprises a full complement of all four arenavirus ORFs. Thus, in some embodiments, the tri-segmented arenavirus particle is an infectious and replication competent tri-segmented arenavirus particle. In specific embodiments, the two L segments of the tri-segmented arenavirus particle have been engineered to carry one of their ORFs in a position other than the wild-type position. In more specific embodiments, the two L segments comprise a full complement of the L segment ORF's. In certain specific embodiments, the S segment has been engineered to carry one of their ORFs in a position other than the wild-type position or the S segment can be the wild-type genomic segment.

[00278] In certain embodiments, one of the two L segments can be:

- (xxxi) an L segment, wherein the ORF encoding the GP is under control of an arenavirus 5' UTR;
- (xxxii) an L segment, wherein the ORF encoding NP is under control of an arenavirus 5' UTR;
- (xxxiii) an L segment, wherein the ORF encoding the L protein is under control of an arenavirus 5' UTR;
- (xxxiv) an L segment, wherein the ORF encoding the GP is under control of an arenavirus 3' UTR;
- (xxxv) an L segment, wherein the ORF encoding the NP is under control of an arenavirus 3' UTR; and

(xxxvi)an L segment, wherein the ORF encoding the Z protein is under control of an arenavirus 3' UTR.

[00279] In certain embodiments, the tri-segmented arenavirus particle comprising one L segment and two S segments can comprise a duplicate ORF (*i.e.*, two wild-type L segment ORFs *e.g.*, Z protein or L protein). In specific embodiments, the tri-segmented arenavirus particle comprising two L segments and one S segment can comprise one duplicate ORF (*e.g.*, (Z protein, Z protein)) or two duplicate ORFs (*e.g.*, (Z protein, Z protein) and (L protein, L protein)).

[00280] Table 3, below, is an illustration of the genome organization of a tri-segmented arenavirus particle comprising two L segments and one S segment, wherein intersegmental recombination of the two L segments in the tri-segmented arenavirus genome does not result in a replication-competent bi-segmented viral particle and abrogates arenaviral promoter activity (*i.e.*, the S segment is made up of two 3'UTRs instead of a 3' UTR and a 5' UTR). Based on Table 3 similar combinations could be predicted for generating an arenavirus particle made up of two 5' UTRs instead of a 3' UTR and a 5' UTR.

Table 3

Tri-segmented arenavirus particle comprising two L segments and one S segment

*Position 1 is under the control of an arenavirus L segment 5' UTR; position 2 is under the control of an arenavirus L segment 3' UTR; position 3 is under the control of an arenavirus L segment 5' UTR; position 4 is under the control of an arenavirus L segment 3' UTR; position 5 is under the control of an arenavirus S segment 5' UTR; position 6 is under the control of an arenavirus S segment 3' UTR.

* ORF indicates that a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein has been inserted.

Position 1	Position 2	Position 3	Position 4	Position 5	Position 6
ORF*	Z	ORF*	L	NP	GP
ORF*	Z	ORF*	L	GP	NP
ORF*	Z	GP	L	ORF*	NP
ORF*	Z	ORF*	GP	NP	L
ORF*	Z	GP	ORF*	NP	L
ORF*	Z	NP	ORF*	GP	L
ORF*	ORF*	NP	Z	GP	L
ORF*	Z	GP	NP	ORF*	L
ORF*	Z	NP	GP	ORF*	L

Position 1	Position 2	Position 3	Position 4	Position 5	Position 6
ORF*	L	ORF*	Z	NP	GP
ORF*	L	ORF*	Z	GP	NP
ORF*	L	ORF*	GP	NP	Z
ORF*	L	GP	Z	ORF*	NP
ORF*	L	ORF*	GP	NP	Z
ORF*	L	NP	Z	ORF*	GP
ORF*	L	GP	NP	ORF*	Z
ORF*	L	NP	GP	ORF*	Z
ORF*	GP	ORF*	L	NP	Z
ORF*	GP	NP	L	ORF*	Z
ORF*	GP	ORF*	Z	NP	L
ORF*	GP	NP	Z	ORF*	L
ORF*	NP	ORF*	L	GP	Z
ORF*	NP	GP	L	ORF*	Z
ORF*	NP	GP	Z	ORF*	L
ORF*	NP	ORF*	Z	GP	L
ORF*	L	ORF*	Z	NP	GP
ORF*	L	ORF*	Z	GP	NP
ORF*	L	ORF*	NP	GP	Z
ORF*	L	ORF*	GP	NP	Z
ORF*	L	NP	Z	ORF*	GP
ORF*	Z	ORF*	GP	NP	L
ORF*	Z	GP	L	ORF*	NP
ORF*	Z	NP	GP	ORF*	L
ORF*	Z	GP	NP	ORF*	L
ORF*	GP	ORF*	L	NP	Z
ORF*	GP	ORF*	L	Z	NP
ORF*	GP	ORF*	Z	GP	L
ORF*	GP	NP	L	ORF*	Z
GP	L	ORF*	Z	ORF*	NP
GP	L	ORF*	NP	ORF*	Z
GP	Z	ORF*	L	ORF*	NP
GP	Z	ORF*	L	ORF*	NP
GP	Z	ORF*	NP	ORF*	L
GP	NP	ORF*	Z	ORF*	L
NP	L	ORF*	Z	ORF*	GP
NP	L	ORF*	GP	ORF*	Z
NP	L	ORF*	Z	ORF*	GP

[00281] In certain embodiments, the IGR between position one and position two can be an arenavirus S segment or L segment IGR; the IGR between position two and three can be an arenavirus S segment or L segment IGR; and the IGR between the position five and six can be an arenavirus L segment IGR. In a specific embodiment, the IGR between position one and position two can be an arenavirus L segment IGR; the IGR between position two and three can

be an arenavirus L segment IGR; and the IGR between the position five and six can be an arenavirus S segment IGR. In certain embodiments, other combinations are also possible.

[00282] In certain embodiments, intersegmental recombination of an L segment and an S segment from the tri-segmented arenavirus particle comprising two L segments and one S segment restores a functional segment with two viral genes on only one segment instead of two separate segments. In other embodiments, intersegmental recombination of an L segment and an S segment in the tri-segmented arenavirus particle comprising two L segments and one S segment does not result in a replication-competent bi-segmented viral particle..

[00283] Table 3B, below, is an illustration of the genome organization of a tri-segmented arenavirus particle comprising two L segments and one S segment, wherein intersegmental recombination of an L segment and an S segment in the tri-segmented arenavirus genome does not result in a replication-competent bi-segmented viral particle and abrogates arenaviral promoter activity (*i.e.*, the resulting recombined S segment is made up of two 3'UTRs instead of a 3' UTR and a 5' UTR).

Table 3B

Tri-segmented arenavirus particle comprising two L segments and one S segment

*Position 1 is under the control of an arenavirus L segment 5' UTR; position 2 is under the control of an arenavirus L segment 3' UTR; position 3 is under the control of an arenavirus L segment 5' UTR; position 4 is under the control of an arenavirus L segment 3' UTR; position 5 is under the control of an arenavirus S segment 5' UTR; position 6 is under the control of an arenavirus S segment 3' UTR.

* ORF indicates that a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein has been inserted.

Position 1	Position 2	Position 3	Position 4	Position 5	Position 6
NP	Z	*ORF	GP	L	*ORF
NP	Z	GP	*ORF	*ORF	L
NP	Z	*ORF	GP	L	*ORF
NP	Z	GP	*ORF	*ORF	L
NP	L	*ORF	GP	Z	*ORF
NP	L	GP	*ORF	*ORF	Z
NP	L	*ORF	GP	Z	*ORF
NP	L	GP	*ORF	*ORF	Z
GP	Z	*ORF	NP	L	*ORF
GP	Z	NP	*ORF	*ORF	L
GP	Z	*ORF	NP	L	*ORF
GP	L	NP	*ORF	*ORF	Z
GP	L	*ORF	NP	Z	*ORF
GP	L	NP	*ORF	*ORF	Z

[00284] In certain embodiments, the IGR between position one and position two can be an arenavirus S segment or L segment IGR; the IGR between position two and three can be an arenavirus S segment or L segment IGR; and the IGR between the position five and six can be an arenavirus L segment IGR. In a specific embodiment, the IGR between position one and position two can be an arenavirus L segment IGR; the IGR between position two and three can be an arenavirus L segment IGR; and the IGR between the position five and six can be an arenavirus S segment IGR. In certain embodiments, other combinations are also possible.

[00285] In certain embodiments, one of skill in the art could construct an arenavirus genome with an organization as illustrated in Table 3A or 3B and as described herein, and then use an assay as described in Section 5.2.(h) to determine whether the tri-segmented arenavirus

particle is genetically stable, *i.e.*, does not result in a replication-competent bi-segmented viral particle as discussed herein.

(iii) Replication-Defective Tri-segmented Arenavirus Particle

[00286] In certain embodiments, provided herein is a tri-segmented arenavirus particle in which (i) an ORF is in a position other than the wild-type position of the ORF; and (ii) an ORF encoding GP, NP, Z protein, or L protein has been removed or functionally inactivated such that the resulting virus cannot produce further infectious progeny virus particles (*i.e.*, is replication defective). In certain embodiments, the third arenavirus segment can be an S segment. In other embodiments, the third arenavirus segment can be an L segment. In more specific embodiments, the third arenavirus segment can be engineered to carry an ORF in a position other than the wild-type position of the ORF or the third arenavirus segment can be the wild-type arenavirus genomic segment. In yet more specific embodiments, the third arenavirus segment lacks an arenavirus ORF encoding GP, NP, Z protein, or the L protein.

[00287] In certain embodiments, a tri-segmented genomic segment could be a S or a L segment hybrid (*i.e.*, a genomic segment that can be a combination of the S segment and the L segment). In other embodiments, the hybrid segment is an S segment comprising an L segment IGR. In another embodiment, the hybrid segment is an L segment comprising an S segment IGR. In other embodiments, the hybrid segment is an S segment UTR with an L segment IGR. In another embodiment, the hybrid segment is an L segment UTR with an S segment IGR. In specific embodiments, the hybrid segment is an S segment 5' UTR with an L segment IGR or an S segment 3' UTR with an L segment IGR. In other specific embodiments, the hybrid segment is an L segment 5' UTR with an S segment IGR or an L segment 3' UTR with an S segment IGR.

[00288] A tri-segmented arenavirus particle comprising a genetically modified genome in which one or more ORFs has been deleted or functionally inactivated can be produced in complementing cells (*i.e.*, cells that express the arenavirus ORF that has been deleted or functionally inactivated). The genetic material of the resulting arenavirus particle can be transferred upon infection of a host cell into the host cell, wherein the genetic material can be expressed and amplified. In addition, the genome of the genetically modified arenavirus particle described herein can include a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein.

[00289] In certain embodiments, at least one of the four ORFs encoding GP, NP, Z protein, and L protein is removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In another embodiment, at least one ORF, at least two ORFs, at least three ORFs, or at least four ORFs encoding GP, NP, Z protein and L protein can be removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In specific embodiments, only one of the four ORFs encoding GP, NP, Z protein, and L protein is removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In more specific embodiments, the ORF that encodes GP of the arenavirus genomic segment is removed. In another specific embodiment, the ORF that encodes the NP of the arenavirus genomic segment is removed. In more specific embodiments, the ORF that encodes the Z protein of the arenavirus genomic segment is removed. In yet another specific embodiment, the ORF encoding the L protein is removed.

[00290] In certain embodiments, provided herein is a tri-segmented arenavirus particle comprising one L segment and two S segments in which (i) an ORF is in a position other than the wild-type position of the ORF; and (ii) an ORF encoding GP or NP has been removed or functionally inactivated, such that the resulting virus is replication-defective and not infectious. In a specific embodiment, one ORF is removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In another specific embodiment, two ORFs are removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In other specific embodiments, three ORFs are removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In specific embodiments, the ORF encoding GP is removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In other specific embodiments, the ORF encoding NP is removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In yet more specific embodiments, the ORF encoding NP and the ORF encoding GP are removed and replaced with one or two nucleotide sequences encoding tumor antigens, tumor associated antigens or

antigenic fragments thereof provided herein. Thus, in certain embodiments the tri-segmented arenavirus particle comprises (i) one L segment and two S segments; (ii) an ORF in a position other than the wild-type position of the ORF; (iii) one or more nucleotide sequences encoding tumor antigens, tumor associated antigens or an antigenic fragments thereof provided herein.

[00291] In certain embodiments, provided herein is a tri-segmented arenavirus particle comprising two L segments and one S segment in which (i) an ORF is in a position other than the wild-type position of the ORF; and (ii) an ORF encoding the Z protein, and/or the L protein has been removed or functionally inactivated, such that the resulting virus replication-defective and not infectious. In a specific embodiment, one ORF is removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In another specific embodiment, two ORFs are removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In specific embodiments, the ORF encoding the Z protein is removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In other specific embodiments, the ORF encoding the L protein is removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. In yet more specific embodiments, the ORF encoding the Z protein and the ORF encoding the L protein is removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. Thus, in certain embodiments the tri-segmented arenavirus particle comprises (i) two L segments and one S segment; (ii) an ORF in a position other than the wild-type position of the ORF; (iii) a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein.

[00292] Thus, in certain embodiments, the tri-segmented arenavirus particle provided herein comprises a tri-segmented arenavirus particle (*i.e.*, one L segment and two S segments or two L segments and one S segment) that i) is engineered to carry an ORF in a non-natural position; ii) an ORF encoding GP, NP, Z protein, or L protein is removed; iii) the ORF that is removed is replaced with one or more nucleotide sequences encoding tumor antigens, tumor associated antigens or antigenic fragments thereof provided herein.

[00293] In certain embodiments, the nucleotide sequence encoding an antigenic fragment provided herein is 8 to 100 nucleotides in length, 15 to 100 nucleotides in length, 25 to 100 nucleotides in length, 50 to 200 nucleotide in length, 50 to 400 nucleotide in length, 200 to 500 nucleotide in length, or 400 to 600 nucleotides in length, 500 to 800 nucleotide in length. In other embodiments, the nucleotide sequence encoding an antigenic fragment provided herein is 750 to 900 nucleotides in length, 800 to 100 nucleotides in length, 850 to 1000 nucleotides in length, 900 to 1200 nucleotides in length, 1000 to 1200 nucleotides in length, 1000 to 1500 nucleotides or 10 to 1500 nucleotides in length, 1500 to 2000 nucleotides in length, 1700 to 2000 nucleotides in length, 2000 to 2300 nucleotides in length, 2200 to 2500 nucleotides in length, 2500 to 3000 nucleotides in length, 3000 to 3200 nucleotides in length, 3000 to 3500 nucleotides in length, 3200 to 3600 nucleotides in length, 3300 to 3800 nucleotides in length, 4000 nucleotides to 4400 nucleotides in length, 4200 to 4700 nucleotides in length, 4800 to 5000 nucleotides in length, 5000 to 5200 nucleotides in length, 5200 to 5500 nucleotides in length, 5500 to 5800 nucleotides in length, 5800 to 6000 nucleotides in length, 6000 to 6400 nucleotides in length, 6200 to 6800 nucleotides in length, 6600 to 7000 nucleotides in length, 7000 to 7200 nucleotides in lengths, 7200 to 7500 nucleotides in length, or 7500 nucleotides in length. In some embodiments, the nucleotide sequence encodes a peptide or polypeptide that is 5 to 10 amino acids in length, 10 to 25 amino acids in length, 25 to 50 amino acids in length, 50 to 100 amino acids in length, 100 to 150 amino acids in length, 150 to 200 amino acids in length, 200 to 250 amino acids in length, 250 to 300 amino acids in length, 300 to 400 amino acids in length, 400 to 500 amino acids in length, 500 to 750 amino acids in length, 750 to 1000 amino acids in length, 1000 to 1250 amino acids in length, 1250 to 1500 amino acids in length, 1500 to 1750 amino acids in length, 1750 to 2000 amino acids in length, 2000 to 2500 amino acids in length, or more than 2500 or more amino acids in length. In some embodiments, the nucleotide sequence encodes a polypeptide that does not exceed 2500 amino acids in length. In specific embodiments the nucleotide sequence does not contain a stop codon. In certain embodiments, the nucleotide sequence is codon-optimized. In certain embodiments the nucleotide composition, nucleotide pair composition or both can be optimized. Techniques for such optimizations are known in the art and can be applied to optimize a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein.

[00294] Any nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein may be included in the tri-segmented arenavirus particle. In one embodiment, the a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein is capable of eliciting an immune response.

[00295] In certain embodiments, the growth and infectivity of the arenavirus particle is not affected by the nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein.

[00296] Techniques known to one skilled in the art may be used to produce an arenavirus particle comprising an arenavirus genomic segment engineered to carry an arenavirus ORF in a position other than the wild-type position and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein. For example, reverse genetics techniques may be used to generate such arenavirus particle. In other embodiments, the replication-defective arenavirus particle (*i.e.*, the arenavirus genomic segment engineered to carry an arenavirus ORF in a position other than the wild-type position, wherein an ORF encoding GP, NP, Z protein, L protein, has been deleted) can be produced in a complementing cell.

[00297] In certain embodiments, a tri-segmented arenavirus particle provided herein comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof as provided herein further comprises at least one nucleotide sequence encoding at least one immunomodulatory peptide, polypeptide or protein. In certain embodiments, the immunomodulatory peptide, polypeptide or protein is Calreticulin (CRT), or a fragment thereof; Ubiquitin or a fragment thereof; Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), or a fragment thereof; Invariant chain (CD74) or an antigenic fragment thereof; Mycobacterium tuberculosis Heat shock protein 70 or an antigenic fragment thereof; Herpes simplex virus 1 protein VP22 or an antigenic fragment thereof; CD40 ligand or an antigenic fragment thereof; or Fms-related tyrosine kinase 3 (Flt3) ligand or an antigenic fragment thereof.

[00298] Arenaviruses for use with the methods and compositions provided herein can be Old World viruses, for example Lassa virus, Lymphocytic choriomeningitis virus (LCMV), Mobala virus, Mopeia virus, or Ippy virus, or New World viruses, for example Amapari virus,

Flexal virus, Guanarito virus, Junin virus, Latino virus, Machupo virus, Oliveros virus, Parana virus, Pichinde virus, Pirital virus, Sabia virus, Tacaribe virus, Tamiami virus, Bear Canyon virus, or Whitewater Arroyo virus.

[00299] In certain embodiments, the tri-segmented arenavirus particle as described herein is suitable for use as a vaccine and methods of using such arenavirus particle in a vaccination and treatment for a neoplastic disease, for example, cancer, is provided. More detailed description of the methods of using the arenavirus particle described herein is provided in Section 5.2.(f)

[00300] In certain embodiments, the tri-segmented arenavirus particle as described herein is suitable for use as a pharmaceutical composition and methods of using such arenavirus particle in a vaccination and treatment for a neoplastic disease, for example, cancer, is provided. More detailed description of the methods of using the arenavirus particle described herein is provided in Section 5.2.(g).

(c) Tumor Antigens, Tumor Associated Antigens and Antigenic Fragments

[00301] In certain embodiments, arenavirus particles with nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein can be used with the methods and compositions provided herein, such as combinations with a chemotherapeutic agent. In certain embodiments, a tumor antigen or tumor associated antigen for use with the methods and compositions described herein is an immunogenic protein expressed in or on a neoplastic cell or tumor, such as a cancer cell or malignant tumor. In certain embodiments, a tumor antigen or tumor associated antigen for use with the methods and compositions described herein is a non-specific, mutant, overexpressed or abnormally expressed protein, which can be present on both a neoplastic cell or tumor and a normal cell or tissue. In certain embodiments, a tumor antigen or tumor associated antigen for use with the methods and compositions described herein is a tumor-specific antigen which is restricted to tumor cells. In certain embodiments, a tumor antigen for use with the methods and compositions described herein is a cancer-specific antigen which is restricted to cancer cells.

[00302] In certain embodiments, a tumor antigen or tumor associated antigen can exhibit one, two, three, or more, including all, of the following characteristics: overexpressed / accumulated (*i.e.*, expressed by both normal and neoplastic tissue, but highly expressed in neoplasia), oncofetal (*i.e.*, usually only expressed in fetal tissues and in cancerous somatic cells), oncoviral or oncogenic viral (*i.e.*, encoded by tumorigenic transforming viruses), cancer-testis

(*i.e.*, expressed only by cancer cells and adult reproductive tissues, *e.g.*, the testis), lineage-restricted (*i.e.*, expressed largely by a single cancer histotype), mutated (*i.e.*, only expressed in neoplastic tissue as a result of genetic mutation or alteration in transcription), post-translationally altered (*e.g.*, tumor-associated alterations in glycosylation), or idiotypic (*i.e.*, developed from malignant clonal expansions of B or T lymphocytes).

[00303] In certain embodiments, the tumor antigen or tumor associated antigen for use with the methods and compositions described herein includes antigens from neoplastic diseases including acute lymphoblastic leukemia; acute lymphoblastic lymphoma; acute lymphocytic leukaemia; acute myelogenous leukemia; acute myeloid leukemia (adult / childhood); adrenocortical carcinoma; AIDS-related cancers; AIDS-related lymphoma; anal cancer; appendix cancer; astrocytomas; atypical teratoid/rhabdoid tumor; basal-cell carcinoma; bile duct cancer, extrahepatic (cholangiocarcinoma); bladder cancer; bone osteosarcoma/malignant fibrous histiocytoma; brain cancer (adult / childhood); brain tumor, cerebellar astrocytoma (adult / childhood); brain tumor, cerebral astrocytoma/malignant glioma brain tumor; brain tumor, ependymoma; brain tumor, medulloblastoma; brain tumor, supratentorial primitive neuroectodermal tumors; brain tumor, visual pathway and hypothalamic glioma; brainstem glioma; breast cancer; bronchial adenomas/carcinoids; bronchial tumor; Burkitt lymphoma; cancer of childhood; carcinoid gastrointestinal tumor; carcinoid tumor; carcinoma of adult, unknown primary site; carcinoma of unknown primary; central nervous system embryonal tumor; central nervous system lymphoma, primary; cervical cancer; childhood adrenocortical carcinoma; childhood cancers; childhood cerebral astrocytoma; chordoma, childhood; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloid leukemia; chronic myeloproliferative disorders; colon cancer; colorectal cancer; craniopharyngioma; cutaneous T-cell lymphoma; desmoplastic small round cell tumor; emphysema; endometrial cancer; ependymblastoma; ependymoma; esophageal cancer; ewing's sarcoma in the Ewing family of tumors; extracranial germ cell tumor; extragonadal germ cell tumor; extrahepatic bile duct cancer; gallbladder cancer; gastric (stomach) cancer; gastric carcinoid; gastrointestinal carcinoid tumor; gastrointestinal stromal tumor; germ cell tumor: extracranial, extragonadal, or ovarian gestational trophoblastic tumor; gestational trophoblastic tumor, unknown primary site; glioma; glioma of the brain stem; glioma, childhood visual pathway and hypothalamic; hairy cell leukemia; head and neck cancer; heart cancer; hepatocellular (liver) cancer; hodgkin lymphoma;

hypopharyngeal cancer; hypothalamic and visual pathway glioma; intraocular melanoma; islet cell carcinoma (endocrine pancreas); Kaposi Sarcoma; kidney cancer (renal cell cancer); langerhans cell histiocytosis; laryngeal cancer; lip and oral cavity cancer; liposarcoma; liver cancer (primary); lung cancer, non-small cell; lung cancer, small cell; lymphoma, primary central nervous system; macroglobulinemia, Waldenström; male breast cancer; malignant fibrous histiocytoma of bone/osteosarcoma; medulloblastoma; medulloepithelioma; melanoma; melanoma, intraocular (eye); merkel cell cancer; merkel cell skin carcinoma; mesothelioma; mesothelioma, adult malignant; metastatic squamous neck cancer with occult primary; mouth cancer; multiple endocrine neoplasia syndrome; multiple myeloma/plasma cell neoplasm; mycosis fungoides, myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; myelogenous leukemia, chronic; myeloid leukemia, adult acute; myeloid leukemia, childhood acute; myeloma, multiple (cancer of the bone-marrow); myeloproliferative disorders, chronic; nasal cavity and paranasal sinus cancer; nasopharyngeal carcinoma; neuroblastoma, non-small cell lung cancer; non-hodgkin lymphoma; oligodendroglioma; oral cancer; oral cavity cancer; oropharyngeal cancer; osteosarcoma/malignant fibrous histiocytoma of bone; ovarian cancer; ovarian epithelial cancer (surface epithelial-stromal tumor); ovarian germ cell tumor; ovarian low malignant potential tumor; pancreatic cancer; pancreatic cancer, islet cell; papillomatosis; paranasal sinus and nasal cavity cancer; parathyroid cancer; penile cancer; pharyngeal cancer; pheochromocytoma; pineal astrocytoma; pineal germinoma; pineal parenchymal tumors of intermediate differentiation; pineoblastoma and supratentorial primitive neuroectodermal tumors; pituitary tumor; pituitary adenoma; plasma cell neoplasia/multiple myeloma; pleuropulmonary blastoma; primary central nervous system lymphoma; prostate cancer; rectal cancer; renal cell carcinoma (kidney cancer); renal pelvis and ureter, transitional cell cancer; respiratory tract carcinoma involving the NUT gene on chromosome 15; retinoblastoma; rhabdomyosarcoma, childhood; salivary gland cancer; sarcoma, Ewing family of tumors; Sézary syndrome; skin cancer (melanoma); skin cancer (non-melanoma); small cell lung cancer; small intestine cancer soft tissue sarcoma; soft tissue sarcoma; spinal cord tumor; squamous cell carcinoma; squamous neck cancer with occult primary, metastatic; stomach (gastric) cancer; supratentorial primitive neuroectodermal tumor; T-cell lymphoma, cutaneous (Mycosis Fungoides and Sézary syndrome); testicular cancer; throat cancer; thymoma; thymoma and thymic carcinoma; thyroid cancer; thyroid cancer, childhood; transitional cell cancer of the renal pelvis and ureter; urethral

cancer; uterine cancer, endometrial; uterine sarcoma; vaginal cancer; vulvar cancer; and Wilms Tumor.

[00304] In certain embodiments, the tumor antigen or tumor associated antigen for use with the methods and compositions disclosed herein includes oncogenic viral antigens, cancer-testis antigens, oncofetal antigens, tissue differentiation antigens, mutant protein antigens, Adipophilin, AIM-2, ALDH1AI, BCLX (L), BING-4, CALCA, CD45, CPSF, cyclin D1, DKKI, ENAH (hMena), Ga733 (EpCAM), EphA3, EZH2, FGF5, glypican-3, G250 /MN/CAIX, HER-2/neu, IDO1, IGF2B3, IL13Ralpha2, Intestinal carboxyl esterase, alpha-foetoprotein, Kallikrein 4, KIF20A, Lengsin, M-CSF, MCSP, mdm-2, Meloe, MMP-2, MMP-7, MUC1, MUC5AC, p53 (non-mutant), PAX5, PBF, PRAME, PSMA, RAGE, RAGE-1, RGS5, RhoC, RNF43, RU2AS, secernin 1, SOX10, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), survivin, Telomerase, VEGF, WT1, EGF-R, CEA, CD20, CD33, CD52, MELANA/MART1, MART2, NY-ESO-1, p53, MAGE A1, MAGE A3, MAGE-4, MAGE-5, MAGE-6, CDK4, alpha-actinin-4, ARTC1, BCR-ABL, BCR-ABL fusion protein (b3a2), B-Raf, CASP-5, CASP-8, beta-catenin, Cdc27, CDK4, CDKN2A, CLPP, COA-1, dek-can fusion protein, EFTUD2, Elongation factor 2, ETV6-AML, ETV6-AML1 fusion protein, FLT3-ITD, FNL, GPNMB, LDLR-fucosyltransferaseAS fusion protein, NFYC, OGT, OS-9, pml-RARalpha fusion protein, PRDX5, PTPRK, H-ras, K-ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene), N-ras, RBAF600, SIRT2, SNRPDI, SSX, SSX2, SYT-SSX1 or-SSX2 fusion protein, TGF-betaRII, Triosephosphate isomerase, ormdm-2, LMP2, HPV E6 / E7, EGFRvIII (epidermal growth factor variant III), Idiotype, GD2, ganglioside G2), Ras-mutant, p53 (mutant), Proteinase3 (PR1), Tyrosinase, PSA, hTERT, Sarcoma translocation breakpoints, EphA2, prostatic acid phosphatase PAP, neo-PAP, ML-IAP, AFP, ERG (TMPRSS2 ETS Fusion gene), NA17, PAX3, ALK, Androgen Receptor, Cyclin B1, Polysialic acid, MYCN, TRP2, TRP2-Int2, GD3, Fucosyl GM1, Mesothelin, PSCA, sLe(a), cyp1B1, PLAC1, GM3, BORIS, Tn, GLobH, NY-BR-1, SART3, STn, Carbonic Anhydrase IX, OY-TES1, Sperm protein 17, LCK, high molecular weight melanoma-associated antigen (HMWMAA), AKAP-4, SSX2, XAGE 1, B7H3, Legumain, Tie 2, Page4, VEGFR2, MAD-CT-1, FAP, PDGFR-beta, MAD-CT-2, For-related antigen 1, TRP-1, GP100, CA-125, CA19-9, Calretinin, Epithelial membrane antigen (EMA), Epithelial tumor antigen (ETA), CD19, CD34, CD99, CD117, Chromogranin, Cytokeratin, Desmin, Glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45

antigen, Myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), BAGE BAGE-1, CAGE, CTAGE, FATE, GAGE, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, HCA661, HOM-TES-85, MAGEA, MAGEB, MAGEC, NA88, NY-SAR-35, SPANXB1, SPA17, SSX, SYCP1, TPTE, Carbohydrate / ganglioside GM2 (oncofetal antigen-immunogenic-1 OFA-I-1), GM3, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA 50, CAM 43, CEA, EBNA, EF2, Epstein-Barr virus antigen, HLA-A2, HLA-A11, HSP70-2, KIAA0205, MUM-1, MUM-2, MUM-3, Myosin class I, GnTV, Herv-K-mel, LAGE-1, LAGE-2, (sperm protein) SP17, SCP-1, P15(58), Hom/Mel-40, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, TSP-180, P185erbB2, p180erbB-3, c-met, nm-23H1, TAG-72, TAG-72-4, CA-72-4, CAM 17.1, NuMa, 13-catenin, P16, TAGE, CT7, 43-9F, 5T4, 791Tgp72, 13HCG, BCA225, BTAA, CD68\KP1, CO-029, HTgp-175, M344, MG7-Ag, MOV18, NB\70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TLP, TPS, CD22, CD27, CD30, CD70, prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, integrin $\alpha v \beta 3$ (CD61), galactin, or Ral-B, CD123, CLL-1, CD38, CS-1, CD138, and ROR1.

[00305] In certain embodiments, the tumor antigen or tumor associated antigen is a neoantigen. A “neoantigen,” as used herein, means an antigen that arises by mutation in a tumor cell and such an antigen is not generally expressed in normal cells or tissue. Without being bound by theory, because healthy tissues generally do not possess these antigens, neoantigens represent a preferred target. Additionally, without being bound by theory, in the context of the present invention, since the T cells that recognize the neoantigen may not have undergone negative thymic selection, such cells can have high avidity to the antigen and mount a strong immune response against tumors, while lacking the risk to induce destruction of normal tissue and autoimmune damage. In certain embodiments, the neoantigen is an MHC class I-restricted neoantigen. In certain embodiments, the neoantigen is an MHC class II-restricted neoantigen. In certain embodiments, a mutation in a tumor cell of the patient results in a novel protein that produces the neoantigen.

[00306] In certain embodiments, the tumor antigen or tumor associated antigen can be an antigen ortholog, *e.g.*, a mammalian (*i.e.*, non-human primate, pig, dog, cat, or horse) to a human tumor antigen or tumor associated antigen.

[00307] In certain embodiments, an antigenic fragment of a tumor antigen or tumor associated antigen described herein is encoded by the nucleotide sequence included within the arenavirus. In certain embodiments, a fragment is antigenic when it is capable of (i) eliciting an antibody immune response in a host (*e.g.*, mouse, rabbit, goat, donkey or human) wherein the resulting antibodies bind specifically to an immunogenic protein expressed in or on a neoplastic cell (*e.g.*, a cancer cell); and/or (ii) eliciting a specific T cell immune response.

[00308] In certain embodiments, the nucleotide sequence encoding antigenic fragment of a tumor antigen or tumor associated antigen is 8 to 100 nucleotides in length, 15 to 100 nucleotides in length, 25 to 100 nucleotides in length, 50 to 200 nucleotide in length, 50 to 400 nucleotide in length, 200 to 500 nucleotide in length, or 400 to 600 nucleotides in length, 500 to 800 nucleotide in length. In other embodiments, the heterologous ORF is 750 to 900 nucleotides in length, 800 to 100 nucleotides in length, 850 to 1000 nucleotides in length, 900 to 1200 nucleotides in length, 1000 to 1200 nucleotides in length, 1000 to 1500 nucleotides or 10 to 1500 nucleotides in length, 1500 to 2000 nucleotides in length, 1700 to 2000 nucleotides in length, 2000 to 2300 nucleotides in length, 2200 to 2500 nucleotides in length, 2500 to 3000 nucleotides in length, 3000 to 3200 nucleotides in length, 3000 to 3500 nucleotides in length, 3200 to 3600 nucleotides in length, 3300 to 3800 nucleotides in length, 4000 nucleotides to 4400 nucleotides in length, 4200 to 4700 nucleotides in length, 4800 to 5000 nucleotides in length, 5000 to 5200 nucleotides in length, 5200 to 5500 nucleotides in length, 5500 to 5800 nucleotides in length, 5800 to 6000 nucleotides in length, 6000 to 6400 nucleotides in length, 6200 to 6800 nucleotides in length, 6600 to 7000 nucleotides in length, 7000 to 7200 nucleotides in lengths, 7200 to 7500 nucleotides in length, or 7500 nucleotides in length. In some embodiments, the heterologous ORF encodes a peptide or polypeptide that is 5 to 10 amino acids in length, 10 to 25 amino acids in length, 25 to 50 amino acids in length, 50 to 100 amino acids in length, 100 to 150 amino acids in length, 150 to 200 amino acids in length, 200 to 250 amino acids in length, 250 to 300 amino acids in length, 300 to 400 amino acids in length, 400 to 500 amino acids in length, 500 to 750 amino acids in length, 750 to 1000 amino acids in length, 1000 to 1250 amino acids in length, 1250 to 1500 amino acids in length, 1500 to 1750 amino acids in length, 1750 to 2000 amino acids in length, 2000 to 2500 amino acids in length, or more than 2500 or more amino acids in length. In some embodiments, the nucleotide sequence encodes a polypeptide that does not exceed 2500 amino acids in length. In specific embodiments the nucleotide sequence does

not contain a stop codon. In certain embodiments, the nucleotide sequence is codon-optimized. In certain embodiments the nucleotide composition, nucleotide pair composition or both can be optimized. Techniques for such optimizations are known in the art and can be applied to optimize a nucleotide sequence of a tumor antigen or tumor associated antigen.

[00309] In certain embodiments, the arenavirus genomic segment, the arenavirus particle or the tri-segmented arenavirus particle can comprise one or more nucleotide sequences encoding tumor antigens, tumor associated antigens, or antigenic fragments thereof. In other embodiments, the arenavirus genomic segment, the arenavirus particle or the tri-segmented arenavirus particle can comprise at least one nucleotide sequence encoding a tumor antigen, tumor associated antigen, or antigenic fragment thereof, at least two nucleotide sequences encoding tumor antigens, tumor associated antigens, or antigenic fragments thereof, at least three nucleotide sequences encoding tumor antigens, tumor associated antigens, or antigenic fragments thereof, or more nucleotide sequences encoding tumor antigens, tumor associated antigens, or antigenic fragments thereof.

[00310] In certain embodiments, an arenavirus particle comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof as provided herein further comprises at least one nucleotide sequence encoding at least one immunomodulatory peptide, polypeptide or protein. In certain embodiments, the immunomodulatory peptide, polypeptide or protein is Calreticulin (CRT), or a fragment thereof; Ubiquitin or a fragment thereof; Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), or a fragment thereof; Invariant chain (CD74) or an antigenic fragment thereof; Mycobacterium tuberculosis Heat shock protein 70 or an antigenic fragment thereof; Herpes simplex virus 1 protein VP22 or an antigenic fragment thereof; CD40 ligand or an antigenic fragment thereof; or Fms-related tyrosine kinase 3 (Flt3) ligand or an antigenic fragment thereof.

[00311] In certain embodiments, an arenavirus particle provided herein comprises a genomic segment that a) has a removal or functional inactivation of an ORF that is present in the wild type form of the genomic segment; and b) encodes (either in sense or antisense): (i) one or more tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and (ii) one or more immunomodulatory peptide, polypeptide or protein provided herein.

[00312] In certain embodiments, the nucleotide sequence encoding the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the nucleotide

sequence encoding the immunomodulatory peptide, polypeptide or protein provided herein, are on the same position of the viral genome. In certain embodiments, the nucleotide sequence encoding the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the nucleotide sequence encoding the immunomodulatory peptide, polypeptide or protein provided herein, are on different positions of the viral genome.

[00313] In certain embodiments, the nucleotide sequence encoding the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the nucleotide sequence encoding the immunomodulatory peptide, polypeptide or protein provided herein, are separated via a spacer sequence. In certain embodiments, the sequence encoding the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the nucleotide sequence encoding the immunomodulatory peptide, polypeptide or protein provided herein, are separated by an internal ribosome entry site, or a sequence encoding a protease cleavage site. In certain embodiments, the nucleotide sequence encoding the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the nucleotide sequence encoding the immunomodulatory peptide, polypeptide or protein provided herein, are separated by a nucleotide sequence encoding a linker or a self-cleaving peptide. Any linker peptide or self-cleaving peptide known to the skilled artisan can be used with the compositions and methods provided herein. A non-limiting example of a peptide linker is GSG. Non-limiting examples of a self-cleaving peptide are Porcine teschovirus-1 2A peptide, Thoseaasignavirus 2A peptide, or Foot-and-mouth disease virus 2A peptide.

[00314] In certain embodiments, the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the immunomodulatory peptide, polypeptide or protein provided herein, are directly fused together. In certain embodiments, the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the immunomodulatory peptide, polypeptide or protein provided herein, are fused together via a peptide linker. In certain embodiments, the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the immunomodulatory peptide, polypeptide or protein provided herein are separated from each other via a self-cleaving peptide. A non-limiting example of a peptide linker is GSG. Non-limiting examples of a self-cleaving peptide are Porcine teschovirus-1 2A peptide, Thoseaasignavirus 2A peptide, or Foot-and-mouth disease virus 2A peptide.

[00315] In certain embodiments, the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the immunomodulatory peptide, polypeptide or protein provided herein are expressed on the same arenavirus particle. In certain embodiments, the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the immunomodulatory peptide, polypeptide or protein provided herein are expressed on different arenavirus particles. In certain embodiments, the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the immunomodulatory peptide, polypeptide or protein provided herein are expressed on different viruses of the same strain. In certain embodiments, the tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, and the immunomodulatory peptide, polypeptide or protein provided herein are expressed on different viruses of different strains.

[00316] In certain embodiments, an arenavirus particle generated to encode one or more tumor antigens, tumor associated antigens or antigenic fragments thereof comprises one or more nucleotide sequences encoding tumor antigens, tumor associated antigens or antigenic fragments thereof provided herein. In specific embodiments the tumor antigens, tumor associated antigens or antigenic fragments thereof provided herein are separated by various one or more linkers, spacers, or cleavage sites as described herein.

(d) Generation of an arenavirus particle and a tri-segmented arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof

[00317] Generally, arenavirus particles for use in the methods and compositions provided herein, such as combinations with a chemotherapeutic agent, can be recombinantly produced by standard reverse genetic techniques as described for LCMV (see Flatz *et al.*, 2006, Proc Natl Acad Sci USA 103:4663-4668; Sanchez *et al.*, 2006, Virology 350:370; Ortiz-Riano *et al.*, 2013, J Gen Virol. 94:1175-88, which are incorporated by reference herein). To generate the arenavirus particles provided herein, these techniques can be applied as described below. The genome of the viruses can be modified as described herein.

(i) Non-natural Position Open Reading Frame

[00318] The generation of an arenavirus particle comprising a genomic segment that has been engineered to carry a viral ORF in a position other than the wild-type position of the ORF and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic

fragment thereof can be recombinantly produced by any reverse genetic techniques known to one skilled in the art.

(A) Infectious and Replication Competent Arenavirus Particle

[00319] In certain embodiments, the method of generating the arenavirus particle comprises (i) transfecting into a host cell the cDNA of the first arenavirus genomic segment; (ii) transfecting into a host cell the cDNA of the second arenavirus genomic segment; (iii) transfecting into a host cell plasmids expressing the arenavirus' minimal trans-acting factors NP and L; (iv) maintaining the host cell under conditions suitable for virus formation; and (v) harvesting the arenavirus particle. In certain more specific embodiments, the cDNA is comprised in a plasmid.

[00320] Once generated from cDNA, arenavirus particles (*e.g.*, infectious and replication competent) can be propagated. In certain embodiments, the arenavirus particle can be propagated in any host cell that allows the virus to grow to titers that permit the uses of the virus as described herein. In one embodiment, the host cell allows the arenavirus particle to grow to titers comparable to those determined for the corresponding wild-type.

[00321] In certain embodiments, the arenavirus particle may be propagated in host cells. Specific examples of host cells that can be used include BHK-21, HEK 293, VERO or other. In a specific embodiment, the arenavirus particle may be propagated in a cell line.

[00322] In certain embodiments, the host cells are kept in culture and are transfected with one or more plasmid(s). The plasmid(s) express the arenavirus genomic segment(s) to be generated under control of one or more expression cassettes suitable for expression in mammalian cells, *e.g.*, consisting of a polymerase I promoter and terminator.

[00323] Plasmids that can be used for the generation of the arenavirus particle can include: i) a plasmid encoding the S genomic segment *e.g.*, pol-I S, ii) a plasmid encoding the L genomic segment *e.g.*, pol-I L. In certain embodiments, the plasmid encoding an arenavirus polymerase that direct intracellular synthesis of the viral L and S segments can be incorporated into the transfection mixture. For example, a plasmid encoding the L protein and/or a plasmid encoding NP (pC-L and pC-NP, respectively) can be present. The L protein and NP are the minimal trans-acting factors necessary for viral RNA transcription and replication. Alternatively, intracellular synthesis of viral L and S segments, together with NP and L protein

can be performed using an expression cassette with pol-I and pol-II promoters reading from opposite sides into the L and S segment cDNAs of two separate plasmids, respectively.

[00324] In certain embodiments, the arenavirus genomic segments are under the control of a promoter. Typically, RNA polymerase I-driven expression cassettes, RNA polymerase II-driven cassettes or T7 bacteriophage RNA polymerase driven cassettes can be used. In certain embodiments, the plasmid(s) encoding the arenavirus genomic segments can be the same, *i.e.*, the genome sequence and transacting factors can be transcribed by a promoter from one plasmid. Specific examples of promoters include an RNA polymerase I promoter, an RNA polymerase II promoter, an RNA polymerase III promoter, a T7 promoter, an SP6 promoter or a T3 promoter.

[00325] In addition, the plasmid(s) can feature a mammalian selection marker, *e.g.*, puromycin resistance, under control of an expression cassette suitable for gene expression in mammalian cells, *e.g.*, polymerase II expression cassette as above, or the viral gene transcript(s) are followed by an internal ribosome entry site, such as the one of encephalomyocarditis virus, followed by the mammalian resistance marker. For production in *E.coli*, the plasmid additionally features a bacterial selection marker, such as an ampicillin resistance cassette.

[00326] Transfection of a host cell with a plasmid(s) can be performed using any of the commonly used strategies such as calcium-phosphate, liposome-based protocols or electroporation. A few days later the suitable selection agent, *e.g.*, puromycin, is added in titrated concentrations. Surviving clones are isolated and subcloned following standard procedures, and high-expressing clones are identified using Western blot or flow cytometry procedures with antibodies directed against the viral protein(s) of interest.

[00327] For recovering the arenavirus particle described herein, the following procedures are envisaged. First day: cells, typically 80% confluent in M6-well plates, are transfected with a mixture of the plasmids, as described above. For this one can exploit any commonly used strategies such as calcium-phosphate, liposome-based protocols or electroporation.

[00328] 3-5 days later: The cultured supernatant (arenavirus vector preparation) is harvested, aliquoted and stored at 4 °C, -20 °C, or -80 °C, depending on how long the arenavirus vector should be stored prior use. The arenavirus vector preparation's infectious titer is assessed by an immunofocus assay. Alternatively, the transfected cells and supernatant may be passaged to a larger vessel (*e.g.*, a T75 tissue culture flask) on day 3-5 after transfection, and culture supernatant is harvested up to five days after passage.

[00329] The present application furthermore relates to expression of a heterologous ORF, wherein a plasmid encoding the genomic segment is modified to incorporate a heterologous ORF. The heterologous ORF can be incorporated into the plasmid using restriction enzymes.

(B) Infectious, Replication-Defective Arenavirus Particle

[00330] Infectious, replication-defective arenavirus particles can be rescued as described above. However, once generated from cDNA, the infectious, replication-deficient arenaviruses provided herein can be propagated in complementing cells. Complementing cells are cells that provide the functionality that has been eliminated from the replication-deficient arenavirus by modification of its genome (*e.g.*, if the ORF encoding the GP protein is deleted or functionally inactivated, a complementing cell does provide the GP protein).

[00331] Owing to the removal or functional inactivation of one or more of the ORFs in arenavirus vectors (here deletion of the glycoprotein, GP, will be taken as an example), arenavirus vectors can be generated and expanded in cells providing *in trans* the deleted viral gene(s), *e.g.*, the GP in the present example. Such a complementing cell line, henceforth referred to as C-cells, is generated by transfecting a cell line such as BHK-21, HEK 293, VERO or other with one or more plasmid(s) for expression of the viral gene(s) of interest (complementation plasmid, referred to as C-plasmid). The C-plasmid(s) express the viral gene(s) deleted in the arenavirus vector to be generated under control of one or more expression cassettes suitable for expression in mammalian cells, *e.g.*, a mammalian polymerase II promoter such as the EF1alpha promoter with a polyadenylation signal. In addition, the complementation plasmid features a mammalian selection marker, *e.g.*, puromycin resistance, under control of an expression cassette suitable for gene expression in mammalian cells, *e.g.*, polymerase II expression cassette as above, or the viral gene transcript(s) are followed by an internal ribosome entry site, such as the one of encephalomyocarditis virus, followed by the mammalian resistance marker. For production in *E. coli*, the plasmid additionally features a bacterial selection marker, such as an ampicillin resistance cassette.

[00332] Cells that can be used, *e.g.*, BHK-21, HEK 293, MC57G or other, are kept in culture and are transfected with the complementation plasmid(s) using any of the commonly used strategies such as calcium-phosphate, liposome-based protocols or electroporation. A few days later the suitable selection agent, *e.g.*, puromycin, is added in titrated concentrations. Surviving clones are isolated and subcloned following standard procedures, and high-expressing

C-cell clones are identified using Western blot or flow cytometry procedures with antibodies directed against the viral protein(s) of interest. As an alternative to the use of stably transfected C-cells transient transfection of normal cells can complement the missing viral gene(s) in each of the steps where C-cells will be used below. In addition, a helper virus can be used to provide the missing functionality *in trans*.

[00333] Plasmids can be of two types: i) two plasmids, referred to as TF-plasmids for expressing intracellularly in C-cells the minimal transacting factors of the arenavirus, is derived from *e.g.*, NP and L proteins of LCMV in the present example; and ii) plasmids, referred to as GS-plasmids, for expressing intracellularly in C-cells the arenavirus vector genome segments, *e.g.*, the segments with designed modifications. TF-plasmids express the NP and L proteins of the respective arenavirus vector under control of an expression cassette suitable for protein expression in mammalian cells, typically *e.g.*, a mammalian polymerase II promoter such as the CMV or EF1alpha promoter, either one of them preferentially in combination with a polyadenylation signal. GS-plasmids express the small (S) and the large (L) genome segments of the vector. Typically, polymerase I-driven expression cassettes or T7 bacteriophage RNA polymerase (T7-) driven expression cassettes can be used, the latter preferentially with a 3'-terminal ribozyme for processing of the primary transcript to yield the correct end. In the case of using a T7-based system, expression of T7 in C-cells must be provided by either including in the recovery process an additional expression plasmid, constructed analogously to TF-plasmids, providing T7, or C-cells are constructed to additionally express T7 in a stable manner. In certain embodiments, TF and GS plasmids can be the same, *i.e.*, the genome sequence and transacting factors can be transcribed by T7, polII and polIII promoters from one plasmid.

[00334] For recovering of the arenavirus vector, the following procedures can be used. First day: C-cells, typically 80% confluent in M6-well plates, are transfected with a mixture of the two TF-plasmids plus the two GS-plasmids. In certain embodiments, the TF and GS plasmids can be the same, *i.e.*, the genome sequence and transacting factors can be transcribed by T7, polII and polIII promoters from one plasmid. For this one can exploit any of the commonly used strategies such as calcium-phosphate, liposome-based protocols or electroporation.

[00335] 3-5 days later: The culture supernatant (arenavirus vector preparation) is harvested, aliquoted and stored at 4 °C, -20 °C or -80 °C depending on how long the arenavirus vector should be stored prior to use. Then the arenavirus vector preparation's infectious titer is

assessed by an immunofocus assay on C-cells. Alternatively, the transfected cells and supernatant may be passaged to a larger vessel (*e.g.*, a T75 tissue culture flask) on day 3-5 after transfection, and culture supernatant is harvested up to five days after passage.

[00336] The invention furthermore relates to expression of a antigen in a cell culture wherein the cell culture is infected with an infectious, replication-deficient arenavirus expressing an antigen. When used for expression of a antigen in cultured cells, the following two procedures can be used:

i) The cell type of interest is infected with the arenavirus vector preparation described herein at a multiplicity of infection (MOI) of one or more, *e.g.*, two, three or four, resulting in production of the antigen in all cells already shortly after infection.

ii) Alternatively, a lower MOI can be used and individual cell clones can be selected for their level of virally driven antigen expression. Subsequently individual clones can be expanded infinitely owing to the non-cytolytic nature of arenavirus vectors. Irrespective of the approach, the antigen can subsequently be collected (and purified) either from the culture supernatant or from the cells themselves, depending on the properties of the antigen produced. However, the invention is not limited to these two strategies, and other ways of driving expression of antigen using infectious, replication-deficient arenaviruses as vectors may be considered.

(ii) Generation of a Tri-segmented Arenavirus Particle

[00337] A tri-segmented arenavirus particle comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof can be recombinantly produced by reverse genetic techniques known in the art, for example as described by Emonet *et al.*, 2008, PNAS, 106(9):3473-3478; Popkin *et al.*, 2011, J. Virol., 85 (15):7928–7932, which are incorporated by reference herein. The generation of the tri-segmented arenavirus particle provided herein can be modified as described in Section 5.2(b).

(A) Infectious and Replication Competent Tri-segmented arenavirus Particle

[00338] In certain embodiments, the method of generating the tri-segmented arenavirus particle comprises (i) transfecting into a host cell the cDNAs of the one L segment and two S segments or two L segments and one S segment; (ii) transfecting into a host cell plasmids

expressing the arenavirus' minimal trans-acting factors NP and L; (iii) maintaining the host cell under conditions suitable for virus formation; and (iv) harvesting the arenavirus particle.

[00339] Once generated from cDNA, the tri-segmented arenavirus particle (*i.e.*, infectious and replication competent) can be propagated. In certain embodiments tri-segmented arenavirus particle can be propagated in any host cell that allows the virus to grow to titers that permit the uses of the virus as described herein. In one embodiment, the host cell allows the tri-segmented arenavirus particle to grow to titers comparable to those determined for the corresponding wild-type.

[00340] In certain embodiments, the tri-segmented arenavirus particle may be propagated in host cells. Specific examples of host cells that can be used include BHK-21, HEK 293, VERO or other. In a specific embodiment, the tri-segmented arenavirus particle may be propagated in a cell line.

[00341] In certain embodiments, the host cells are kept in culture and are transfected with one or more plasmid(s). The plasmid(s) express the arenavirus genomic segment(s) to be generated under control of one or more expression cassettes suitable for expression in mammalian cells, *e.g.*, consisting of a polymerase I promoter and terminator.

[00342] In specific embodiments, the host cells are kept in culture and are transfected with one or more plasmid(s). The plasmid(s) express the viral gene(s) to be generated under control of one or more expression cassettes suitable for expression in mammalian cells, *e.g.*, consisting of a polymerase I promoter and terminator.

[00343] Plasmids that can be used for generating the tri-segmented arenavirus comprising one L segment and two S segments can include: i) two plasmids each encoding the S genome segment *e.g.*, pol-I S, ii) a plasmid encoding the L genome segment *e.g.*, pol-I L. Plasmids needed for the tri-segmented arenavirus comprising two L segments and one S segments are: i) two plasmids each encoding the L genome segment *e.g.*, pol-L, ii) a plasmid encoding the S genome segment *e.g.*, pol-I S.

[00344] In certain embodiments, plasmids encoding an arenavirus polymerase that direct intracellular synthesis of the viral L and S segments can be incorporated into the transfection mixture. For example, a plasmid encoding the L protein and a plasmid encoding NP (pC-L and pC-NP, respectively). The L protein and NP are the minimal trans-acting factors necessary for viral RNA transcription and replication. Alternatively, intracellular synthesis of viral L and S

segments, together with NP and L protein can be performed using an expression cassette with pol-I and pol-II promoters reading from opposite sides into the L and S segment cDNAs of two separate plasmids, respectively.

[00345] In addition, the plasmid(s) features a mammalian selection marker, *e.g.*, puromycin resistance, under control of an expression cassette suitable for gene expression in mammalian cells, *e.g.*, polymerase II expression cassette as above, or the viral gene transcript(s) are followed by an internal ribosome entry site, such as the one of encephalomyocarditis virus, followed by the mammalian resistance marker. For production in *E.coli*, the plasmid additionally features a bacterial selection marker, such as an ampicillin resistance cassette.

[00346] Transfection of BHK-21 cells with a plasmid(s) can be performed using any of the commonly used strategies such as calcium-phosphate, liposome-based protocols or electroporation. A few days later the suitable selection agent, *e.g.*, puromycin, is added in titrated concentrations. Surviving clones are isolated and subcloned following standard procedures, and high-expressing clones are identified using Western blot or flow cytometry procedures with antibodies directed against the viral protein(s) of interest.

[00347] Typically, RNA polymerase I-driven expression cassettes, RNA polymerase II-driven cassettes or T7 bacteriophage RNA polymerase driven cassettes can be used, , the latter preferentially with a 3'-terminal ribozyme for processing of the primary transcript to yield the correct end. In certain embodiments, the plasmids encoding the arenavirus genomic segments can be the same, *i.e.*, the genome sequence and transacting factors can be transcribed by T7, polI and polII promoters from one plasmid.

[00348] For recovering the arenavirus the tri-segmented arenavirus vector, the following procedures are envisaged. First day: cells, typically 80% confluent in M6-well plates, are transfected with a mixture of the plasmids, as described above. For this one can exploit any commonly used strategies such as calcium-phosphate, liposome-based protocols or electroporation.

[00349] 3-5 days later: The cultured supernatant (arenavirus vector preparation) is harvested, aliquoted and stored at 4 °C, -20 °C, or -80 °C, depending on how long the arenavirus vector should be stored prior use. The arenavirus vector preparation's infectious titer is assessed by an immunofocus assay. Alternatively, the transfected cells and supernatant may be passaged

to a larger vessel (*e.g.*, a T75 tissue culture flask) on day 3-5 after transfection, and culture supernatant is harvested up to five days after passage.

[00350] In certain embodiments, expression of a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof is provided, wherein a plasmid encoding the genomic segment is modified to incorporated a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof. The nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof can be incorporated into the plasmid using restriction enzymes.

(B) Infectious, Replication-Defective Tri-segmented
Arenavirus Particle

[00351] Infectious, replication-defective tri-segmented arenavirus particles can be rescued as described above. However, once generated from cDNA, the infectious, replication-deficient arenaviruses provided herein can be propagated in complementing cells. Complementing cells are cells that provide the functionality that has been eliminated from the replication-deficient arenavirus by modification of its genome (*e.g.*, if the ORF encoding the GP protein is deleted or functionally inactivated, a complementing cell does provide the GP protein).

[00352] Owing to the removal or functional inactivation of one or more of the ORFs in arenavirus vectors (here deletion of the glycoprotein, GP, will be taken as an example), arenavirus vectors can be generated and expanded in cells providing *in trans* the deleted viral gene(s), *e.g.*, the GP in the present example. Such a complementing cell line, henceforth referred to as C-cells, is generated by transfecting a mammalian cell line such as BHK-21, HEK 293, VERO or other (here BHK-21 will be taken as an example) with one or more plasmid(s) for expression of the viral gene(s) of interest (complementation plasmid, referred to as C-plasmid). The C-plasmid(s) express the viral gene(s) deleted in the arenavirus vector to be generated under control of one or more expression cassettes suitable for expression in mammalian cells, *e.g.*, a mammalian polymerase II promoter such as the CMV or EF1alpha promoter with a polyadenylation signal. In addition, the complementation plasmid features a mammalian selection marker, *e.g.*, puromycin resistance, under control of an expression cassette suitable for gene expression in mammalian cells, *e.g.*, polymerase II expression cassette as above, or the viral gene transcript(s) are followed by an internal ribosome entry site, such as the one of encephalomyocarditis virus, followed by the mammalian resistance marker. For production in E.

coli, the plasmid additionally features a bacterial selection marker, such as an ampicillin resistance cassette.

[00353] Cells that can be used, *e.g.*, BHK-21, HEK 293, MC57G or other, are kept in culture and are transfected with the complementation plasmid(s) using any of the commonly used strategies such as calcium-phosphate, liposome-based protocols or electroporation. A few days later the suitable selection agent, *e.g.*, puromycin, is added in titrated concentrations. Surviving clones are isolated and subcloned following standard procedures, and high-expressing C-cell clones are identified using Western blot or flow cytometry procedures with antibodies directed against the viral protein(s) of interest. As an alternative to the use of stably transfected C-cells transient transfection of normal cells can complement the missing viral gene(s) in each of the steps where C-cells will be used below. In addition, a helper virus can be used to provide the missing functionality *in trans*.

[00354] Plasmids of two types can be used: i) two plasmids, referred to as TF-plasmids for expressing intracellularly in C-cells the minimal transacting factors of the arenavirus, is derived from *e.g.*, NP and L proteins of LCMV in the present example; and ii) plasmids, referred to as GS-plasmids, for expressing intracellularly in C-cells the arenavirus vector genome segments, *e.g.*, the segments with designed modifications. TF-plasmids express the NP and L proteins of the respective arenavirus vector under control of an expression cassette suitable for protein expression in mammalian cells, typically *e.g.*, a mammalian polymerase II promoter such as the CMV or EF1alpha promoter, either one of them preferentially in combination with a polyadenylation signal. GS-plasmids express the small (S) and the large (L) genome segments of the vector. Typically, polymerase I-driven expression cassettes or T7 bacteriophage RNA polymerase (T7-) driven expression cassettes can be used, the latter preferentially with a 3'-terminal ribozyme for processing of the primary transcript to yield the correct end. In the case of using a T7-based system, expression of T7 in C-cells must be provided by either including in the recovery process an additional expression plasmid, constructed analogously to TF-plasmids, providing T7, or C-cells are constructed to additionally express T7 in a stable manner. In certain embodiments, TF and GS plasmids can be the same, *i.e.*, the genome sequence and transacting factors can be transcribed by T7, polII and polIII promoters from one plasmid.

[00355] For recovering of the arenavirus vector, the following procedures can be used. First day: C-cells, typically 80% confluent in M6-well plates, are transfected with a mixture of

the two TF-plasmids plus the two GS-plasmids. In certain embodiments, the TF and GS plasmids can be the same, *i.e.*, the genome sequence and transacting factors can be transcribed by T7, polII and polIII promoters from one plasmid. For this one can exploit any of the commonly used strategies such as calcium-phosphate, liposome-based protocols or electroporation.

[00356] 3-5 days later: The culture supernatant (arenavirus vector preparation) is harvested, aliquoted and stored at 4 °C, -20 °C or -80 °C depending on how long the arenavirus vector should be stored prior to use. Then the arenavirus vector preparation's infectious titer is assessed by an immunofocus assay on C-cells. Alternatively, the transfected cells and supernatant may be passaged to a larger vessel (*e.g.*, a T75 tissue culture flask) on day 3-5 after transfection, and culture supernatant is harvested up to five days after passage.

[00357] The invention furthermore relates to expression of an antigen in a cell culture wherein the cell culture is infected with an infectious, replication-deficient tri-segmented arenavirus expressing a antigen. When used for expression of a CMV antigen in cultured cells, the following two procedures can be used:

i) The cell type of interest is infected with the arenavirus vector preparation described herein at a multiplicity of infection (MOI) of one or more, *e.g.*, two, three or four, resulting in production of the tumor antigen, tumor associated antigen, or antigenic fragment thereof in all cells already shortly after infection.

ii) Alternatively, a lower MOI can be used and individual cell clones can be selected for their level of virally driven expression of a tumor antigen, tumor associated antigen or antigenic fragment thereof. Subsequently individual clones can be expanded infinitely owing to the non-cytolytic nature of arenavirus vectors. Irrespective of the approach, the tumor antigen, tumor associated antigen or antigenic fragment thereof can subsequently be collected (and purified) either from the culture supernatant or from the cells themselves, depending on the properties of the tumor antigen, tumor associated antigen or antigenic fragment produced. However, the invention is not limited to these two strategies, and other ways of driving expression of tumor antigen, tumor associated antigen or antigenic fragment thereof using infectious, replication-deficient arenaviruses as vectors may be considered.

(e) Nucleic Acids, Vector Systems and Cell Lines

[00358] In certain embodiments, provided herein are cDNAs comprising or consisting of the arenavirus genomic segment or the tri-segmented arenavirus particle as described herein,

which can be used with the methods and compositions provided herein, such as combinations with a chemotherapeutic agent. .

(i) Non-natural Position Open Reading Frame

[00359] In one embodiment, provided herein are nucleic acids that encode an arenavirus genomic segment as described in Section 5.2.(a). In more specific embodiments, provided herein is a DNA nucleotide sequence or a set of DNA nucleotide sequences as set forth in Table 1. Host cells that comprise such nucleic acids are also provided Section 5.2.(a).

[00360] In specific embodiments, provided herein is a cDNA of the arenavirus genomic segment engineered to carry an ORF in a position other than the wild-type position of the ORF and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof, wherein the arenavirus genomic segment encodes a heterologous ORF as described in Section 5.2(a)

[00361] In one embodiment, provided herein is a DNA expression vector system that encodes the arenavirus genomic segment engineered to carry an ORF in a position other than the wild-type position of the ORF and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof. Specifically, provided herein is a DNA expression vector system wherein one or more vectors encodes two arenavirus genomic segments, namely, an L segment and an S segment, of an arenavirus particle described herein. Such a vector system can encode a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof.

[00362] In another embodiment, provided herein is a cDNA of the arenavirus S segment that has been engineered to carry an ORF in a position other than the wild-type position and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof that is part of or incorporated into a DNA expression system. In other embodiments, provided herein is a cDNA of the arenavirus L segment that has been engineered to carry an ORF in a position other than the wild-type position and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof that is part of or incorporated into a DNA expression system. In certain embodiments, is a cDNA of the arenavirus genomic segment that has been engineered to carry (i) an ORF in a position other than the wild-type position of the ORF; and (ii) and ORF encoding GP, NP, Z protein, or L protein has been

removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof.

[00363] In certain embodiments, the cDNA provided herein can be derived from a particular strain of LCMV. Strains of LCMV include Clone 13, MP strain, Arm CA 1371, Arm E-250, WE, UBC, Traub, Pasteur, 810885, CH-5692, Marseille #12, HP65-2009, 200501927, 810362, 811316, 810316, 810366, 20112714, Douglas, GR01, SN05, CABN and their derivatives. In specific embodiments, the cDNA is derived from LCMV Clone 13. In other specific embodiments, the cDNA is derived from LCMV MP strain.

[00364] In certain embodiments, the vector generated to encode an arenavirus particle or a tri-segmented arenavirus particle as described herein may be based on a specific strain of LCMV. Strains of LCMV include Clone 13, MP strain, Arm CA 1371, Arm E-250, WE, UBC, Traub, Pasteur, 810885, CH-5692, Marseille #12, HP65-2009, 200501927, 810362, 811316, 810316, 810366, 20112714, Douglas, GR01, SN05, CABN and their derivatives. In certain embodiments, an arenavirus particle or a tri-segmented arenavirus particle as described herein may be based on LCMV Clone 13. In other embodiments, the vector generated to encode an arenavirus particle or a tri-segmented arenavirus particle as described herein LCMV MP strain.

[00365] In another embodiment, provided herein is a cell, wherein the cell comprises a cDNA or a vector system described above in this section. Cell lines derived from such cells, cultures comprising such cells, methods of culturing such cells infected are also provided herein. In certain embodiments, provided herein is a cell, wherein the cell comprises a cDNA of the arenavirus genomic segment that has been engineered to carry an ORF in a position other than the wild-type position of the ORF and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof. In some embodiments, the cell comprises the S segment and/or the L segment.

(ii) Tri-segmented Arenavirus Particle

[00366] In one embodiment, provided herein are nucleic acids that encode a tri-segmented arenavirus particle as described in Section 5.2.(b). In more specific embodiments, provided herein is a DNA nucleotide sequence or a set of DNA nucleotide sequences, for example, as set forth in Table 2 or Table 3. Host cells that comprise such nucleic acids are also provided Section 5.2(b).

[00367] In specific embodiments, provided herein is a cDNA consisting of a cDNA of the tri-segmented arenavirus particle that has been engineered to carry an ORF in a position other than the wild-type position of the ORF. In other embodiments, is a cDNA of the tri-segmented arenavirus particle that has been engineered to (i) carry an arenavirus ORF in a position other than the wild-type position of the ORF; and (ii) wherein the tri-segmented arenavirus particle encodes a heterologous ORF as described in Section 5.2(b).

[00368] In one embodiment, provided herein is a DNA expression vector system that together encode the tri-segmented arenavirus particle comprising a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof as described herein. Specifically, provided herein is a DNA expression vector system wherein one or more vectors encode three arenavirus genomic segments, namely, one L segment and two S segments or two L segments and one S segment of a tri-segmented arenavirus particle described herein. Such a vector system can encode a tumor antigen, tumor associated antigen or antigenic fragment thereof.

[00369] In another embodiment, provided herein is a cDNA of the arenavirus S segment(s) that has been engineered to carry an ORF in a position other than the wild-type position and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof that is part of or incorporated into a DNA expression system. In other embodiments, a cDNA of the arenavirus L segment(s) that has been engineered to carry an ORF in a position other than the wild-type position and a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof that is part of or incorporated into a DNA expression system. In certain embodiments, is a cDNA of the tri-segmented arenavirus particle that has been engineered to carry (i) an ORF in a position other than the wild-type position of the ORF; and (ii) an ORF encoding GP, NP, Z protein, or L protein has been

removed and replaced with a nucleotide sequence encoding a tumor antigen, tumor associated antigen or antigenic fragment thereof.

[00370] In certain embodiments, the cDNA provided herein can be derived from a particular strain of LCMV. Strains of LCMV include Clone 13, MP strain, Arm CA 1371, Arm E-250, WE, UBC, Traub, Pasteur, 810885, CH-5692, Marseille #12, HP65-2009, 200501927, 810362, 811316, 810316, 810366, 20112714, Douglas, GR01, SN05, CABN and their derivatives. In specific embodiments, the cDNA is derived from LCMV Clone 13. In other specific embodiments, the cDNA is derived from LCMV MP strain.

[00371] In certain embodiments, the vector generated to encode an arenavirus particle or a tri-segmented arenavirus particle as described herein may be based on a specific strain of LCMV. Strains of LCMV include Clone 13, MP strain, Arm CA 1371, Arm E-250, WE, UBC, Traub, Pasteur, 810885, CH-5692, Marseille #12, HP65-2009, 200501927, 810362, 811316, 810316, 810366, 20112714, Douglas, GR01, SN05, CABN and their derivatives. In certain embodiments, an arenavirus particle or a tri-segmented arenavirus particle as described herein may be based on LCMV Clone 13. In other embodiments, the vector generated to encode an arenavirus particle or a tri-segmented arenavirus particle as described herein LCMV MP strain.

[00372] In another embodiment, provided herein is a cell, wherein the cell comprises a cDNA or a vector system described above in this section. Cell lines derived from such cells, cultures comprising such cells, methods of culturing such cells infected are also provided herein. In certain embodiments, provided herein is a cell, wherein the cell comprises a cDNA of the tri-segmented arenavirus particle. In some embodiments, the cell comprises the S segment and/or the L segment.

(f) Methods of Use

[00373] Vaccines have been successful for preventing and/or treating infectious diseases, such as those for polio virus and measles. However, therapeutic immunization in the setting of established, chronic disease, including cancer has been less successful. The ability to generate an arenavirus particle that is used in combination with a chemotherapeutic agent represents a new novel vaccine strategy.

[00374] In certain embodiments, provided herein are methods of treating a neoplastic disease in a subject. Such methods can include administering to a subject in need thereof an arenavirus particle provided herein and a chemotherapeutic agent provided herein. In certain

embodiments, the arenavirus particle used in the methods is an infectious, replication-deficient arenavirus particle provided herein. In certain embodiments, the arenavirus particle used in the methods is a tri-segmented arenavirus particle provided herein, including an infectious, replication-deficient tri-segmented arenavirus particle or a replication-competent tri-segmented arenavirus particle. Thus, in certain embodiments, the arenavirus particle, including a tri-segmented arenavirus particle, used in the methods is replication-deficient, wherein the arenavirus particle is engineered to contain a genome comprising: (1) a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; and (2) the ability to amplify and express its genetic information in infected cells but unable to produce further infectious progeny particles in non-complementing cells. Moreover, in certain embodiments, a tri-segmented arenavirus particle used in the methods is replication-competent, wherein the arenavirus particle is engineered to contain a genome comprising: (1) a nucleotide sequence encoding a tumor antigen, tumor associated antigen or an antigenic fragment thereof; (2) the ability to amplify and express its genetic information in infected cells; and (3) the ability to produce further infectious progeny particles in normal, not genetically engineered cells.

[00375] In one embodiment, provided herein are methods of treating a neoplastic disease in a subject comprising administering to the subject one or more arenavirus particles expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof as provided herein or a composition thereof, and a chemotherapeutic agent provided herein. In a specific embodiment, a method for treating a neoplastic disease described herein comprises administering to a subject in need thereof a therapeutically effective amount of one or more arenavirus particles expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein or a composition thereof, and a chemotherapeutic agent provided herein. The subject can be a mammal, such as but not limited to a human, a mouse, a rat, a guinea pig, a domesticated animal, such as, but not limited to, a cow, a horse, a sheep, a pig, a goat, a cat, a dog, a hamster, a donkey. In a specific embodiment, the subject is a human.

[00376] In another embodiment, provided herein are methods for inducing an immune response against a neoplastic cell or tissue, such as a cancer cell or tumor, in a subject comprising administering to the subject an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein.

[00377] In another embodiment, the subjects to whom an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered have, are susceptible to, or are at risk for a neoplastic disease.

[00378] In another embodiment, the subjects to whom an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered have, are susceptible to, or are at risk for development of a neoplastic disease, such as cancer, or exhibit a pre-cancerous tissue lesion. In another specific embodiment, the subjects to whom arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered are diagnosed with a neoplastic disease, such as cancer, or exhibit a pre-cancerous tissue lesion.

[00379] In another embodiment, the subjects to whom an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered are suffering from, are susceptible to, or are at risk for, a neoplastic disease selected from, but not limited to, acute lymphoblastic leukemia; acute lymphoblastic lymphoma; acute lymphocytic leukaemia; acute myelogenous leukemia; acute myeloid leukemia (adult / childhood); adrenocortical carcinoma; AIDS-related cancers; AIDS-related lymphoma; anal cancer; appendix cancer; astrocytomas; atypical teratoid/rhabdoid tumor; basal-cell carcinoma; bile duct cancer, extrahepatic (cholangiocarcinoma); bladder cancer; bone osteosarcoma/malignant fibrous histiocytoma; brain cancer (adult / childhood); brain tumor, cerebellar astrocytoma (adult / childhood); brain tumor, cerebral astrocytoma/malignant glioma brain tumor; brain tumor, ependymoma; brain tumor, medulloblastoma; brain tumor, supratentorial primitive neuroectodermal tumors; brain tumor, visual pathway and hypothalamic glioma; brainstem glioma; breast cancer; bronchial adenomas/carcinoids; bronchial tumor; Burkitt lymphoma; cancer of childhood; carcinoid gastrointestinal tumor; carcinoid tumor; carcinoma of adult, unknown primary site; carcinoma of unknown primary; central nervous system embryonal tumor; central nervous system lymphoma, primary; cervical cancer; childhood adrenocortical carcinoma; childhood cancers; childhood cerebral astrocytoma; chordoma, childhood; chronic

lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloid leukemia; chronic myeloproliferative disorders; colon cancer; colorectal cancer; craniopharyngioma; cutaneous T-cell lymphoma; desmoplastic small round cell tumor; emphysema; endometrial cancer; ependymblastoma; ependymoma; esophageal cancer; ewing's sarcoma in the Ewing family of tumors; extracranial germ cell tumor; extragonadal germ cell tumor; extrahepatic bile duct cancer; gallbladder cancer; gastric (stomach) cancer; gastric carcinoid; gastrointestinal carcinoid tumor; gastrointestinal stromal tumor; germ cell tumor: extracranial, extragonadal, or ovarian gestational trophoblastic tumor; gestational trophoblastic tumor, unknown primary site; glioma; glioma of the brain stem; glioma, childhood visual pathway and hypothalamic; hairy cell leukemia; head and neck cancer; heart cancer; hepatocellular (liver) cancer; hodgkin lymphoma; hypopharyngeal cancer; hypothalamic and visual pathway glioma; intraocular melanoma; islet cell carcinoma (endocrine pancreas); Kaposi Sarcoma; kidney cancer (renal cell cancer); langerhans cell histiocytosis; laryngeal cancer; lip and oral cavity cancer; liposarcoma; liver cancer (primary); lung cancer, non-small cell; lung cancer, small cell; lymphoma, primary central nervous system; macroglobulinemia, Waldenström; male breast cancer; malignant fibrous histiocytoma of bone/osteosarcoma; medulloblastoma; medulloepithelioma; melanoma; melanoma, intraocular (eye); merkel cell cancer; merkel cell skin carcinoma; mesothelioma; mesothelioma, adult malignant; metastatic squamous neck cancer with occult primary; mouth cancer; multiple endocrine neoplasia syndrome; multiple myeloma/plasma cell neoplasm; mycosis fungoides, myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; myelogenous leukemia, chronic; myeloid leukemia, adult acute; myeloid leukemia, childhood acute; myeloma, multiple (cancer of the bone-marrow); myeloproliferative disorders, chronic; nasal cavity and paranasal sinus cancer; nasopharyngeal carcinoma; neuroblastoma, non-small cell lung cancer; non-hodgkin lymphoma; oligodendroglioma; oral cancer; oral cavity cancer; oropharyngeal cancer; osteosarcoma/malignant fibrous histiocytoma of bone; ovarian cancer; ovarian epithelial cancer (surface epithelial-stromal tumor); ovarian germ cell tumor; ovarian low malignant potential tumor; pancreatic cancer; pancreatic cancer, islet cell; papillomatosis; paranasal sinus and nasal cavity cancer; parathyroid cancer; penile cancer; pharyngeal cancer; pheochromocytoma; pineal astrocytoma; pineal germinoma; pineal parenchymal tumors of intermediate differentiation; pineoblastoma and supratentorial primitive neuroectodermal tumors; pituitary tumor; pituitary adenoma; plasma cell neoplasia/multiple myeloma; pleuropulmonary

blastoma; primary central nervous system lymphoma; prostate cancer; rectal cancer; renal cell carcinoma (kidney cancer); renal pelvis and ureter, transitional cell cancer; respiratory tract carcinoma involving the NUT gene on chromosome 15; retinoblastoma; rhabdomyosarcoma, childhood; salivary gland cancer; sarcoma, Ewing family of tumors; Sézary syndrome; skin cancer (melanoma); skin cancer (non-melanoma); small cell lung cancer; small intestine cancer soft tissue sarcoma; soft tissue sarcoma; spinal cord tumor; squamous cell carcinoma; squamous neck cancer with occult primary, metastatic; stomach (gastric) cancer; supratentorial primitive neuroectodermal tumor; T-cell lymphoma, cutaneous (Mycosis Fungoides and Sézary syndrome); testicular cancer; throat cancer; thymoma; thymoma and thymic carcinoma; thyroid cancer; thyroid cancer, childhood; transitional cell cancer of the renal pelvis and ureter; urethral cancer; uterine cancer, endometrial; uterine sarcoma; vaginal cancer; vulvar cancer; and Wilms Tumor.

[00380] In another embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject of any age group suffering from, are susceptible to, or are at risk for a neoplastic disease. In a specific embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject with a compromised immune system, a pregnant subject, a subject undergoing an organ or bone marrow transplant, a subject taking immunosuppressive drugs, a subject undergoing hemodialysis, a subject who has cancer, or a subject who is suffering from, are susceptible to, or are at risk for a neoplastic disease. In a more specific embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject who is a child of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 years of age suffering from, are susceptible to, or are at risk for a neoplastic disease. In yet another specific embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject who is an infant suffering from, is susceptible to, or is at risk for a neoplastic disease. In yet another specific embodiment, an arenavirus particle expressing a tumor antigen, tumor

associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject who is an infant of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months of age suffering from, is susceptible to, or is at risk for a neoplastic disease. In yet another specific embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to an elderly subject who is suffering from, is susceptible to, or is at risk for a neoplastic disease. In a more specific embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject who is a senior subject of 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 years of age. Provided herein is a method for preventing a cancer in a subject susceptible to, or is at risk for a neoplastic disease.

[00381] In another embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to subjects with a heightened risk of cancer metastasis. In a specific embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to subjects in the neonatal period with a neonatal and therefore immature immune system.

[00382] In another embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject having grade 0 (*i.e.*, in situ neoplasm), grade 1, grade 2, grade 3 or grade 4 cancer or a subcategory thereof, such as grade 3A, 3B, or 3C, or an equivalent thereof.

[00383] In another embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject having cancer at a Tumor, Node, Metastasis (TNM) stage of any combination selected from Tumor T1, T2, T3, and T4, and Node N0, N1, N2, or N3, and Metastasis M0 and M1.

[00384] Successful treatment of a cancer patient can be assessed as prolongation of expected survival, induction of an anti-tumor immune response, or improvement of a particular characteristic of a cancer. Examples of characteristics of a cancer that might be improved include tumor size (*e.g.*, T0, T1, or T1-4), state of metastasis (*e.g.*, M0, M1), number of observable tumors, node involvement (*e.g.*, N0, N1-4, Nx), grade (*i.e.*, grades 1, 2, 3, or 4), stage (*e.g.*, 0, I, II, III, or IV), presence or concentration of certain markers on the cells or in bodily fluids (*e.g.*, AFP, B2M, beta-HCG, BTA, CA 15-3, CA 27.29, CA 125, CA 72.4, CA 19-9, calcitonin, CEA, chromograinin A, EGFR, hormone receptors, HER2, HCG, immunoglobulins, NSE, NMP22, PSA, PAP, PSMA, S-100, TA-90, and thyroglobulin), and/or associated pathologies (*e.g.*, ascites or edema) or symptoms (*e.g.*, cachexia, fever, anorexia, or pain). The improvement, if measureable by percent, can be at least 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, or 90% (*e.g.*, survival, or volume or linear dimensions of a tumor).

[00385] In another embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject having a dormant cancer (*e.g.*, the subject is in remission). Thus, provided herein is a method for preventing reactivation of a cancer. Also provided herein are methods for reducing the frequency of reoccurrence of a cancer.

[00386] In another embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject having a recurrent a cancer.

[00387] In another embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject with a genetic predisposition for a cancer. In another embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to a subject with risk factors. Exemplary risk factors include, aging, tobacco, sun exposure, radiation exposure, chemical exposure, family history, alcohol, poor diet, lack of physical activity, or being overweight.

[00388] In another embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is administered to subjects who suffer from one or more types of cancers. In other embodiments, any type of neoplastic disease, such as cancer, that is susceptible to treatment with the compositions described herein might be targeted.

[00389] In another embodiment, administering an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided or a composition thereof to subjects confer cell-mediated immunity (CMI) against a neoplastic cell or tumor, such as a cancer cell or tumor. Without being bound by theory, in another embodiment, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided or a composition thereof infects and expresses antigens of interest in antigen presenting cells (APC) of the host (*e.g.*, macrophages) for direct presentation of antigens on Major Histocompatibility Complex (MHC) class I and II. In another embodiment, administering an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, to subjects induces plurifunctional IFN- γ and TNF- α co-producing cancer-specific CD4⁺ and CD8⁺ T cell responses (IFN- γ is produced by CD4⁺ and CD8⁺ T cells and TNF- α is produced by CD4⁺ T cells) of high magnitude to treat a neoplastic disease.

[00390] In another embodiment, administering an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein increases or improves one or more clinical outcome for cancer treatment. Non-limiting examples of such outcomes are overall survival, progression-free survival, time to progression, time to treatment failure, event-free survival, time to next treatment, overall response rate and duration of response. The increase or improvement in one or more of the clinical outcomes can be by at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or more, compared to a patient or group of patients having the same neoplastic disease in the absence of such treatment.

[00391] Changes in cell-mediated immunity (CMI) response function against a neoplastic cell or tumor, including a cancer cell or tumor, induced by administering an arenavirus particle

expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided, or a composition thereof, in subjects can be measured by any assay known to the skilled artisan including, but not limited to flow cytometry (see, *e.g.*, Perfetto S.P. et al., Nat Rev Immun. 2004; 4(8):648-55), lymphocyte proliferation assays (see, *e.g.*, Bonilla F.A. et al., Ann Allergy Asthma Immunol. 2008; 101:101-4; and Hicks M.J. et al., Am J Clin Pathol. 1983; 80:159-63), assays to measure lymphocyte activation including determining changes in surface marker expression following activation of measurement of cytokines of T lymphocytes (see, *e.g.*, Caruso A. et al., Cytometry. 1997;27:71-6), ELISPOT assays (see, *e.g.*, Czerkinsky C.C. et al., J Immunol Methods. 1983; 65:109-121; and Hutchings P.R. et al., J Immunol Methods. 1989; 120:1-8), or Natural killer cell cytotoxicity assays (see, *e.g.*, Bonilla F.A. et al., Ann Allergy Asthma Immunol. 2005 May; 94(5 Suppl 1):S1-63).

[00392] Chemotherapeutic agents described herein can be alkylating agents (*e.g.*, cyclophosphamide), platinum-based therapeutics, antimetabolites, topoisomerase inhibitors, cytotoxic antibiotics, intercalating agents, mitosis inhibitors, taxanes, or combinations of two or more thereof. In certain embodiments, the alkylating agent is a nitrogen mustard, a nitrosourea, an alkyl sulfonate, a non-classical alkylating agent, or a triazene. In certain embodiments, the chemotherapeutic agent comprises one or more of cyclophosphamide, thiotepa, mechlorethamine (chlormethine/mustine), uramustine, melphalan, chlorambucil, ifosfamide, chlornaphazine, cholophosphamide, estramustine, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, bendamustine, busulfan, improsulfan, piposulfan, carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine, streptozucin, cisplatin, carboplatin, nedaplatin, oxaliplatin, satraplatin, triplatin tetranitrate, procarbazine, altretamine, dacarbazine, mitozolomide, temozolomide, paclitaxel, docetaxel, vinblastine, vincristine, vinorelbine, cabazitaxel, dactinomycin (actinomycin D), calicheamicin, dynemicin, amsacrine, doxorubicin, daunorubicin, epirubicin, mitoxantrone, idarubicin, pirarubicin, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolomelamine, bullatacin, bullatacinone, camptothecin, topotecan, bryostatin, callystatin, CC-1065, adozelesin, carzelesin, bizelesin, cryptophycin, dolastatin, duocarmycin, KW-2189, CB1-TM1, eleutherobin, pancratistatin, sarcodictyin, spongistatin, clodronate, esperamicin, neocarzinostatin chromophore, aclacinomycin, anthramycin, azaserine, bleomycin, cactinomycin, carabycin, carminomycin, carzinophilin,

chromomycinis, detorubicin, 6-diazo-5-oxo-L-norleucine, esorubicin, idarubicin, marcellomycin, mitomycin, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, methotrexate, 5-fluorouracil (5-FU), denopterin, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiothane, testolactone, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elformithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansine, ansamitocins, mitoguazone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, PSK polysaccharide complex, razoxane, rhizoxin, sizofiran, spirogermanium, tenuazonic acid, triaziquone, 2,2',2''-trichlorotriethylamine; T-2 toxin, verracurin A, roridin A and anguidine, urethan, vindesine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside ("Ara-C"), etoposide (VP-16), vinorelbine, novantrone, teniposide, edatrexate, aminopterin, xeloda, ibandronate, irinotecan (e.g., CPT-11), topoisomerase inhibitor RFS 2000, difluoromethylthylornithine (DMFO), retinoic acid, capecitabine, plicomycin, gemcitabine, navelbine, transplatinum, and pharmaceutically acceptable salts, acids, or derivatives of any of the above. In specific embodiments, the chemotherapeutic agent comprises cyclophosphamide. In certain embodiments, the nitrogen mustard is mechlorethamine, cyclophosphamide, melphalan, chlorambucil, ifosfamide, or busulfan. In certain embodiments, the chemotherapeutic agent alkylates DNA. In certain embodiments, the chemotherapeutic agent alkylates DNA, resulting in the formation of interstrand cross-links ("ICLs").

[00393] In certain embodiments, chemotherapeutic agents described herein are used in combination with an immune checkpoint inhibitor that inhibits, decreases or interferes with the activity of a negative checkpoint regulator. In certain embodiments, the negative checkpoint regulator is selected from the group consisting of Cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD80, CD86, Programmed cell death 1 (PD-1), Programmed cell death ligand 1 (PD-L1), Programmed cell death ligand 2 (PD-L2), Lymphocyte activation gene-3 (LAG-3; also known as CD223), Galectin-3, B and T lymphocyte attenuator (BTLA), T-cell membrane protein 3

(TIM3), Galectin-9 (GAL9), B7-H1, B7-H3, B7-H4, T-Cell immunoreceptor with Ig and ITIM domains (TIGIT/Vstm3/WUCAM/VSIG9), V-domain Ig suppressor of T-Cell activation (VISTA), Glucocorticoid-induced tumor necrosis factor receptor-related (GITR) protein, Herpes Virus Entry Mediator (HVEM), OX40, CD27, CD28, CD137. CGEN-15001T, CGEN-15022, CGEN-15027, CGEN-15049, CGEN-15052, and CGEN-15092. In certain embodiments, the immune checkpoint inhibitor is an anti-PD-1 antibody.

[00394] In certain embodiments, an arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, and a chemotherapeutic agent provided herein is preferably administered in multiple injections (*e.g.*, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 25, 30, 40, 45, or 50 injections) or by continuous infusion (*e.g.*, using a pump) at multiple sites (*e.g.*, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, or 14 sites). In certain embodiments, the arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, is administered in two or more separate injections over a 6-month period, a 12-month period, a 24-month period, or a 48-month period. In certain embodiments, the arenavirus particle expressing a tumor antigen, tumor associated antigen or an antigenic fragment thereof provided herein, or a composition thereof, is administered with a first dose at an elected date, a second dose at least 2 months after the first dose, and a third dose 6 months after the first dose.

[00395] In one example, cutaneous injections are performed at multiple body sites to reduce extent of local skin reactions. On a given vaccination day, the patient receives the assigned total dose administered from one syringe in 3 to 5 separate intradermal injections of the dose (*e.g.*, at least 0.4 ml, 0.2 ml, or 0.1 ml) each in an extremity spaced at least about 5 cm (*e.g.*, at least 4.5, 5, 6, 7, 8, 9, or cm) at needle entry from the nearest neighboring injection. On subsequent vaccination days, the injection sites are rotated to different limbs in a clockwise or counter-clockwise manner.

[00396] In certain embodiments, the methods further comprise co-administration of the arenavirus particle provided herein and a chemotherapeutic agent. In certain embodiments, the co-administration is simultaneous. In another embodiment, the arenavirus particle is administered prior to administration of the chemotherapeutic agent. In other embodiments, the arenavirus particle is administered after administration of the chemotherapeutic agent. In certain embodiments, the interval between administration of the arenavirus particle and the

chemotherapeutic agent is about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, or about 12 hours. In certain embodiments, the interval between administration of the arenavirus particle and the chemotherapeutic agent is about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks. In certain embodiments, the interval between administration of the arenavirus particle and the chemotherapeutic agent is about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, or about 6 months. In some embodiments, the method further includes administering at least one additional therapy.

[00397] In another embodiment, two arenavirus particles are administered in a treatment regime at molar ratios ranging from about 1:1 to 1:1000, in particular including: 1:1 ratio, 1:2 ratio, 1:5 ratio, 1:10 ratio, 1:20 ratio, 1:50 ratio, 1:100 ratio, 1:200 ratio, 1:300 ratio, 1:400 ratio, 1:500 ratio, 1:600 ratio, 1:700 ratio, 1:800 ratio, 1:900 ratio, 1:1000 ratio.

[00398] In certain embodiments, provided herein is a method of treating neoplastic disease wherein a first arenavirus particle is administered first as a “prime,” and a second arenavirus particle is administered as a “boost.” The first and the second arenavirus particles can express the same or different tumor antigens, tumor associated antigens or antigenic fragments thereof. Alternatively, or additionally, some certain embodiments, the “prime” and “boost” administration are performed with an arenavirus particle derived from different species. In certain specific embodiments, the “prime” administration is performed with an arenavirus particle derived from LCMV, and the “boost” is performed with an arenavirus particle derived from Junin virus. In certain specific embodiments, the “prime” administration is performed with an arenavirus particle derived from Junin virus, and the “boost” is performed with an arenavirus particle derived from LCMV. In certain embodiments, the “prime” administration is performed with an arenavirus particle derived from Pichinde virus, and the “boost” is performed with an arenavirus particle derived from LCMV. In certain embodiments, the “prime” administration is performed with an arenavirus particle derived from Pichinde virus, and the “boost” is performed with an arenavirus particle derived from Junin virus. In certain embodiments, the “prime” administration is performed with an arenavirus particle derived from LCMV, and the “boost” is

performed with an arenavirus particle derived from Pichinde virus. In certain embodiments, the “prime” administration is performed with an arenavirus particle derived from Junin virus, and the “boost” is performed with an arenavirus particle derived from Pichinde virus. In certain embodiments, the “prime” administration and/or the “boost” administration are performed in combination with the administration of an immunomodulatory peptide, polypeptide, or protein. In certain embodiments, the “prime” administration and/or the “boost” administration are performed in combination with the administration of a chemotherapeutic agent.

[00399] In certain embodiments, administering a first arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof, followed by administering a second arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof results in a greater antigen specific CD8⁺ T cell response than administering a single arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof. In certain embodiments, the antigen specific CD8⁺ T cell count increases by 50%, 100%, 150% or 200% after the second administration compared to the first administration. In certain embodiments, administering a third arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof results in a greater antigen specific CD8⁺ T cell response than administering two consecutive arenavirus particles expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof. In certain embodiments, the antigen specific CD8⁺ T cell count increases by about 50%, about 100%, about 150%, about 200% or about 250% after the third administration compared to the first administration.

[00400] In certain embodiments, provided herein are methods for treating a neoplastic disease comprising administering two or more arenavirus particles, wherein the two or more arenavirus particles are homologous, and wherein the time interval between each administration is about 1 week, about 2 weeks, about 3 week, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about 12 months, about 18 months, or about 24 months.

[00401] In certain embodiments, administering a first arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof and a second, heterologous, arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof elicits a greater CD8⁺ T cell response than administering a first arenavirus particle

expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof and a second, homologous, arenavirus particle expressing a tumor antigen, tumor associated antigen or antigenic fragment thereof.

(g) Compositions, Administration, and Dosage

[00402] In certain embodiments, immunogenic compositions (*e.g.*, vaccine formulations), and pharmaceutical compositions comprising an arenavirus particle provided herein can be used with the methods and compositions provided herein, such as combinations with a chemotherapeutic agent. Such vaccines, immunogenic compositions and pharmaceutical compositions can be formulated according to standard procedures in the art.

[00403] In another embodiment, provided herein are compositions comprising an infectious, replication-deficient arenavirus particle described herein, and, in certain embodiments, a chemotherapeutic agent provided herein. Such compositions can be used in methods of treating a neoplastic disease. In another specific embodiment, the immunogenic compositions provided herein can be used to induce an immune response in a host to whom the composition is administered. The immunogenic compositions described herein can be used as vaccines and can accordingly be formulated as pharmaceutical compositions. In a specific embodiment, the immunogenic compositions described herein are used in the treatment of a neoplastic disease a subject (*e.g.*, human subject). In other embodiments, the vaccine, immunogenic composition or pharmaceutical composition are suitable for veterinary and/or human administration.

[00404] In certain embodiments, provided herein are immunogenic compositions comprising an arenavirus particle (or a combination of different arenavirus particles) as described herein. In certain embodiments, such an immunogenic composition further comprises a pharmaceutically acceptable excipient. In certain embodiments, such an immunogenic composition further comprises an adjuvant. The adjuvant for administration in combination with a composition described herein may be administered before, concomitantly with, or after administration of said composition. In some embodiments, the term “adjuvant” refers to a compound that when administered in conjunction with or as part of a composition described herein augments, enhances and/or boosts the immune response to an infectious, replication-deficient arenavirus particle, but when the compound is administered alone does not generate an immune response to the infectious, replication-deficient arenavirus particle. In some

embodiments, the adjuvant generates an immune response to the infectious, replication-deficient arenavirus particle and does not produce an allergy or other adverse reaction. Adjuvants can enhance an immune response by several mechanisms including, *e.g.*, lymphocyte recruitment, stimulation of B and/or T cells, and stimulation of macrophages. When a vaccine or immunogenic composition of the invention comprises adjuvants or is administered together with one or more adjuvants, the adjuvants that can be used include, but are not limited to, mineral salt adjuvants or mineral salt gel adjuvants, particulate adjuvants, microparticulate adjuvants, mucosal adjuvants, and immunostimulatory adjuvants. Examples of adjuvants include, but are not limited to, aluminum salts (alum) (such as aluminum hydroxide, aluminum phosphate, and aluminum sulfate), 3 De-O-acylated monophosphoryl lipid A (MPL) (see GB 2220211), MF59 (Novartis), AS03 (GlaxoSmithKline), AS04 (GlaxoSmithKline), polysorbate 80 (Tween 80; ICL Americas, Inc.), imidazopyridine compounds (see International Application No. PCT/US2007/064857, published as International Publication No. WO2007/109812), imidazoquinoxaline compounds (see International Application No. PCT/US2007/064858, published as International Publication No. WO2007/109813) and saponins, such as QS21 (see Kensil et al., in Vaccine Design: The Subunit and Adjuvant Approach (eds. Powell & Newman, Plenum Press, NY, 1995); U.S. Pat. No. 5,057,540). In some embodiments, the adjuvant is Freund's adjuvant (complete or incomplete). Other adjuvants are oil in water emulsions (such as squalene or peanut oil), optionally in combination with immune stimulants, such as monophosphoryl lipid A (see Stoute et al., N. Engl. J. Med. 336, 86-91 (1997)).

[00405] The compositions comprise the infectious, replication-deficient arenavirus particles described herein alone or together with a pharmaceutically acceptable carrier and/or a chemotherapeutic agent. Suspensions or dispersions of genetically engineered arenavirus particles, especially isotonic aqueous suspensions or dispersions, can be used. The pharmaceutical compositions may be sterilized and/or may comprise excipients, *e.g.*, preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers and are prepared in a manner known per se, for example by means of conventional dispersing and suspending processes. In certain embodiments, such dispersions or suspensions may comprise viscosity-regulating agents. The suspensions or dispersions are kept at temperatures around 2-8°C, or preferentially for longer storage may be frozen and then thawed shortly before use. For injection, the vaccine or immunogenic

preparations may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[00406] In certain embodiments, the compositions described herein additionally comprise a preservative, *e.g.*, the mercury derivative thimerosal. In a specific embodiment, the pharmaceutical compositions described herein comprise 0.001% to 0.01% thimerosal. In other embodiments, the pharmaceutical compositions described herein do not comprise a preservative.

[00407] The pharmaceutical compositions comprise from about 10^3 to about 10^{11} focus forming units of the genetically engineered arenavirus particles. Unit dose forms for parenteral administration are, for example, ampoules or vials, *e.g.*, vials containing from about 10^3 to 10^{10} focus forming units or 10^5 to 10^{15} physical particles of genetically engineered arenavirus particles.

[00408] In another embodiment, a vaccine or immunogenic composition provided herein is administered to a subject by, including but not limited to, oral, intradermal, intramuscular, intraperitoneal, intravenous, topical, subcutaneous, percutaneous, intranasal and inhalation routes, and via scarification (scratching through the top layers of skin, *e.g.*, using a bifurcated needle). Specifically, subcutaneous, intramuscular or intravenous routes can be used.

[00409] For administration intranasally or by inhalation, the preparation for use according to the present invention can be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflators may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[00410] The dosage of the active ingredient depends upon the type of vaccination and upon the subject, and their age, weight, individual condition, the individual pharmacokinetic data, and the mode of administration.

[00411] In certain embodiments, the compositions can be administered to the patient in a single dosage comprising a therapeutically effective amount of the arenavirus particle and/or a therapeutically effective amount of a chemotherapeutic agent. In some embodiments, the

arenavirus particle can be administered to the patient in a single dose comprising an arenavirus particle and a chemotherapeutic agent, each in a therapeutically effective amount.

[00412] In certain embodiments, the composition is administered to the patient as a single dose followed by a second dose three to six weeks later. In accordance with these embodiments, the booster inoculations may be administered to the subjects at six to twelve month intervals following the second inoculation. In certain embodiments, the booster inoculations may utilize a different arenavirus particle or composition thereof. In some embodiments, the administration of the same composition as described herein may be repeated and separated by at least 1 day, 2 days, 3 days, 4 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or at least 6 months.

[00413] In certain embodiments, the vaccine, immunogenic composition, or pharmaceutical composition comprising an arenavirus particle can be used as a live vaccination. Exemplary doses for a live arenavirus particle may vary from 10-100, or more, PFU of live virus per dose. In some embodiments, suitable dosages of an arenavirus particle or the tri-segmented arenavirus particle are 10^2 , 5×10^2 , 10^3 , 5×10^3 , 10^4 , 5×10^4 , 10^5 , 5×10^5 , 10^6 , 5×10^6 , 10^7 , 5×10^7 , 10^8 , 5×10^8 , 1×10^9 , 5×10^9 , 1×10^{10} , 5×10^{10} , 1×10^{11} , 5×10^{11} or 10^{12} pfu, and can be administered to a subject once, twice, three or more times with intervals as often as needed. In another embodiment, a live arenavirus is formulated such that a 0.2-mL dose contains $10^{6.5}$ - $10^{7.5}$ fluorescent focal units of live arenavirus particle. In another embodiment, an inactivated vaccine is formulated such that it contains about 15 μ g to about 100 μ g, about 15 μ g to about 75 μ g, about 15 μ g to about 50 μ g, or about 15 μ g to about 30 μ g of an arenavirus

[00414] Also provided are processes and uses of an arenavirus particle and a chemotherapeutic agent for the manufacture of vaccines in the form of pharmaceutical preparations, which comprise the arenavirus particle and the chemotherapeutic agent as an active ingredient. Still further provided is a combination of an arenavirus particle provided herein and a chemotherapeutic agent provided herein for use in the treatment of a neoplastic disease described herein. In certain embodiments, the combination is in the same pharmaceutical composition. In certain embodiments, the combination is not in the same pharmaceutical composition, such as when the arenavirus particle and the chemotherapeutic agent are to be separately administered. The pharmaceutical compositions of the present application are prepared in a manner known per se, for example by means of conventional mixing and/or dispersing processes.

[00415] Also provided herein are kits that can be used to perform the methods described herein. In certain embodiments, the kit provided herein can include one or more containers. These containers can hold for storage the compositions (*e.g.*, pharmaceutical, immunogenic or vaccine composition) provided herein. Also included in the kit are instructions for use. These instructions describe, in sufficient detail, a treatment protocol for using the compositions contained therein. For example, the instructions can include dosing and administration instructions as provided herein for the methods of treating a neoplastic disease.

[00416] In certain embodiments, a kit provided herein includes containers that each contains the active ingredients for performing the methods described herein. Thus, in certain embodiments, the kit provided herein includes two or more containers and instructions for use, wherein one of the containers comprises an infectious, replication-deficient arenavirus particle provided herein and another container that comprises a chemotherapeutic agent provided herein.

(h) Assays

(i) Arenavirus Detection Assays

[00417] The skilled artisan could detect an arenavirus genomic segment or tri-segmented arenavirus particle, as described herein using techniques known in the art. For example, RT-PCR can be used with primers that are specific to an arenavirus to detect and quantify an arenavirus genomic segment that has been engineered to carry an ORF in a position other than the wild-type position of the ORF or a tri-segmented arenavirus particle. Western blot, ELISA, radioimmunoassay, immunoprecipitation, immunocytochemistry, or immunocytochemistry in conjunction with FACS can be used to quantify the gene products of the arenavirus genomic segment or tri-segmented arenavirus particle.

(ii) Assay to Measure Infectivity

[00418] Any assay known to the skilled artisan can be used for measuring the infectivity of an arenavirus vector preparation. For example, determination of the virus/vector titer can be done by a “focus forming unit assay” (FFU assay). In brief, complementing cells, *e.g.*, MC57 cells are plated and inoculated with different dilutions of a virus/vector sample. After an incubation period, to allow cells to form a monolayer and virus to attach to cells, the monolayer is covered with Methylcellulose. When the plates are further incubated, the original infected cells release viral progeny. Due to the Methylcellulose overlay the spread of the new viruses is

restricted to neighboring cells. Consequently, each infectious particle produces a circular zone of infected cells called a Focus. Such Foci can be made visible and by that countable using antibodies against LCMV- NP or another protein expressed by the arenavirus particle or the tri-segmented arenavirus particle and a HRP-based color reaction. The titer of a virus / vector can be calculated in focus-forming units per milliliter (FFU/mL).

(iii) Growth of an Arenavirus Particle

[00419] Growth of an arenavirus particle described herein can be assessed by any method known in the art or described herein (*e.g.*, cell culture). Viral growth may be determined by inoculating serial dilutions of an arenavirus particle described herein into cell cultures (*e.g.*, Vero cells or BHK-21 cells). After incubation of the virus for a specified time, the virus is isolated using standard methods.

(iv) Serum ELISA

[00420] Determination of the humoral immune response upon vaccination of animals (*e.g.*, mice, guinea pigs) can be done by antigen-specific serum ELISA's (enzyme-linked immunosorbent assays). In brief, plates are coated with antigen (*e.g.*, recombinant protein), blocked to avoid unspecific binding of antibodies and incubated with serial dilutions of sera. After incubation, bound serum-antibodies can be detected, *e.g.*, using an enzyme-coupled anti-species (*e.g.*, mouse, guinea pig)-specific antibody (detecting total IgG or IgG subclasses) and subsequent color reaction. Antibody titers can be determined as, *e.g.*, endpoint geometric mean titer.

Immunocapture ELISA (IC-ELISA) may also be performed (*see* Shanmugham et al., 2010, Clin. Vaccine Immunol. 17(8):1252-1260), wherein the capture agents are cross-linked to beads.

(v) Assay to Measure the Neutralizing Activity of Induced Antibodies

[00421] Determination of the neutralizing antibodies in sera is performed with the following cell assay using ARPE-19 cells from ATCC and a GFP-tagged virus. In addition supplemental guinea pig serum as a source of exogenous complement is used. The assay is started with seeding of 6.5×10^3 cells/well (50 μ l/well) in a 384 well plate one or two days before using for neutralization. The neutralization is done in 96-well sterile tissue culture plates without cells for 1 h at 37 °C. After the neutralization incubation step the mixture is added to the cells and incubated for additional 4 days for GFP-detection with a plate reader. A positive

neutralizing human sera is used as assay positive control on each plate to check the reliability of all results. Titers (EC50) are determined using a 4 parameter logistic curve fitting. As additional testing the wells are checked with a fluorescence microscope.

(A) Plaque Reduction Assay

[00422] In brief, plaque reduction (neutralization) assays for LCMV can be performed by use of a replication-competent or –deficient LCMV that is tagged with green fluorescent protein, 5% rabbit serum may be used as a source of exogenous complement, and plaques can be enumerated by fluorescence microscopy. Neutralization titers may be defined as the highest dilution of serum that results in a 50%, 75%, 90% or 95% reduction in plaques, compared with that in control (pre-immune) serum samples. qPCR LCMV RNA genomes are isolated using QIAamp Viral RNA mini Kit (QIAGEN), according to the protocol provided by the manufacturer. LCMV RNA genome equivalents are detected by quantitative PCR carried out on an StepOnePlus Real Time PCR System (Applied Biosystems) with SuperScript® III Platinum® One-Step qRT-PCR Kit (Invitrogen) and primers and probes (FAM reporter and NFQ-MGB Quencher) specific for part of the LCMV NP coding region or another genomic stretch of the arenavirus particle or the tri-segmented arenavirus particle. The temperature profile of the reaction may be : 30 min at 60 °C, 2 min at 95 °C, followed by 45 cycles of 15 s at 95 °C, 30 s at 56 °C. RNA can be quantified by comparison of the sample results to a standard curve prepared from a log10 dilution series of a spectrophotometrically quantified, in vitro-transcribed RNA fragment, corresponding to a fragment of the LCMV NP coding sequence or another genomic stretch of the arenavirus particle or the tri-segmented arenavirus particle containing the primer and probe binding sites.

(B) Neutralization Assay in guinea pig lung fibroblast (GPL) cells

[00423] In brief, serial dilutions of test and control (pre-vaccination) sera were prepared in GPL complete media with supplemental rabbit serum (1%) as a source of exogenous complement. The dilution series spanned 1:40 through 1:5120. Serum dilutions were incubated with eGFP tagged virus (100-200 pfu per well) for 30 min at 37°C, and then transferred to 12-well plates containing confluent GPL cells. Samples were processed in triplicate. After 2 hours incubation at 37°C the cells were washed with PBS, re-fed with GPL complete media and incubated at 37°C / 5% CO₂ for 5 days. Plaques were visualized by fluorescence microscopy,

counted, and compared to control wells. That serum dilution resulting in a 50% reduction in plaque number compared to controls was designated as the neutralizing titer.

(C) Western Blotting

[00424] Infected cells grown in tissue culture flasks or in suspension are lysed at indicated timepoints post infection using RIPA buffer (Thermo Scientific) or used directly without cell-lysis. Samples are heated to 99 °C for 10 minutes with reducing agent and NuPage LDS Sample buffer (NOVEX) and chilled to room temperature before loading on 4-12% SDS-gels for electrophoresis. Proteins are blotted onto membranes using Invitrogens iBlot Gel transfer Device and visualized by Ponceau staining. Finally, the preparations are probed with a primary antibodies directed against proteins of interest and alkaline phosphatase conjugated secondary antibodies followed by staining with 1-Step NBT/BCIP solution (INVITROGEN).

(D) MHC-Peptide Multimer Staining Assay for Detection of Antigen-Specific CD8⁺ T-cell proliferation

[00425] Any assay known to the skilled artisan can be used to test antigen-specific CD8⁺ T-cell responses. For example, the MHC-peptide tetramer staining assay can be used (see, *e.g.*, Altman J.D. *et al.*, Science. 1996; 274:94-96; and Murali-Krishna K. *et al.*, Immunity. 1998; 8:177-187). Briefly, the assay comprises the following steps, a tetramer assay is used to detect the presence of antigen specific T-cells. In order for a T-cell to detect the peptide to which it is specific, it must both recognize the peptide and the tetramer of MHC molecules custom made for a defined antigen specificity and MHC haplotype of T-cells (typically fluorescently labeled). The tetramer is then detected by flow cytometry via the fluorescent label.

(E) ELISPOT Assay for Detection of Antigen-Specific CD4⁺ T-cell Proliferation.

[00426] Any assay known to the skilled artisan can be used to test antigen-specific CD4⁺ T-cell responses. For example, the ELISPOT assay can be used (see, *e.g.*, Czerkinsky C.C. *et al.*, J Immunol Methods. 1983; 65:109-121; and Hutchings P.R. *et al.*, J Immunol Methods. 1989; 120:1-8). Briefly, the assay comprises the following steps: An immunospot plate is coated with an anti-cytokine antibody. Cells are incubated in the immunospot plate. Cells secrete cytokines and are then washed off. Plates are then coated with a second biotinylated-anticytokine antibody and visualized with an avidin-HRP system.

(F) Intracellular Cytokine Assay for Detection of Functionality of CD8+ and CD4+ T-cell Responses.

[00427] Any assay known to the skilled artisan can be used to test the functionality of CD8+ and CD4+ T cell responses. For example, the intracellular cytokine assay combined with flow cytometry can be used (see, *e.g.*, Suni M.A. *et al.*, J Immunol Methods. 1998; 212:89-98; Nomura L.E. *et al.*, Cytometry. 2000; 40:60-68; and Ghanekar S.A. *et al.*, Clinical and Diagnostic Laboratory Immunology. 2001; 8:628-63). Briefly, the assay comprises the following steps: activation of cells via specific peptides or protein, an inhibition of protein transport (*e.g.*, brefeldin A) is added to retain the cytokines within the cell. After a defined period of incubation, typically 5 hours, a washing steps follows, and antibodies to other cellular markers can be added to the cells. Cells are then fixed and permeabilized. The flurochrome-conjugated anti-cytokine antibodies are added and the cells can be analyzed by flow cytometry.

(G) Assay for Confirming Replication-Deficiency of Viral Vectors

[00428] Any assay known to the skilled artisan that determines concentration of infectious and replication-competent virus particles can also be used as a to measure replication-deficient viral particles in a sample. For example, FFU assays with non-complementing cells can be used for this purpose.

[00429] Furthermore, plaque-based assays are the standard method used to determine virus concentration in terms of plaque forming units (PFU) in a virus sample. Specifically, a confluent monolayer of non-complementing host cells is infected with the virus at varying dilutions and covered with a semi-solid medium, such as agar to prevent the virus infection from spreading indiscriminately. A viral plaque is formed when a virus successfully infects and replicates itself in a cell within the fixed cell monolayer, and spreads to surrounding cells (see, *e.g.*, Kaufmann, S.H.; Kabelitz, D. (2002). Methods in Microbiology Vol.32:Immunology of Infection. Academic Press. ISBN 0-12-521532-0). Plaque formation can take 2 – 14 days, depending on the virus being analyzed. Plaques are generally counted manually and the results, in combination with the dilution factor used to prepare the plate, are used to calculate the number of plaque forming units per sample unit volume (PFU/mL). The PFU/mL result represents the number of infective replication-competent particles within the sample. When C-cells are used,

the same assay can be used to titrate replication-deficient arenavirus particles or tri-segmented arenavirus particles.

(vi) Assay for Expression of Viral Antigen

[00430] Any assay known to the skilled artisan can be used for measuring expression of viral antigens. For example, FFU assays can be performed. For detection, mono- or polyclonal antibody preparation(s) against the respective viral antigens are used (transgene-specific FFU).

(vii) Animal Models

[00431] To investigate recombination and infectivity of an arenavirus particle described herein *in vivo* animal models can be used. In certain embodiments, the animal models that can be used to investigate recombination and infectivity of a tri-segmented arenavirus particle include mouse, guinea pig, rabbit, and monkeys. In a preferred embodiment, the animal models that can be used to investigate recombination and infectivity of an arenavirus include mouse. In a more specific embodiment, the mice can be used to investigate recombination and infectivity of an arenavirus particle are triple-deficient for type I interferon receptor, type II interferon receptor and recombination activating gene 1 (RAG1).

[00432] In certain embodiments, the animal models can be used to determine arenavirus infectivity and transgene stability. In some embodiments, viral RNA can be isolated from the serum of the animal model. Techniques are readily known by those skilled in the art. The viral RNA can be reverse transcribed and the cDNA carrying the arenavirus ORFs can be PCR-amplified with gene-specific primers. Flow cytometry can also be used to investigate arenavirus infectivity and transgene stability.

(A) Chemotherapeutic Agent Assays

[00433] A number of assays have been devised that are capable of assessing properties of proposed chemotherapeutic agents. Tumor models that can be used to test the methods and compositions disclosed herein include Colon26 (CT26), MC38 (mouse colon adenocarcinoma), B16F10 (B16), Lewis Lung (LLC), Madison109 (Mad 109), EMT-6 (murine breast cancer), 4T1 (4T1) (murine breast cancer), HcMel3 (murine melanoma), HgfxCDK4^{R24C/R24C} (murine melanoma), and (RENCA) (murine renal cancer).

[00434] In certain embodiments, in these model systems, “transplantable tumors” can be generated by subcutaneous (*e.g.*, CT26, 4T1, MAD109, RENCA, LLC, or B16) or intracerebral

(*e.g.*, GL261, ONC26M4) inoculation of tumor cell lines into rodents, for example in adult female mice. Tumors can be developed over pre-determined time intervals, for example several days. These tumors are grown in syngeneic, immunocompetent rodent, *e.g.*, mouse, strains. For example CT26, 4T1, MAD109, and RENCA can be grown in BALB/c mice, LLC, B16, and GL261 can be grown in C57BL/6 mice, and ONC26M4 can be grown in FVBN mice.

“Spontaneous tumors” can be generated by intracerebral injection of DNA plasmids encoding a number (*e.g.*, one, two, three or more) of oncogenes and encoding one or more reporter, *e.g.*, firefly luciferase reporter, into neonatal C57BL/6 or FVBN mice to transform endogenous brain cells. Growth of gliomas can be monitored by techniques known in the art, *e.g.*, bioluminescence imaging. Growth of subcutaneous tumors can be monitored by techniques known in the art, *e.g.*, caliper measurements in three dimensions at specified time intervals.

5.3 Heterologous Prime Boost

[00435] In certain embodiments, provided herein are methods and compositions relating to a heterologous prime/boost using the replication-defective viruses or the tri-segmented, replication competent viruses described herein (see Sections 5.1 and 5.2). In specific embodiments, such heterologous prime/boost treatment regimens are conducted without concurrent chemotherapy or without concurrent treatment with immune checkpoint modulators. In other embodiments, chemotherapy and/or therapy with immune checkpoint modulators has been concluded prior to the initiation of the heterologous prime/boost regimen described in this section. In even other embodiments, a patient to be treated with the heterologous prime/boost regimen has not previously been treated for the present condition with chemotherapy and/or therapy with immune checkpoint modulators and is also not concurrently being treated with chemotherapy and/or therapy with immune checkpoint modulators. In certain embodiments, a patient is treated with multiple and/or successive heterologous prime/boost regimens.

[00436] In certain embodiments, the heterologous prime/boost regimen comprises administering a first arenavirus-derived construct as described herein followed by administering a second arenavirus-derived construct as described herein. In a specific embodiment the first and the second arenavirus-based constructs comprise a nucleotide sequence encoding the same tumor antigen, tumor associated antigen or antigenic fragment thereof. The tumor antigen or tumor-associated antigen can be an antigen listed in Section 5.1.(a), 5.1.(b), 5.2.(a), 5.2.(b), or 5.2.(c).

In a specific embodiment, both arenavirus-derived constructs comprise a nucleotide sequence encoding an antigen of an oncogenic virus, such as an HPV antigen, such as HPV16 E7/E6 fusion (*eg*, as described in WO2015/082570, which is incorporated herein in its entirety).

[00437] In certain embodiments, the first and the second arenavirus-based constructs are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or at least 14 days apart; at least 1, 2, 3, 4, 5, 6, 7, or at least 8 weeks apart; at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or at least 12 months apart. In certain embodiments, the first and the second arenavirus-based constructs are administered at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or at most 14 days apart; at most 1, 2, 3, 4, 5, 6, 7, or at most 8 weeks apart; at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or at most 12 months apart.

[00438] In certain embodiments, the first arenavirus-based construct has a genomic organization as shown in Figure 1 (ie, the open reading frame for the GP protein is deleted or functionally inactivated and replaced with an open reading frame for the tumor antigen or tumor-associated antigen or antigen of a oncogenic virus) or as shown in Figure 2 as outlined for r3LCMV-GFP^{artificial} except that in place of the open reading frame encoding GFP, the virus has an open reading frame for a tumor antigen or tumor-associated antigen or antigen of a oncogenic virus. In certain embodiments, the second arenavirus-based construct has a genomic organization as shown in Figure 1 (ie, the open reading frame for the GP protein is deleted or functionally inactivated and replaced with an open reading frame for the tumor antigen or tumor-associated antigen or antigen of a oncogenic virus) or as shown in Figure 2 as outlined for r3LCMV-GFP^{artificial} except that in place of the open reading frame encoding GFP, the virus has an open reading frame for a tumor antigen or tumor-associated antigen or antigen of a oncogenic virus. In a specific embodiment, the first and the second arenavirus-based constructs have a genomic organization as shown in Figure 1 (ie, the open reading frame for the GP protein is deleted or functionally inactivated and replaced with an open reading frame for the tumor antigen or tumor-associated antigen or antigen of a oncogenic virus) or as shown in Figure 2 as outlined for r3LCMV-GFP^{artificial} except that in place of the open reading frame encoding GFP, the virus has an open reading frame for a tumor antigen or tumor-associated antigen or antigen of a oncogenic virus.

[00439] In a specific embodiment, the first and the second arenavirus-based constructs have a genomic organization as shown in Figure 2 as outlined for r3LCMV-GFP^{artificial} except

that in place of the open reading frame encoding GFP, the viruses have an open reading frame for a tumor antigen or tumor-associated antigen or antigen of an oncogenic virus (such as an HPV16 E7/E6 fusion protein). Further, the first arenavirus-based vaccine is derived from a Pichinde, Junin, or LCMV; and the second arenavirus-based vaccine is derived from a Pichinde, Junin, or LCMV (but different from the viral backbone of the first construct). In an even more specific embodiment, the first construct (prime) is derived from Pichinide virus and the second construct (boost) is derived from LCMV. The first and the second construct can be administered as viral particles as described herein.

[00440] In certain embodiments, provided herein are kits wherein the kit comprises two or more of the components of the treatment regimen provided herein. For example, in one embodiment, such a kit comprises (i) a container with a viral particle as described herein (eg, an arenavirus-based construct comprising an open reading frame encoding an antigen of interest); and (ii) a container with a chemotherapeutic agent. In another embodiment, such a kit comprises (i) a container with a first viral particle (for “prime”); and (ii) a container with a second viral construct (for “boost”); and optionally (iii) a container with a chemotherapeutic agent.

6. EQUIVALENTS

[00441] The viruses, nucleic acids, methods, host cells, and compositions disclosed herein are not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the viruses, nucleic acids, methods, host cells, and compositions in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

[00442] Various publications, patents and patent applications are cited herein, the disclosures of which are incorporated by reference in their entireties.

7. SEQUENCES

[00443] The sequences in Table 4 are illustrative amino acid sequences and nucleotide sequences that can be used with the methods and compositions described herein. In some

instances a DNA sequence is used to describe the RNA sequence of a viral genomic segment. The RNA sequence can be readily deduced from the DNA sequence.

Table 4

SEQ ID NO.	Description	Sequence
1	Lymphocytic choriomeningitis virus clone 13 segment L, complete sequence (GenBank: DQ361066.1) (The genomic segment is RNA, the sequence in SEQ ID NO: 1 is shown for DNA; however, exchanging all thymidines ('T') in SEQ ID NO: 1 for uridines ('U') provides the RNA sequence.)	GCGCACCGGGGATCCTAGGCGTTTAGTTGCGCTGTTTGGTTGCACAACCT TTCTTCGTGAGGCTGTGAGAAGTGGACCTGGCTGATAGCGATGGGGTCAA GGCAAGTCCAGAGAGGAGAAAGGCACCAATAGTACAAAACAGGGCCGAAA TCCTACCAGATACCACCTATCTTGCCCTTTAAGCTGCAAATCTTGCTG GCAGAAATTTGACAGCTTGGTAAGATGCCATGACCACTACCTTTGCAGG CACTGTTTTAAACCTTCTGCTGTGAGTATCCGACAGGTGTCCTCTTTGTA AATATCCATTACCAACCAGATTGAAGATATCAACAGCCCCAAGCTCTCC ACCTCCCTACGAAGAGTAACACCGTCCGGCCCCGGCCCCGACAAACAGC CCAGCACAAGGGAACCGCACGTCAACCAACGCACACAGACACAGCACCC AACACAGAACACGCACACACACACACACACACACACACCCACACGCACGCGCC CCCACCACCGGGGGCGCCCCCCCCCGGGGGGCGCCCCCGGGAGCCC GGGCGGAGCCCCACGGAGATGCCCATCAGTCGATGTCTCGGCCACCGA CCCGCCcAGCCAATCGTCGAGGACCTCCCCTTGAGTCTAAACCTGCCC CCCCTgTTTCATACATCAAAGTGCTCCTAGATTTGCTAAAACAAAGTC TGCAATCCTTAAAGGCGAACCAGTCTGGCAAAGCGACAGTGGAATCAG CAGAATAGATCTGTCTATACATAGTTCTTGAGGATTACACTTATCTCT GAACCCAAACAATGTTTACCAGTTCTGAATCGATGCAGGAAGAGGTTCC CAAGGACATCACTAATCTTTTCATAGCCCTCAAGTCTGCTAGAAAGAC TTTCATGTCTTGGTCTCCAGCTTCACAATGATATTTTGGACAAGGTTT CTTCCTTCAAAAAGGGCACCCATCTTTACAGTCAGTGGCACAGGCTCCC ACTCAGGTCCAACCTCTCTCAAAGTCAATAGATCTAATCCCATCCAGTAT TCTTTTGGAGCCCAACAACCTCAAGCTCAAGAGAATCACCAAGTATCAAG GGATCTTCCATGTAATCCTCAAACCTCTTCAGATCTGATATCAAAGACAC CATCGTTCACCTTGAAGACAGAGTCTGTCTCAGTAAGTGGAGGCATTC ATCCAACATTCTTCTATCTATCTCACCTTAAAGAGGTGAGAGCATGAT AAAAGTTCAGCCACACCTGGATTCTGTAATTGGCACCTAACCAAGATA TCAATGAAAATTTCTTAAACAGTCAGTATTATTCTGATTGTGCGTAAA GTCCACTGAAATTGAAAACCTCAATACCCCTTTTGTGTAGTTGAGCATG TAGTCCACAGATCCTTTAAGGATTTAAATGCCTTTGGGTTTGTGACGGC CCTGCCTAATCAACATGGCAGCATTACACACAACATCTCCCATTCGGTA AGAGAACCACCCAAAACCAAACCTGCAAATCATTCTAAACATAGGCCTC TCCACATTTTTGTTCACCACTTTGAGACAAATGATTGAAAGGGGCCCA GTGCCTCAGCACCATCTTCAGATGGCATCATTTCTTTATGAGGGAACCA TGAAAAATTGCCTAATGTCTGTTGTTGCAACAAATTCTCGAACAAAT GATTCAAATACACCTGTTTTAAGAAGTTCTTGACAGACATCCCTCGTGC TAACAACAAATTCATCAACCAGACTGGAGTCAGATCGCTGATGAGAATT GGCAAGGTCAGAAAACAGAACAGTGTAATGTTTCATCCCTTTTCCACTTA ACAACATGAGAAATGAGTGACAAGGATTCTGAGTTAATATCAATTAATA CACAGAGGTCAAGGAATTTAATTCTGGGACTCCACCTCATGTTTTTTGA GCTCATGTGACACATAAATGGAAGAAGCTGATCCTCAAAGATCTTGGGA TATAGCCGCCTCACAGATTGAATCACTTGGTTCAAATTCATTTGTCTCT CCAGTAGCCTTGAGCTCTCAGGCTTTCTTGCTACATAATCACATGGGTT TAAGTGCTTAAGAGTTAGGTTCTCACTGTTATTCTTCCCTTTGGTCCGT TCTGCTAGGACCCAAACACCACTCAAAAGAGTTGCTCAATGAAATAC AAATGTAGTCCCAAAGAAGAGGCCTTAAAGGCATATGATGATCAGGTG GGCTTCTGGATGAGACTGTTTGTCAAAATGTACAGCGTTATACCATCC CGATTGCAAACCTCTGTGACATGATCATCTGTGGTTAGATCCTCAAGCA

	GCTTTTTGATATACAGATTTTCCCTATTTTTGTTTCTCACACACCTGCT TCCTAGAGTTTTTGCAAAGGCCTATAAAGCCAGATGAGATACAACCTCTGG AAAGCTGACTTGTTGATTGCTTCTGACAGCAGCTTCTGTGCACCCCTTG TGAATTTACTACAAAGTTTGTTCTGGAGTGTCTTGATCAATGATGGGAT TCTTTCCTCTTGGAAAGTCATCACTGATGGATAAAACCACCTTTTTGTCTT AAAACCATCCTTAATGGGAACATTTCAATCAAATTAACACAGTTAACAT CTGCTAACTGATTGAGATCTTCTTCAAGACCGAGGAGGTCTCCCAATTG AAGAATGGCCTCCTTTTTATCTCTGTTAAATAGGTCTAAGAAAAATTCT TCATTAAATTCACCATTTTTGAGCTTATGATGCAGTTTTCTTACAAGCT TTCTTACAACCTTTGTTTCATTAGGACACAGTTCCTCAATGAGTCTTTG TATTCTGTAACCTCTAGAACCATCCAGCCAATCTTTCACATCAGTGTTG GTATTGAGTAGAAATGGATCCAAAGGGAAATTGGCATACTTTAGGAGGT CCAGTGTTCTCCTTTGGATACTATTAAGTAGGGAGACTGGGACGCCATT TGCGATGGCTTGATCTGCAATTGTATCTATTGTTTCAAAAAGTTGATGT GGCTCTTTTACTTGGACATTGTGTAGCGCTGCAGATACAACTTTGTGA GAAGAGGGACTTCCTCCCCCATACATAGAATCTAGATTTAAATTCTGC AGCGAACCTCCCAGCCACACTTTTTGGGCTGATAAATTTGTTTAAACAAG CCGCTCAGATGAGATTGGAATTCACACAGGACAAGGACTTCCTCCGGAT CACTTACAACCAGGTCACTCAGCCTCCTATCAAATAAAGTGATCTGATC ATCACTTGATGTGTAAGCCTCTGGTCTTTCGCCAAAGATAACACCAATG CAGTAGTTGATGAACCTCTCGCTAAGCAAACCTAGAAGTCAGAACAT TATGCAAGATTCCCTGCCCCATATCAATAAGGCTGGATATATGGGATGG CACTATCCCCATTTCAAATATTGTCTGAAAATTCTCTCAGTAACAGTT GTTTCTGAACCCCTGAGAAGTTTGTAGCTTCGACTTGACATATGATTTCA TCATTGCATTCAACAAGGAAAGGGGACCTCGACAAGCTTATGCATGTG CCAAGTTAACAAGTGCTAACATGATCTTTCGGAACGCACATACTGG TCATCACCTAGTTTGAGATTTTGTAGAAACATTAAGAACAAAAATGGGC ACATCATTGGTCCCCATTTGCTGTGATCCATACTATAGTTTAAAGAACCC TTCCCGCACATTGATAGTCATTGACAAGATTGCATTTTCAAATTCCTTA TCATTGTTTAAACAGGAGCCTGAAAAGAACTTGAAAAAGACTCAAAAT AATCTTCTATTAACCTTGTGAACATTTTTGTCTCAAATCTCCAATATA GAGTTCTCTATTTCCCCCAACCTGCTCTTTATAAGATAGTGCAAAATTC AGCCTTCCAGAGTCAGGACCTACTGAGGTGTATGATGTTGGTGATTCTT CTGAGTAGAAGCACAGATTTTTCAAAGCAGCACTCATACATTGTGTCAA CGACAGAGCTTTACTAAGGGACTCAGAATTACTTTCCCTCTCACTGATT CTCACGTCTTCTCCAGTTTGTCCCAGTCAAATTTGAAATTCAAGCCTT GCCTTTGCATATGCCTGTATTTCCCTGAGTACGCATTTGCATTCAATTG CAACAGAATCATCTTCATGCAAGAAAACCAATCTCAGAAAAAGAAC TTTCTACAAAGGTTTTTTGCCATCTCATCGAGGCCACACTGATCTTTAA TGACTGAGGTGAAATACAAAGGTGACAGCTCTGTGGAACCCCTCAACAGC CTCACAGATAAATTTATGTCATCATTGGTTAGACATGATGGGTCAAAG TCTTCTACTAAATGGAAAGATATTTCTGACAAGATAACTTTTTCTTAAGT GAGCCATCTTCCCTGTTAGAATAAGCTGTAAATGATGTAGTCCTTTTGT ATTTGTAAGTTTTTCTCCATCTCCTTTGTCAATTGGCCCTCCTACCTCTT CTGTACCGTGCTATTGTGGTGTGACCTTTTCTTCGAGACTTTTGAAGA AGCTTGTCTCTTCTTCTCCATCAAAACATATTTCTGCCAGGTTGTCTTC CGATCTCCCTGTCTCTTCTCCCTTGGAAACCGATGACCAATCTAGAGACT AAGTTGAAACTTTATATTCATAGTCTGAGTGGCTCAACTTATACTTTT GTTTTCTTACGAACTCTCCGTAATTTGACTCACAGCACTAACAAAGCAA TTTGTTAAAGTCATATTCAGAAGTCGTTCTCCATTTAGATGCTTATTA ACCACCACACTTTTGTTACTAGCAAGATCTAATGCTGTGCGACATCCAG AGTTAGTCATGGGATCTAGGCTGTTTAGCTTCTTCTCTCTTTGAAAAAT TAAAGTGCCGTTGTTAAATGAAGACACCATTAGGCTAAAGGCTTCCAGA TTAACACCTGGAGTTGTATGCTGACAGTCAATTTCTTACTAGTGAATC TCTTCATTTGCTCATAGAACACACATTCTTCTCAGGAGTGATTGCTTC CTTGGGGTTGACAAAAAACCAATTGACTTTTGGGCTCAAAGAAGCTTT
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		TCAAAACATTTTATCTGATCTGTTAGCCTGTCAGGGGTCTCCTTTGTGA TCAAATGACACAGGTATGACACATTCAACATAAAATTTAAATTTTGCAC CAACAACACCTTCTCACCAGTACCAAAAATAGTTTTTATTAGGAATCTA AGCAGCTTATACACCACCTTCTCAGCAGGTGTGATCAGATCCTCCCTCA ACTTATCCATTAATGATGTAGATGAAAAATCTGACACTATTGCCATCAC CAAATATCTGACACTCTGTACCTGCTTTTGATTTCTCTTTGTTGGGTTG GTGAGCATTAGCAACAATAGGGTCCTCAGTGCAACCTCAATGTCGGTGA GACAGTCTTTCAAATCAGGACATGATCTAATCCATGAAATCATGATGTC TATCATATTGTATAAGACCTCATCTGAAAAAATTGGTAAAAAGAACCTT TTAGGATCTGCATAGAAGGAAATTAATGACCATCCGGGCCTTGATGG AGTAGCACCTTGAAGATTCTCCAGTCTTCTGGTATAATAGGTGGTATTC TTCAGAGTCCAGTTTTATTACTTGGCAAAACACTTCTTTGCATTCTACC ACTTGATATCTCACAGACCCTATTTGATTTTGCCTTAGTCTAGCAACTG AGCTAGTTTTTCATACTGTTTGTAAAGGCCAGACAAACAGATGATAATCT TCTCAGGCTCTGTATGTTCTTCAGCTGCTCTGTGCTGGGTTGGAAATTG TAATCTTCAAACCTTCGTATAATACATTATCGGGTGAGCTCCAATTTTCA TAAAGTTCTCAAATTCAGTGAATGGTATGTGGCATTCTTGCTCAAGGTG TTCAGACAGTCCGTAATGCTCGAACTCAGTCCCACCACTAACAGGCAT TTTTGAATTTTTGCAATGAACTCACTAATAGATGCCCTAAACAATTCCT CAAAAGACACCTTTCTAAACACCTTTGACTTTTTCTATTCTCAAAAG TCTAATGAACTCCTCTTTAGTGCTGTGAAAGCTTACCAGCTATCATTC ACACTACTATAGCAACAACCCACCCAGTGTTTATCATTTTTTAACCTTT TGAATTTTCGACTGTTTTATCAATGAGGAAAGACACAAAACATCCAGATT TAACAACCTGTCTCCTTCTAGTATTCAACAGTTTCAAACCTTTGACTTTG TTTAACATAGAGAGGAGCCTCTCATATTGAGTGCTAGTCTCACTTCCCC TTTCGTGCCCATGGGTCTCTGCAGTTATGAATCTCATCAAAGGACAGGA TTCGACTGCCTCCCTGCTTAATGTTAAGATATCATCACTATCAGCAAGG TTTTCATAGAGCTCAGAGAATTCCTTGATCAAGCCTTCAGGGTTTACTT TCTGAAAGTTTCTCTTTAATTTCCCACTTTCTAAATCTCTTCTAAACCT GCTGAAAAGAGAGTTTATTCCAAAAACCACATCATCACAGCTCATGTTG GGGTTGATGCCTTCGTGGCACATCCTCATAATTTTCATCATTGTGAGTTG ACCTCGCATCTTTCAGAATTTTCATAGAGTCCATACCGGAGCGCTTGTC GATAGTAGTCTTCAGGGACTCACAGAGTCTAAAATATTCAGACTCTTCA AAGACTTTCTCATTTTGGTTAGAATACTCCAAAAGTTTGAATAAAAGGT CTCTAAATTTGAAGTTTGCCCACTCTGGCATAAACTATTATCATAATC ACAACGACCATCTACTATTGGAACATAATGTGACACCCGCAACAGCAAGG TCTTCCCTGATGCATGCCAATTTGTTAGTGTCTCTATAAAATTTCTTCT CAAACTGGCTGGAGTCTCCTAACAAAACACTCAAGAAAGATGAGAGA ATTGTCTATCAGCTTGTAACCATCAGGAATGATAAGTGGTAGTCCTGGG CATACAATTCAGACTCCACCAAAATTTGTTTCCACAGACTTATCGTCGT GGTTGTGTGTGCAGCCACTCTTGTCTGCACTGTCTATTTCAATGCAGCG TGACAGCAACTTGAGTCCCTCAATCAGAACCATTCTGGGTTCCCTTTGT CCCAGAAAGTTGAGTTTCTGCCTTGACAACCTCTCATCCTGTTCTATAT AGTTTAAACATAACTCTCTCAATTCTGAGATGATTTTCATCCATTGCGCA TCAAAAAGCCTAGGATCCTCGGTGCG
2	Lymphocytic choriomeningitis virus segment S, complete sequence (The genomic segment is RNA, the sequence in SEQ ID NO: 2 is shown for DNA; however, exchanging all	CGCACCGGGGATCCTAGGCTTTTTGGATTGCGCTTTCCTC TAGATCAACTGGGTGTGAGGCCCTATCCTACAGAAGGATG GGTCAGATTGTGACAATGTTTGAGGCTCTGCCTCACATCA TCGATGAGGTGATCAACATTGTGATTATTGTGCTTATCGT GATCACGGGTATCAAGGCTGTCTACAATTTGCCACCTGT GGGATATTTCGATTGATCAGTTTCTACTTCTGGCTGGCA GGTCCTGTGGCATGTACGGTCTTAAGGGACCCGACATTTA CAAAGGAGTTTACCAATTTAAGTCAGTGGAGTTTGATATG TCACATCTGAACCTGACCATGCCAACGCATGTTTCAGCCA ACAACCTCCACCATACATCAGTATGGGGACTTCTGGACT

	thymidines (‘‘T’’) in SEQ ID NO: 2 for uridines (‘‘U’’) provides the RNA sequence.)	AGAATTGACCTTCACCAATGATTCCATCATCAGTCACAAC TTTTGCAATCTGACCTCTGCCTTCAACAAAAAGACCTTTG ACCACACACTCATGAGTATAGTTTCGAGCCTACACCTCAG TATCAGAGGGAACCTCCAACATAAGGCAGTATCCTGCGAC TTCAACAATGGCATAACCATCCAATACAACCTTGACATTCT CAGATCGACAAAGTGCTCAGAGCCAGTGTAGAACCTTCAG AGGTAGAGTCCTAGATATGTTTAGAACTGCCTTCGGGGGG AAATACATGAGGAGTGGCTGGGGCTGGACAGGCTCAGATG GCAAGACCACCTGGTGTAGCCAGACGAGTTACCAATACCT GATTATACAAAATAGAACCTGGGAAAACCACTGCACATAT GCAGGTCTTTTGGGATGTCCAGGATTCTCCTTTCCCAAG AGAAGACTAAGTTCTTCACTAGGAGACTAGCGGGCACATT CACCTGGACTTTGTGCACTCTTCAGGGGTGGAGAATCCA GGTGGTTATTGCCTGACCAAATGGATGATTCTTGCTGCAG AGCTTAAGTGTTCGGGAACACAGCAGTTGCGAAATGCAA TGTAATCATGATGCCGAATTCTGTGACATGCTGCGACTA ATTGACTACAACAAGGCTGCTTTGAGTAAGTTCAAAGAGG ACGTAGAATCTGCCTTGCACTTATTCAAAACAACAGTGAA TTCTTTGATTTAGATCAACTACTGATGAGGAACCACTTG AGAGATCTGATGGGGGTGCCATATTGCAATTACTCAAAGT TTTGGTACCTAGAACATGCAAAGACCGGCGAAACTAGTGT CCCCAAGTGCTGGCTTGTCAACAATGGTTCTTACTTAAAT GAGACCCACTTCAGTGATCAAATCGAACAGGAAGCCGATA ACATGATTACAGAGATGTTGAGGAAGGATTACATAAAGAG GCAGGGGAGTACCCCCCTAGCATTGATGGACCTTCTGATG TTTTCCACATCTGCATATCTAGTCAGCATCTTCTGCACC TTGTCAAATAACCAACACACAGGCACATAAAGGTGGCTC ATGTCAAAGCCACACCGATTAAACCAACAAAGGAATTTGT AGTTGTGGTGCATTTAAGGTGCCTGGTGTAAAAACCGTCT GGAAAAGACGCTGAAGAACAGCGCCTCCCTGACTCTCCAC CTCGAAAGAGGTGGAGAGTCAGGGAGGCCAGAGGGTCTT AGAGTGTCAACATTTGGGCCTCTAAAAATTAGGTCATG TGGCAGAATGTTGTGAACAGTTTTTCAGATCTGGGAGCCTT GCTTTGGAGGCGCTTTCAAAAATGATGCAGTCCATGAGTG CACAGTGCGGGGTGATCTCTTTCTTCTTTTGTCCCTTAC TATTCCAGTATGCATCTTACACAACCAGCCATATTTGTCC CACACTTTGTCTTCATACTCCCTCGAAGCTTCCCTGGTCA TTTCAACATCGATAAGCTTAATGTCTTCTTCTATTCTGTGA GTCCAGAAGCTTTCTGATGTCATCGGAGCCTTGACAGCTT AGAACCATCCCCTGCGGAAGAGCACCTATAACTGACGAGG TCAACCCGGGTTGCGCATTGAAGAGGTCGGCAAGATCCAT GCCGTGTGAGTACTTGGAATCTTGCTTGAATTGTTTTTGA TCAACGGGTTCCCTGTAAAAGTGTATGAACTGCCCGTTCT GTGGTTGGAAAATTGCTATTTCCACTGGATCATTAATCT ACCTCAATGTCAATCCATGTAGGAGCGTTGGGGTCAATT CCTCCCATGAGGTCTTTTAAAAGCATTGTCTGGCTGTAGC TTAAGCCCACCTGAGGTGGACCTGCTGCTCCAGGCGCTGG CCTGGGTGAATTGACTGCAGGTTTCTCGCTTGTGAGATCA ATTGTTGTGTTTTCCCATGCTCTCCCCACAATCGATGTTT TACAAGCTATGTATGGCCATCCTTCACCTGAAAGGCAAAAC TTTATAGAGGATGTTTTTATAAGGGTTCCTGTCCCCAACT TGGTCTGAAACAAACATGTTGAGTTTTCTCTTGGCCCCGA GAACTGCCTTCAAGAGGTCCTCGCTGTTGCTTGGCTTGAT CAAAATTGACTCTAACATGTTACCCCCATCCAACAGGGCT GCCCCCTGCCTTCACGGCAGCACCAAGACTAAAGTTATAGC CAGAAATGTTGATGCTGGACTGCTGTTTCACTGATGACCCC
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		CAGAACTGGGTGCTTGTCTTTTCAGCCTTTTCAAGATCATT AGATTTGGATACTTGACTGTGTAAAGCAAGCCAAGGTCTG TGAGCGCTTGTACAACGTCATTGAGCGGAGTCTGTGACTG TTTGGCCATACAAGCCATAGTTAGACTTGGCATTGTGCCA AATTGATTGTTCAAAAGTGATGAGTCTTTTCACATCCCAAA CTCTTACCACACCACTTGCACCCTGCTGAGGCTTTCTCAT CCCAACTATCTGTAGGATCTGAGATCTTTGGTCTAGTTGC TGTGTTGTTAAGTTCCCATATATAACCCCTGAAGCCTGGG GCCTTTTCAGACCTCATGATCTTGGCCTTCAGCTTCTCAAG GTCAGCCGCAAGAGACATCAGTTCTTCTGCACTGAGCCTC CCCACTTTCAAAACATTCTTCTTTGATGTTGACTTTAAAT CCACAAGAGAATGTACAGTCTGGTTGAGACTTCTGAGTCT CTGTAGGTCTTTGTCATCTCTCTTTTCTTCTCATGATC CTCTGAACATTGCTGACCTCAGAGAAGTCCAACCCATTCA GAAGGTTGGTTGCATCCTTAATGACAGCAGCCTTCACATC TGATGTGAAGCTCTGCAATTCTCTTCTCAATGCTTGCGTC CATTGGAAGCTCTTAACTTCCTTAGACAAGGACATCTTGT TGCTCAATGGTTTCTCAAGACAAATGCGCAATCAAATGCC TAGGATCCACTGTGCG
3	Lymphocytic choriomeningitis virus clone 13 segment S, complete sequence (GenBank: DQ361065.2) (The genomic segment is RNA, the sequence in SEQ ID NO: 3 is shown for DNA; however, exchanging all thymidines ('T') in SEQ ID NO: 3 for uridines ('U') provides the RNA sequence.)	GCGCACCGGGGATCCTAGGCTTTTTGGATTGCGCTTTTCT CTAGATCAACTGGGTGTCAGGCCCTATCCTACAGAAGGAT GGGTGAGATTGTGACAATGTTTGAGGCTCTGCCTCACATC ATCGATGAGGTGATCAACATTGTGATTATTGTGCTTATCG TGATCACGGGTATCAAGGCTGTCTACAATTTTGCCACCTG TGGGATATTGCGATTGATCAGTTTCTACTTCTGGCTGGC AGGTCTGTGGCATGTACGGTCTTAAGGGACCCGACATTT ACAAAGGAGTTTACCAATTTAAGTCAGTGGAGTTTGATAT GTCACATCTGAACCTGACCATGCCCAACGCATGTTTCAGCC AACAACCTCCCACCATTACATCAGTATGGGGACTTCTGGAC TAGAATTGACCTTCACCAATGATTCCATCATCAGTCACAA CTTTTGCAATCTGACCTCTGCCTTCAACAAAAGACCTTT GACCACACACTCATGAGTATAGTTTCGAGCCTACACCTCA GTATCAGAGGGAACCTCAACTATAAGGCAGTATCCTGCGA CTTCAACAATGGCATAACCATCCAATACAACCTTGACATTC TCAGATGCACAAAGTGCTCAGAGCCAGTGTAGAACCTTCA GAGGTAGAGTCTTAGATATGTTTAGAACTGCCTTCGGGGG GAAATACATGAGGAGTGGCTGGGGCTGGACAGGCTCAGAT GGCAAGACCACCTGGTGTAGCCAGACGAGTTACCAATACC TGATTATACAAAATAGAACCTGGGAAAACCACTGCACATA TGCAGGTCCTTTTGGGATGTCCAGGATTCTCCTTTCCCAA GAGAAGACTAAGTTCTCTACTAGGAGACTAGCGGGCACAT TCACCTGGACTTTGTGCACTCTTCAGGGGTGGAGAATCC AGGTGTTTATTGCCTGACCAAAATGGATGATTCTTGCTGCA GAGCTTAAGTGTTCGGAACACAGCAGTTGCGAAATGCA ATGTAAATCATGATGAAGAATTCTGTGACATGCTGCGACT AATTGACTACAACAAGGCTGCTTTGAGTAAGTTCAAAGAG GACGTAGAATCTGCCTTGCACTTATTCAAAACAACAGTGA ATTCTTTGATTTGAGATCAACTACTGATGAGGAACCACTT GAGAGATCTGATGGGGGTGCCATATTGCAATTACTCAAAG TTTTGGTACCTAGAACATGCAAAGACCGGCGAACTAGTG TCCCCAAGTGCTGGCTTGTACCAATGGTTCTTACTTAAA TGAGACCCACTTCAGTGACCAAATCGAACAGGAAGCCGAT AACATGATTACAGAGATGTTGAGGAAGGATTACATAAAGA GGCAGGGGAGTACCCCCCTAGCATTGATGGACCTTCTGAT GTTTTCCACATCTGCATATCTAGTCAGCATCTTCTCTGCAC

		CTTGTCAAAATACCAACACACAGGCACATAAAAGGTGGCT CATGTCCAAAGCCACACCGATTAAACCAACAAAGGAATTTG TAGTTGTGGTGCATTTAAGGTGCCTGGTGTAAAAACCGTC TGAAAAAGACGCTGAAGAACAGCGCCTCCCTGACTCTCCA CCTCGAAAGAGGTGGAGAGTCAGGGAGGCCAGAGGGTCT TAGAGTGTCAACATTTGGGCCTCTAAAAATTAGGTCAT GTGGCAGAATGTTGTGAACAGTTTTTCAGATCTGGGAGCCT TGCTTTGGAGGCGCTTTCAAAAATGATGCAGTCCATGAGT GCACAGTGCGGGGTGATCTCTTTCTTCTTTTGTCCCTTA CTATTCCAGTATGCATCTTACACAACCAGCCATATTTGTC CCACACTTTGTCTTCATACTCCCTCGAAGCTTCCCTGGTC ATTTCAACATCGATAAGCTTAATGTCCTTCTTATTCTGTG AGTCCAGAAGCTTTCTGATGTCATCGGAGCCTTGACAGCT TAGAACCATCCCCTGCGGAAGAGCACCTATAACTGACGAG GTCAACCCGGGTTGCGCATTGAAGAGGTGCGCAAGATCCA TGCCGTGTGAGTACTTGGAATCTTGCTTGAATTGTTTTTG ATCAACGGGTTCCCTGTAAAAGTGTATGAACTGCCCGTTC TGTGGTTGGAAAATTGCTATTTCCACTGGATCATTAAATC TACCCTCAATGTCAATCCATGTAGGAGCGTTGGGGTCAAT TCCTCCCATGAGGTCTTTTAAAAGCATTGTCTGGCTGTAG CTTAAGCCCCACCTGAGGTGGACCTGCTGCTCCAGGCGTG GCCTGGGTGAATTGACTGCAGGTTTCTCGCTTGTGAGATC AATTGTTGTGTTTTCCCATGCTCTCCCCACAATCGATGTT CTACAAGCTATGTATGGCCATCCTTCACCTGAAAGGCAAAA CTTTATAGAGGATGTTTTTATAAGGGTTCCTGTCCCCAAC TTGGTCTGAAACAAACATGTTGAGTTTTCTTGGCCCCG AGAACTGCCTTCAAGAGGTCCTCGCTGTTGCTTGGCTTGA TCAAAATTGACTCTAACATGTTACCCCCATCCAACAGGGC TGCCCCCTGCCTTCACGGCAGCACCAAGACTAAAGTTATAG CCAGAAATGTTGATGCTGGACTGCTGTTTCAAGTATGACCC CCAGAACTGGGTGCTTGTCTTTTCAAGATCATT AAGATTTGGATACTTGACTGTGTAAAGCAAGCCAAGGTCT GTGAGCGCTTGTACAACGTCATTGAGCGGAGTCTGTGACT GTTTGGCCATACAAGCCATAGTTAGACTTGGCATTGTGCC AAATTGATTGTTCAAAAGTGATGAGTCTTTCACATCCCAA ACTCTTACCACACCACTTGCACCCTGCTGAGGCTTTCTCA TCCCAACTATCTGTAGGATCTGAGATCTTTGGTCTAGTTG CTGTGTTGTTAAGTTCCCCATATATACCCCTGAAGCCTGG GGCCTTTTCAAGACCTCATGATCTTGGCCTTCAGCTTCTCAA GGTCAGCCGCAAGAGACATCAGTTCTTCTGCACTGAGCCT CCCCACTTTCAAAACATTCTTCTTTGATGTTGACTTTAAA TCCACAAGAGAATGTACAGTCTGGTTGAGACTTCTGAGTC TCTGTAGGTCTTTGTCTCTCTCTTTTCTTCTCTCATGAT CCTCTGAACATTGCTGACCTCAGAGAAGTCCAACCCATTC AGAAGGTTGGTTGCATCCTTAATGACAGCAGCCTTCACAT CTGATGTGAAGCTCTGCAATTCTCTTCTCAATGCTTGCGT CCATTGGAAGCTCTTAACCTTCTTAGACAAGGACATCTTG TTGCTCAATGGTTTCTCAAGACAAATGCGCAATCAAATGC CTAGGATCCACTGTGCG
4	Lymphocytic choriomeningitis strain MP segment L, complete sequence	GCGCACCGGGGATCCTAGGCATTTTTGTTGCGCATTTTGT TGTGTTATTTGTTGCACAGCCCTTCATCGTGGGACCTTCA CAAACAAACCAACCAGCCATGGGCCAAGGCAAGTCC AAAGAGGGAAGGGATGCCAGCAATACGAGCAGAGCTGAAA TTCTGCCAGACACCACCTATCTCGGACCTCTGAACTGCAA GTCATGCTGGCAGAGATTTGACAGTTTAGTCAGATGCCAT

	(The genomic segment is RNA, the sequence in SEQ ID NO:4 is shown for DNA; however, exchanging all thymidines ('T') in SEQ ID NO:4 for uridines ('U') provides the RNA sequence.)	GACCACTATCTCTGCAGACACTGCCTGAACCTCCTGCTGT CAGTCTCCGACAGGTGCCCTCTCTGCAAACATCCATTGCC AACCAAACCTGAAAATATCCACGGCCCCAAGCTCTCCACCC CCTTACGAGGAGTGACGCCCCGAGCCCCAACACCGACACA AGGAGGCCACCAACACAACGCCCAACACGGAACACACACA CACACACCCACACACACATCCACACACACGCGCCCCCACA ACGGGGGCGCCCCCGGGGGTGGCCCCCGGGTGCTCGG GCGGAGCCCCACGGAGAGGCCAATTAGTCGATCTCCTCGA CCACCGACTTGGTCAGCCAGTCATCACAGGACTTGCCCTT AAGTCTGTACTTGCCCACTGTTTCATACATCACCGTG TTCTTTGACTTACTGAAACATAGCCTACAGTCTTTGAAAG TGAACCAGTCAGGCACAAGTGACAGCGGTACCAGTAGAAT GGATCTATCTATACACAACCTCTTGGAGAATTGTGCTAATT TCCGACCCCTGTAGATGCTCACCAGTTCTGAATCGATGTA GAAGAAGGCTCCCAAGGACGTCATCAAAATTTCCATAACC CTCGAGCTCTGCCAAGAAAACCTCATATCCTTGGTCTCC AGTTTCACAACGATGTTCTGAACAAGGCTTCTTCCCTCAA AAAGAGCACCCATTCTCACAGTCAAGGGCACAGGCTCCCA TTCAGGCCCAATCCTCTCAAAATCAAGGGATCTGATCCCG TCCAGTATTTTCTTGAGCCTATCAGCTCAAGCTCAAGAG AGTCACCGAGTATCAGGGGGTCTCCATATAGTCTCAAA CTCTTCAGACCTAATGTCAAAAACACCATCGTTACCTTG AAGATAGAGTCTGATCTCAACAGGTGGAGGCATTCTGTCCA AGAACCTTCTGTCCACCTCACCTTTAAAGAGGTGAGAGCA TGATAGGAACTCAGCTACACCTGGACCTTGTAAGTGGCAC TTCATAAAAAGATCAATGAAAACCTTCTCAAACAATCAG TGTTATTCTGGTTGTGAGTGAAATCTACTGTAATTGAGAA CTCTAGCACTCCCTCTGTATTATTTATCATGTAATCCCAC AAGTTTCTCAAAGACTTGAATGCCTTTGGATTTGTCAAGC CTTGTTTGATTAGCATGGCAGCATTGCACACAATATCTCC CAATCGGTAAGAGAACCATCCAAATCCAAATTGCAAGTCA TTCCTAAACATGGGCCTCTCCATATTTTTGTTCACACTT TTAAGATGAATGATTGGAAAGGCCCAATGCTTCAGCGCC ATCTTCAGATGGCATCATGTCTTTATGAGGGAACCATGAA AACTTCCTAGAGTTCTGCTTGTGCTACAAATTCTCGTA CAAATGACTCAAAATACACTTGTTTTAAAGTTTTTGCA GACATCCCTTGTAACGACAAATTCATCAACAAGGCTT GAGTCAGAGCGCTGATGGGAATTTACAAGATCAGAAAATA GAACAGTGTAGTGTTCTGTCCTCTTCCACTTAACATCATG AGAAATGAGCGATAAAGATTCTGAATTGATATCGATCAAT ACGCAAAGGTCAAGGAATTTGATTCTGGGACTCCATCTCA TGTTTTTTTGAGCTCATATCAGACATGAAGGGAAGCAGCTG ATCTTCATAGATTTTAGGGTACAATCGCCTCACAGATTGG ATTACATGGTTTTAACTTATCTTGTCTCCAGTAGCCTTG AACTCTCAGGCTTCCTTGCTACATAATCACATGGGTCAA GTGCTTGAGGCTTGAGCTTCCCTCATTCTTCCCTTTCACA GGTTCAGCTAAGACCCAAACACCCAACTCAAAGGAATTAC TCAGTGAGATGCAAATATAGTCCCAAAGGAGGGGCTCAA GAGACTGATGTGGTCGAGTGAGCTTCTGGATGACTTTGC CTGTCAAAATGTACAACATTATGCCATCATGTCTGTGGA TTGCTGTACATGCGCATCCATAGCTAGATCCTCAAGCAC TTTTCTAATGTATAGATTGTCCCTATTTTTATTTCTCACA CATCTACTTCCCAAAGTTTTGCAAAGACCTATAAAGCCTG ATGAGATGCAACTTTGAAAGGCTGACTTATTGATTGCTTC TGACAGCAACTTCTGTGCACCTCTTGTGAACCTTACTGCAG AGCTTGTTCTGGAGTGTCTTGATTAATGATGGGATTCTTT
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	CCTCTTGGAAAGTCATTACTGATGGATAAAACCACTTTCTG CCTCAAGACCATTCTTAATGGGAACAACCTCATTCAAATTC AGCCAATTTATGTTTGGCAATTGACTTAGATCCTCTTCGA GGCCAAGGATGTTTCCCAACTGAAGAATGGCTTCCTTTT ATCCCTATTGAAGAGGTCTAAGAAGAATTCTTCATTGAAC TCACCATTCTTGAGCTTATGATGTAGTCTCCTTACAAGCC TTCTCATGACCTTCGTTTCACTAGGACACAATTCTTCAAT AAGCCTTTGGATTCTGTAACCTCTAGAGCCATCCAACCAA TCCTTGACATCAGTATTAGTGTTAAGCAAAAATGGGTCCA AGGGAAAGTTGGCATATTTTAAGAGGTCTAATGTTCTCTT CTGGATGCAGTTTACCAATGAACTGGAACACCATTGCA ACAGCTTGATCGGCAATTGTATCTATTGTTTCACAGAGTT GGTGTGGCTCTTTACACTTAACGTTGTGTAATGCTGCTGA CACAAATTTTGTAAAAGTGGGACCTCTTCCCCCACACA TAAAATCTGGATTTAAATTCTGCAGCAAATCGCCCCACCA CACTTTTCGGACTGATGAACTTGTTAAGCAAGCCACTCAA ATGAGAATGAAATTCAGCAATACAAGGACTTCCTCAGGG TCACTATCAACCAGTTCCTCAATCTCCTATCAAATAAGG TGATCTGATCATCACTTGATGTGTAAGATTCTGGTCTCTC ACCAAAAATGACACCGATAACAATAATTAATGAATCTCTCA CTGATTAAAGCCGTAAAAGTCAGAGGCATTATGTAAGATT CCTGTCCCATGTCAATGAGACTGCTTATATGGGAAGGCAC TATTCCTAATTCAAATATTCTCGAAAGATTCTTTCAGTC ACAGTTGTCTCTGAACCCCTAAGAAGTTTCAGCTTTGATT TGATATATGATTTTCATCATTGCATTCAACAAGGAAAAGG GACCTCAACAAGTTTGTGCATGTGCCAAGTTAATAAGGTG CTGATATGATCCTTTCCGGAACGCACATACTGGTCATCAC CCAGTTTGAGATTTTGAAGGAGCATTAAAAACAAAATGG GCACATCATTGGCCCCCATTGCTATGATCCATACTGTAG TTCAACAACCCCTCTCGCACATTGATGGTCATTGATAGAA TTGCATTTTCAAATTCTTTGTCAATTGTTTAAGCATGAACC TGAGAAGAAGCTAGAAAAAGACTCAAAATAATCCTCTATC AATCTTGTAACATTTTGTCTCAAATCCCCAATATAAAA GTTCTCTGTTTCCCTCCAACCTGCTCTTTGTATGATAACGC AACTTCAACCTTCCGGAATCAGGACCAACTGAAGTGTAT GACGTTGGTGACTCCTCTGAGTAAAAACATAAATTCTTTA AAGCAGCACTCATGCATTTTGTCAATGATAGAGCCTTACT TAGAGACTCAGAATTACTTTCCCTTTCACTAATTCTAACA TCTTCTTCTAGTTTGTCCCAGTCAAACCTGAAATTCAGAC CTTGTCTTTGCATGTGCCTGTATTTCCCTGAGTATGCATT TGCATTCATTTGCAGTAGAATCATTTTCATACACGAAAAC CAATCACCCCTCTGAAAAAACTTCTGAGAGGTTTTTTTG CCATTTTCATCCAGACCACATTGTTCTTTGACAGCTGAAGT GAAATACAATGGTGACAGTTCTGTAGAAGTTTCAATAGCC TCACAGATAAATTTTCATGTCATCATTGGTGAGACAAGATG GGTCAAATCTTCCACAAGATGAAAAGAAATTTCTGATAA GATGACCTTCTTAAATATGCCATTTTACCTGACAATATA GTCTGAAGGTGATGCAATCCTTTTGTATTTTCAAACCCCA CCTCATTTTCCCCTTCATTGGTCTTCTTGCTTCTTTTATA CCGCTTTATTGTGGAGTTGACCTTATCTTCTAAATCTTGT AAGAACTTGTCTCTTCTTCCCCATCAAAGCATATGTCTG CTGAGTCACCTTCTAGTTTCCCAGCTTCTGTTTCTTTAGA GCCGATAACCAATCTAGAGACCAACTTTGAAACCTTGTAC TCGTAATCTGAGTGGTTCAATTTGTACTTCTGCTTTCTCA TGAAGCTCTCTGTGATCTGACTCACAGCACTAACAAGCAA TTTGTTAAATCATACTCTAGGAGCCGTTCCCCATTTAAA
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	TGTTTGTAAACAACCACACTTTTGTGCTGGCAAGGTCTA ATGCTGTTGCACACCCAGAGTTAGTCATGGGATCCAAGCT ATTGAGCCTCTTCTCCCTTTGAAAATCAAAGTGCCATTG TTGAATGAGGACACCATCATGCTAAAGGCCTCCAGATTGA CACCTGGGGTTGTGCGCTGACAGTCAACTTCTTTCCAGT GAACTTCTTCATTTGGTCATAAAAAACACACTCTTCCTCA GGGGTGATTGACTCTTTAGGGTTAACAAAGAAGCCAAACT CACTTTTAGGCTCAAAGAATTTCTCAAAGCATTTAATTTG ATCTGTCAGCCTATCAGGGGTTTCCTTTGTGATTAAATGA CACAGGTATGACACATTCAACATGAACTTGAACCTTTCGCGC TCAACAGTACCTTTTACCAGTCCCAAAAACAGTTTTGAT CAAAAATCTGAGCAATTTGTACACTACTTTCTCAGCAGGT GTGATCAAATCCTCCTTCAACTTGTCCATCAATGATGTGG ATGAGAAGTCTGAGACAATGGCCATCACTAAATACCTAAT GTTTTGAACCTGTTTTTGATTCTCTTTGTTGGGTTGGTG AGCATGAGTAATAATAGGGTTCTCAATGCAATCTCAACAT CATCAATGCTGTCCTTCAAGTCAGGACATGATCTGATCCA TGAGATCATGGTGTCAATCATGTTGTGCAACACTTCATCT GAGAAGATTGGTAAAAAGAACCTTTTGGGTCTGCATAAA AAGAGATTAGATGGCCATTGGGACCTTGTATAGAAATAACA CCTTGAGGATTCTCCAGTCTTTTGATACAGCAGGTGATAT TCCTCAGAGTCCAATTTTATCACTTGGCAAAATACCTCTT TACATTCCACCACTTGATACCTTACAGAGCCCAATTGGTT TTGTCTTAATCTAGCAACTGAACTTGTTCATACTGTTT GTCAAAGCTAGACAGACAGATGACAATCTTTTCAAATAT GCATGTTCTTAATTGTTCCGTATTAGGCTGGAAATCATA ATCTTCAAACCTTTGTATAATACATTATAGGATGAGTTCCG GACCTCATGAAATTCTCAAACCTCAATAAATGGTATGTGGC ACTCATGCTCAAGATGTTTCAAGACAGACCATAGTGCCAAA ACTAAGTCCCACCACTGACAAGCACCTTTGAACTTTTAAA ATGAACTCATTTATGGATGTTCTAAACAAATCCTCAAGAG ATACCTTTCTATACGCCTTTGACTTTCTCCTGTTCTTAG AAGTCTGATGAACTCTTCCTTGGTGCTATGAAAGCTCACC AACCTATCATTACACTCCCATAGCAACAACCAACCCAGT GCTTATCATTTTTTGACCCTTTGAGTTTAGACTGTTTGAT CAACGAAGAGAGACACAAGACATCCAAATTCAGTAACTGT CTCCTTCTGGTGTTCATAAATTTTAACTTTTAACTTTGT TCAACATAGAGAGGAGCCTCTCATACTCAGTCTAGTCTC ACTTCCTCTCTCATAACCATGGGTATCTGCTGTGATAAAT CTCATCAAAGGACAGGATTCAACTGCCTCCTTGCTTAGTG CTGAAATGTCATCACTGTGAGCAAGAGTCTCATAAAGCTC AGAGAATTCCTTAATTAAATTTCCGGGGTTGATTTTCTGA AACTCCTCTTGAGCTTCCCAGTTTCCAAGTCTCTTCTAA ACCTGCTGTAAAGGGAGTTTATGCCAAGAACCACATCATC GCAGTTCATGTTTGGGTTGACACCATCATGGCACATTTTC ATAATTTTCATCATTGTGAAATGATCTTGATCTTTCAAGA TTTTTCATAGAGTCTATACCGGAACGCTTATCAACAGTGGT CTTGAGAGATTGCGAAAGTCTGAAGTACTCAGATTCTCA AAGACTTTCTCATCTTGGCTAGAATACTCTAAAAGTTTAA ACAGAAGGTCTCTGAACTTGAAATTCACCCACTCTGGCAT AAAGCTGTTATCATAATCACACCGACCATCCACTATTGGG ACCAATGTGATACCCGCAATGGCAAGGTCTTCTTTGATAC AGGCTAGTTTATTGGTGTCTCTATAAATTTCTTCTCAA ACTAGCTGGTGTGCTTCTAACGAAGCACTCAAGAAGAATG AGGAATTGTCAATCAGTTTATAACCATCAGGAATGATCA AAGGCAGTCCCGGCACACAATCCAGACTCTATTAGAAT
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		TGCCTCAACAGATTTATCATCATGGTTGTGTATGCAGCCG CTCTTGTGAGCACTGTCTATCTCTATACAACGCGACAAAA GTTTGAGTCCCTCTATCAATACCATTCTGGGTTCTCTTTG CCCTAAAAAGTTGAGCTTCTGCCTTGACAACCTCTCATCT TGTTCTATGTGGTTTAAGCACAACTCTCTCAACTCCGAAA TAGCCTCATCCATTGCGCATCAAAAAGCCTAGGATCCTCG GTGCG
5	Lymphocytic choriomeningitis strain MP segment S, complete sequence (The genomic segment is RNA, the sequence in SEQ ID NO: 5 is shown for DNA; however, exchanging all thymidines ('T') in SEQ ID NO: 5 for uridines ('U') provides the RNA sequence.)	CGCACCGGGGATCCTAGGCTTTTTGGATTGCGCTTTCTC AGCTCCGTCTTGTGGGAGAATGGGTCAAATTGTGACGATG TTTGAGGCTCTGCCTCACATCATTGATGAGGTCATTAACA TTGTCATTATCGTGCTTATTATCATCACGAGCATCAAAGC TGTGTACAATTTGCCACCTGCGGGATACTTGCAATTGATC AGCTTTCTTTTTCTGGCTGGCAGGTCCTGTGGAATGTATG GTCTTGATGGGCTGACATTTACAAAGGGGTTTACCGATT CAAGTCAGTGGAGTTTGACATGTCTTACCTTAACCTGACG ATGCCAATGCATGTTTCGGCAAACAACCTCCCATCATTATA TAAGTATGGGGACTTCTGGATTGGAGTTAACCTTCACAAA TGACTCCATCATCACCCACAACCTTTTGTAACTTGACTTCC GCCCTCAACAAGAGGACTTTTGACCACACACTTATGAGTA TAGTCTCAAGTCTGCACCTCAGCATTAGAGGGGTCCCCAG CTACAAAGCAGTGTCTGTGATTTTAAACAATGGCATCACT ATTCAATACAACCTGTCTATTTTCTAATGCACAGAGCGCTC TGAGTCAATGTAAGACCTTCAGGGGGAGAGTCCTGGATAT GTTTCAGAACTGCTTTTGGAGGAAAGTACATGAGGAGTGGC TGGGGCTGGACAGGTTTCAAGTGGCAAGACTACTTGGTGCA GCCAGACAAACTACCAATATCTGATTATACAAAACAGGAC TTGGGAAAACCACTGCAGGTACGCAGGCCCTTTTCGGAATG TCTAGAATTCTCTTCGCTCAAGAAAAGACAAGGTTTCTAA CTAGAAGGCTTGCAGGCACATTCACTTGGACTTTATCAGA CTCATCAGGAGTGGAGAATCCAGGTGGTTACTGCTTGACC AAGTGGATGATCCTCGCTGCAGAGCTCAAGTGTTTTGGGA ACACAGCTGTTGCAAAGTGCAATGTAAATCATGATGAAGA GTTCTGTGATATGCTACGACTGATTGATTACAACAAGGCT GCTTTGAGTAAATTCAAAGAAGATGTAGAATCCGCTCTAC ATCTGTTCAAGACAACAGTGAATTCTTTGATTTCTGATCA GCTTTTGATGAGAAATCACCTAAGAGACTTGATGGGAGTG CCATACTGCAATTACTCGAAATTCTGGTATCTAGAGCATG CAAAGACTGGTGAGACTAGTGTCCCCAAGTGCTGGCTTGT CAGCAATGGTTCTTATTTGAATGAAACCCATTTTCAGCGAC CAAATTGAGCAGGAAGCAGATAATATGATCACAGAAATGC TGAGAAAGGACTACATAAAAAGGCAAGGGAGTACCCCTCT AGCCTTGATGGATCTATTGATGTTTTCTACATCAGCATAT TTGATCAGCATCTTTCTGCATCTTGTGAGGATACCAACAC ACAGACACATAAAGGGCGGCTCATGCCCCAAACCATCG GTTAACCAGCAAGGGAATCTGTAGTTGTGGTGCAATTTAAA GTACCAGGTGTGGAAACCACTGGAAAAGACGCTGAACAG CAGCGCCTCCCTGACTCACCACTCGAAAGAGGTGGTGAG TCAGGGAGGCCAGAGGGTCTTAGAGTGTTACGACATTTG GACCTCTGAAGATTAGGTCATGTGGTAGGATATTGTGGAC AGTTTTTCAGGTCGGGGAGCCTTGCCTTGGAGGCGCTTTCA AAGATGATACAGTCCATGAGTGCACAGTGTGGGTGACCT CTTTCTTTTTCTTGTCCCTCACTATTCCAGTGTGCATCTT GCATAGCCAGCCATATTTGTCCCAGACTTTGTCTCATAT TCTCTTGAAGCTTCTTTAGTCATCTCAACATCGATGAGCT TAATGTCTCTTCTGTTTTGTGAATCTAGGAGTTTCTTGAT

		GTCATCAGATCCCTGACAACTTAGGACCATTCCCTGTGGA AGAGCACCTATTACTGAAGATGTCAGCCCAGGTTGTGCAT TGAAGAGGTGAGCAAGGTCCATGCCATGTGAGTATTTGGA GTCCTGCTTGAATTGTTTTTGATCAGTGGGTTCTCTATAG AAATGTATGTACTGCCCATTCTGTGGCTGAAATATTGCTA TTTCTACCGGGTCATTAAATCTGCCCTCAATGTCAATCCA TGTAGGAGCGTTAGGGTCAATACCTCCCATGAGGTCCTTC AGCAACATTGTTTGGCTGTAGCTTAAGCCCACCTGAGGTG GGCCCGCTGCCCCAGGCGCTGGTTTGGGTGAGTTGGCCAT AGGCCTCTCATTGTGTCAGATCAATTGTTGTGTTCTCCCAT GCTCTCCCTACAAGTATGTTCTACAAGCTATGTATGGCC ACCCCTCCCCTGAAAGACAGACTTTGTAGAGGATGTTCTC GTAAGGATTCCCTGTCTCCAACCTGATCAGAAACAAACATG TTGAGTTTCTTCTTGGCCCCAAGAACTGCTTTTCAGGAGAT CCTCACTGTTGCTTGGCTTAATTAAGATGGATTCCAACAT GTTACCCCCATCTAACAAGGCTGCCCCCTGCTTTCACAGCA GCACCGAGACTGAAATTGTAGCCAGATATGTTGATGCTAG ACTGCTGCTCAGTGTGACTCCCAAGACTGGGTGCTTGTC TTTCAGCCTTTCAAGGTCACTTAGGTTCTGGGTACTTGACT GTGTAAAGCAGCCCCAAGGTCTGTGAGTGTGACCAAGCT CATTGAGTGAGGTTTGTGATTGTTTGGCCATACAAGCCAT TGTTAAGCTTGGCATTGTGCCGAATTGATTGTTTCAGAAGT GATGAGTCCTTCACATCCCAGACCCTCACCACACCATTG CACTCTGCTGAGGTCTCCTCATTCCAACCATTGTCAGAAT CTGAGATCTTTGGTCAAGCTGTTGTGCTGTTAAGTTCCCC ATGTAGACTCCAGAAGTTAGAGGCCTTTTCAGACCTCATGA TTTTAGCCTTCAGTTTTTCAAGGTGAGCTGCAAGGGACAT CAGTTCTTCTGCACTAAGCCTCCCTACTTTTAGAACATTCT TTTTTTGATGTTGACTTTAGGTCCACAAGGGAATACACAG TTTGGTTGAGGCTTCTGAGTCTCTGTAAATCTTTGTCTATC CCTCTTCTCTTCTCCTCATGATCCTCTGAACATTGCTCACC TCAGAGAAGTCTAATCCATTGAGAAGGCTGGTGGCATCCT TGATCACAGCAGCTTTTCACATCTGATGTGAAGCCTTGAAG CTCTCTCCTCAATGCCTGGGTCCATTGAAAGCTTTTAACT TCTTTGGACAGAGACATTTTGTCACTCAGTGGATTTCCTAA GTCAAATGCGCAATCAAAATGCCTAGGATCCACTGTGCG
6	Amino acid sequence of the NP protein of the MP strain of LCMV	MSLSKEVKSFWTQALRRELQGFTSDVKA AVIKDATSLLN GLDFSEVSNVQRIMRKEKRDDKDLQRLRLSLNQTVYSLVDL KSTSKKNVLKVGRLSAEELMSLAADLEKLKAKIMRSEPL TSGVYMGNLTAQQLDQRSQILQVMGMRPQQSANGVVRVW DVKDSSLNNGFGTTPSLTMACMAKQSQTSLNDVVQALTD LGLLYTVKYPNLSDLERLKDHPVLGVITEQQSSINISGY NFSLGA AVKAGAAALLDGGNMLESILIKPSNSEDLKAVLG AKKKNMFVSDQVGDRNPYENILYKVCLSGEGWPYIACRT SVVGRAWENTTIDL TNERPMANSPKPAPGAAGPPQVGLSY SQTMLLKDLMGIDPNAPTWIDIEGRFNDPVEIAIFQPQN GQYIHFYREPTDQKQFKQDSKYSHGMDLADLFNAQPGLTS SVIGALPQGMVLSQGSDDIRKL LDSQNRRDIKLIDVEMT KEASREYEDKVWDKYGWLCKMHTGIVRDKKKKEVTPHICAL MDCIIFESASKARLPDLKTVHNILPHDLIFRGNPVVTL
7	Amino acid sequence of the GP protein of the MP strain of LCMV	MGQIVTMFEALPHIIDEVINIVIIIVLIIITSIKAVYNFAT CGILALISFLFLAGRSCGMYGLDGPDIYKGVYRFKSVFED MSYLNLTMPNACSAANSHHYISMGTSGLELTFNDSIITH NFCNLTSALNKRFTDHTLMSIVSSLHLSIRGVPSYKAVSC DFNNGITIQYNLSFSNAQSALSQCKTFRGRVLD MFRTAFG

		GKYMRSWGWTGSDGKTTWCSQTNYQYLIIQNRTWENHCR YAGPFGMSRILFAQEKTRFLTRRLAGTFTWTLSDSGIVEN PGGYCLTKWMILAAELKCFGNTAVAKCNVNHDEEFCMDLR LIDYNKAALSFKEDVESALHLFKTTVNSLISDQLLMRNH LRDLMGVPYCNYSKFWYLEHAKTGETSVPKCWLVSNGSYL NETHFSDQIEQEADNMITEMLRKDYIKRQGSTPLALMDLL MFSTSAYLISIFLHLVRIPTHRHIKGGSCPKPHRLTSKGI CSCGAFKVPGVETTWKRR
8	amino acid sequence of the L protein of the MP strain of LCMV	MDEAISELRELCLNHIEQDERLSRQKLNFLGQREPRMVL EGLKLLSRCIEIDSADKSGCIHNHDDKSVEAILIESGIVC PGLPLIIPDGYKLIDNSLILLECFVRSTPASFEKKFIEDT NKLACIKEDLAIAGITLVPDIVDGRCDYDNSFMPEWVNFKF RDLLFKLLEYSSQDEKVFEESEYFRLCESLKTTVDKRS DSMKILKDARSFHNDIIMKMCHDGVNPNMNCDDVVLGINS LYSRFRDLETGKLKRSFQKINPGNLIKEFSELYETLADS DDISALSKEAVESCPLMRFITADTHGYERGSETSTEYERL LSMLNKVKSLKLLNTRRRQLLNLDVLCSSLIKQSKLKGS KNDKHWVGCCYGSVNDRLVSFHSTKEEFIRLLNRNRKSKA YRKVSLEDLFRTSINEFILKVQRCLSVVGLSFGHYGLSEH LEHECHIPFIEFENFMRSGTHPIMYYTKFEDYDFQPNT LRNMHSLKRLSSVCLALTNMKTSSVARLRQNQLGSVRYQ VVECKEVFCQVIKLDSEEHLLYQKTGESSRCYSIQGPNG HLISFYADPKRFFLPISDEVLHNMTMISWIRSCPD DSIDDVEIALRTLLMLTNPTKRNQKQVQNIYLVMAIV SDFSSTSLMDKLEDLITPAEKVVYKLLRFLIKTVFGTGE KVLLSAKFKFMNLVSYLCHLITKETPDRLTDQIKCFEKFF EPKSEFGFFVNPKESITPEEECVFYDQMKKFTGKVEDCQR TTPGVNLEAFSMMVSSFNNGTILFKGEKRLNSLDPMTNSG CATALDLASNKSVVVKHLNGERLLEYDFNKLLVSAVSQI TESFMRKQKYKLNHSDYKVKSLVSRVIGSKETEAGKL EGDSADICFDGEEETSFFKNLEDKVNSTIKRYERSKKTNE GENEVGFENTKGLHHLQTILSGKMAYLRKVILSEISFHLV EDFDPSCLTNDDMKFICEAIETSTELSPYFTSAVKEQCG LDEMAKNLCRKFFSEGDFSCMKMILLQMNANAYSGKYRH MQRQGLNFKFDWDKLEEDVRISERESNSESLSKALSITKC MSAALKNLCFYSEESPTSYSVGPDSGRLKFALSYKEQVG GNRELYIGDLRTKMFTRLIEDYFESFSSFFSGSLNNDKE FENAILSMTINVREGLLNYSMDHSKWGPMMPFLFLMLLQ NLKLGDDQYVRSKGDHISTLLTWHMHKLVEVPFVNVAMM KSYIKSKLKLRLGSETTVTERIFREYFELGIVPSHISLI DMGQGILHNASDFYGLISERFINYCIGVIFGERPESYTSS DDQITLFDRLSELVSDPEEVLVLEFHSLSGLLNKFI SPKSVVGRFAAEFKSRFYVWGEEVPLLTKFVSAALHNKVC KEPHQLCETIDTIADQAVANGVPVSLVNCIQKRTLDLLKY ANFPLDPFLLNTNTDVKDWDGSRGYRIQRLIEELCPSET KVMRRLVRRLLHKLKNGEFNEEFFLDLFNRDKKEAILQLG NILGLEEDLSQLANINWLNELFPLRMVLRQKVVPVPSVM TFQEERIPSLIKTLQNKLCCKFTRGAQKLLSEAINKSAFQ SCISSGFIGLCKTLGSRVNRKNRDNLYIRKVLEDLAMDA HVTAIHRHDGIMLYICDRQSHPEAHCDHISLLRPLLDYI CISLSNSFELGVVLAEPVKGKNEGSSSLKHLNPCDYVAR KPESSRLLEDKISLNHVIQSVRRLYPKIYEDQLLPFMSDM SSKNMRWSPRIKFLDLCLVIDINSESLISHVVWKWRDE HYTVLFSDLVNSHQRSDDLVDFFVSTRDVCKNFLKQVY FESFVREFVATSRTLGSFSWFPKDMMPSEDGAEALGPFQ

		SFILKVVNKNMERPMFRNDLQFGFGWFSYRLGDIVCNAAM LIKQGLTNPFAFKSLRNLWDYMINNTEGVLEFSITVDFTH NQNTDCLRKFSLI FLVKQLQGPVAFELSCSHLFKGEV DRRFLDECLHLLRSDSIFKVNDGVFDIRSEEFEDYMEDPL ILGDSLELELIGSRKILDGIRSLDFERIGPEWEPVPLTVR MGALFEGRSLVQNI VVKLETDMRVFLAELEGYGNFDDVL GSLLLHRFRTGEHLQGEISTILQELCIDRSILLVPLSLV PDWFTFKDCRLCFSKSKNTVMYETVVVGKYRLKGKSCDDWL TKSVVEEID
9	Amino acid sequence of the Z protein of the MP strain of LCMV	MGQGSKEGRDASNTSRAEILPDTTYLGPLNCKSCWQRFD SLVRCHDHYLCRHCLNLLLSVSDRCPLCKHPLPTKLKIST APSSPPPYEE
10	Junin virus Candid#1 L segment	GCGCACCGGGGATCCTAGGCGTAACCTTCATCATTAATAATCTCAGATTCT GCTCTGAGTGTGACTTACTGCGAAGAGGCAGACAAATGGGCAACTGCAA CGGGGCATCCAAGTCTAACCAGCCAGACTCCTCAAGAGCCACACAGCCA GCCGCAGAATTTAGGAGGGTAGCTCACAGCAGTCTATATGGTAGATATA ACTGTAAGTGTGCTGGTTTTGCTGATACCAATTTGATAACCTGTAATGA TCACTACCTTTGTTTAAGGTGCCATCAGGGTATGTTAAGGAATTCAGAT CTCTGCAATATCTGCTGGAAGCCCCCT GCCCACCACAATCACAGTACCGGTGGAGCCAACAGCACCACCACCATAG GCAGACTGCACAGGGTCAGACCCGACCCCCGGGGGGCCCCCATGGGGA CCCCCGTGGGGGAACCCGGGGGTGATGCGCCATTAGTCAATGTCTTT GATCTCGACTTTGTGCTTCAGTGGCCTGCATGTCACCCCTTTCAATCTG AACTGCCCTTGGGGATCTGATATCAGCAGGTCAATTTAAAGATCT GCTGAATGCCACCTTGAAATTTGAGAATTCGAACAGTCACCAAATTTA TCAAGTGAACGGATCAACTGCTCTTTGTGTA GATCATAAACGAGGACAAAGTCCTCTTGCTGAAATAATATTGTTTGTGA TGTTGTTTTTTAGATAAGGCCATAGTTGGCTT AATAAGGTTTCCACACTATCAATGTCCTCTAGTGCTCCAATTGCCTTGA CTATGACATCCCCAGACAACCTCAACTCTATA TGTTGACAACCTTTTATTACCTCTGTAAAAGATACCCCTCTTTCAAGACA AGAGGTTCTCTGGGTTATCTGGCCCAATGA GGTCATATGCATACTTGTTACTTAGTTTGAATAAAAAGTCACCAAAGTT GAACTTAACATGGCTCAGAATATTGTCATCA TTTGTGCGCAGCGTAGCCTGCATCAATAAACAAGCCAGCTAGGTCAAAGC TCTCATGGCCTGTGAACAATGGTAGGCTAGC GATAACCAGTGCACCATCCAACAATGAGTGGCTTCCCTCAGACCCAGAA ACACATTGACTCATTGCATCCACATTCAGCT CTAATTCAGGGGTACCGACATCATCCACTCCTAGTGAAGTGAATGGT GTAAGTGTACACCATCTTTCTTCTAAGTTTA AATTTTGTGCGAACTCGTGTGTGTTCTACTTGAATGATCAATTTTAGTT TCACAGCTTCTTGGCAAGCAACATTGCGCAA CACAGTGTGCAGGTCCATCATGTCTTCTGAGGCAACAAGGAGATGTTG TCAACAGAGACACCCTCAAGGAAAACCTTGA TATTATCAAAGCTAGAACTACATAACCCATTGCAATGTCTTCAACAAA CATTGCTCTTGATACTTTATTATTCCCTAACT GACAAGGTAAAATCTGTGAGTTTCACTAGATCTACTTGACTGTCATCTT CTAGATCTAGAACTTCATTGAACCAAAAGAA GGATTTGAGACACGATGTTGACATGACTAGTGGGTTTATCATCGAAGAT AAGACAACCTTGACCATGAAGTTCCTGCAA CTTGCTGTGGGCTGATGCCAAGTTCCTGCAA AACATGGGCTGAAGCGCAATCACTCTGTTTC ACAATATAACATTATTATCTCTTACTTTCAATAAGTGAAGTATAATCC CTAAGTTTTTATTATCATGTCTAGAGCCAC

	ACAGACATCTAGAACTTGAGTCTTCCACTATCCAAAGATCTGTTCACT TGAAGATCATTCTATAAAGGGTGCCAAATGTT CTTCAAATAGTTTGGGGTAATTTCTTCGTATAGAATGCAATACATGGTT CATGCCTAATTGGTCTTCTATCTGTCTGACT GCTTTGGGTTTAAACAGCCCAGAAGAAATTTCTTATTACATAAGACCAGAG GGGCCTGTGGACTCTTAATAGCAGAAAAACAC CCACTCCCCTAACTCACAGGCATTTGTGAGCACCAGAGAGTAATCC CACAAAATTGGTTTGTAGAAAATTGGTTAACTT CTTTAAGTGATTTTTGACAGTAAATAACTTTAGGCTTTCTCTCACAAAT TCCACAAAGACATGGCATTATTTCGAGTAAAT ATGTCTTTTATATACAGAAATCCGCCTTTACCATCCCTAACACACTTAC TCCCCATACTCTTACAAAACCAATGAAGCC TGAGGCAACAGAAGACTGAAATGCAGATTTGTTGATTGACTCTGCCAAG ATCTTCTTTCACGCCTTTTGTGAAATTTCTTG ACAGCCTGGACTGTATTGTCCTTATCAATGTTGGCATCTCTTCTTTCTC TAACACTCTTCGACTTGTCTGAGTTTGGTC CTCAAGACCAACCTCAAGTCCCCAAAGCTCGCTAAATTGACCCATCTGT AGTCTAGAGTTTGTCTGATTTTCATCTTCACT ACACCCGGCATATTGCAGGAATCCGGATAAAGCCTCATCCCCCTCCCTG CTTATCAAGTTGATAAGGTTTTCTCAAAGA TTTTGCCTCTCTTAATGTCATTGAACACTTTTCTCGCGCAGTTCTTAT AAACATTGTCTCCTTATCATCAGAAAAAATA GCTTCAATTTTCTCTGTAGACGGTACCCTCTAGACCCATCAACCCAGT CTTTGACATCTTGTTCTTCAATAGCTCCAAA CGGAGTCTCTCTGTATCCAGAGTATCTAATCAATTGGTTGACTCTAATG GAAATCTTTGACACTATATGAGTGCTAACCC CATTAGCAATACATTGATCACAAATTGTGTCTATGGTCTCTGACAGTTG TGTTGGAGTTTTTACACTTAACGTTGTGTAGA GCAGCAGACACAACTTGGTGAGTAAAGGAGTCTCTTACCCATGACAA AAAATCTTGACTTAACTCAGCAACAAAAGTTCTATCACACTCTTTGG GCTGATAAACTTGTTTAAATTTAGAAGATAAGAATTCATGGAAGCACACC ATTTCCAGCAGTT CTGTCTGTCTTGAACTTTTTCATCACTAAGGCAAGGAATTTTTTATAAG GCTAACCTGGTTCATCGCTGGAGGTATAAGTG ACAGGTATCACATCATAAATAAGTCAAGTGCATAACACAGAAATTGTT CAGTAATTAGCCCATATAAATCTGATGTGTT GTGCAAGATTCCCTGGCCCATGTCCAAGACAGACATTATATGGCTGGGG ACCTGGTCCCTTGACTGCAGATACTGGTGAA AAAACCTCTTCACCAACACTAGTACAGTCACAACCCATTAAACCTAAAGA TCTCTTCAATTTCCCTACACAGTAGGCTTCT GCAACATTAATTGGAACCTCAACGACCTTATGAAGATGCCATTTGAGAA TGTTTCACTTGGTTCAAGATTCACCTTTGT TCTATCTCTGGGATTCTTCAATTCTAATGTGTACAAAAAGAAAGGAAA AGTGCTGGGCTCATAGTTGGTCCCCATTTGG AGTGGTCATATGAACAGGACAAGTCACCATTGTAAACAGCCATTTTCAT ATCACAGATTGCACGTTTGAATTCCTTTTCT GAATTCAGCATGTGTATTTTATTGAACCTACCCACAGCTTCTGAGAAGT CTTCAACTAACCTGGTTCATCAGCTTAGTGTT GAGGTCTCCACATACAGTTCTCTATTTGAGCCAACCTGCTCCTTATAA CTTAGTCCAAATTTCAAGTTCCCTGTATTTG AGCTGATGCTTGTGAACTCTGTAGGAGAGTCGTCTGAATAGAAACATAA ATTCCGTAGGGCTGCATTTGTAAAATAACTT TTGTCTAGCTTATCAGCAATGGCTTCAGAATTGCTTTCCCTGGTACTAA GCCGAACCTCATCCTTTAGTCTCAGAACTTC ACTGGAAAAGCCCAATCTAGATCTACTTCTATGCTCATAACTACCCAAT TTCTGATCATAATGTCCTTGAATTTAAAGAT
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	ACTTGAAGCATTCAAAGAATTCATCTTCTTGGTAGGCTATTGTTGTCAA ATTTTTTAATAACAAACCCAAAGGGCAGATG TCCTGCGGTGCTTCAAGAAAATAAGTCAATTTAAATGGAGATAGATAAA CAGCATCACATAACTCTTTATACACATCAGA CCTGAGCACATCTGGATCAAAATCCTTCACCTCATGCATTGACACCTCT GCTTTAATCTCTCTCAACACTCCAAAAGGGG CCCACAATGACTCAAGAGACTCTCGCTCATCAACAGATGGATTTTTTGA TTTCAACTTGGTGATCTCAACTTTTGTCCCC TCACTATTAGCCATCTTGGCTAGTGTCAATTTGTACGTCATTTCTAATAC CCTCAAAGGCCCTTACTTGATCCTCTGTAA ACTCTCATACATCACTGATAATTCTTCTTGATTGGTTCTGGTTCTTGAA CCGGTGCTCACAAGACCTGTTAGATTTTTTA ATATTAAGTAGTCCATGGAATCAGGATCAAGATTATACCTGCCTTTTGT TTTAAACCTCTCAGCCATAGTAGAAACGCAT GTTGAACAAGTTTCTCCTTATCATAAACAGAAAGAATATTTCCAAGTT CGTCGAGCTTGGGGATTACCACACTTTTATT GCTTGACAGATCCAGAGCTGTGCTAGTGTAGGCTGTAGGGATTG CTTTTCAGTTCACCTGTAACTTTAAGTCTTC CTCTATTGAAGAGAGAAATGCAGAAGGACAAAATCTCTTTACACACTCC TGGAATTTGAGTATCTGAGGAAGTCTTAGCC TCTTTGGAAAAGAATCTGTCCAATCCTCTTATCATGGTGTCTCTTGT CCAGTGTTAGACTCCCACTTAGAGGGGGTT TACAACAACACAATCAAACCTGACTTTGGGCTCAATAAACTTCTCAAAA CACTTTATTTGATCTGTGAGGCGATCAGGTG TCTCTTTGGTTACCAAGTGACACAGATAACTAACATTTAATAGATATTT AAACCTTCTTGCAAAGTAAAGATCTGCATCT TCCCCTTCACCCAAAATTGTCTGGAAAAGTTCCACAGCCATCCTCTGAA TCAGCACCTCTGATCCAGACATGCAGTCGAC CCTTAACCTTTGACATCAAATCCACATGATGGATTTGATTTGCATATGCC ATCAAGAAATATCTTAGACCTTGTA AAAAATG TCTGGTTCCTTTTGGAAAGGGGAACAGAGTACAGCTAACACTAACAACTCT TAATATTGGCCTTGTCATTGTGTCATGAGTTTCG TGGCTAAAATCCAACCAGCTGGTCATTTCTCCTCACACATTTCAATTAACA CATCCTCCGAAAATATAGGCAGGAAAAATCT CTTTGGATCACAGTAAAAAGAGCCTTGTTCTTCCAATACCCCATTGATG GATAGATAGATAGAATAGCACCTTGACTTCT CACCTGTTTTTTTGGTAAAACAAGAGACCAAATGTATTCTTTGTCAGATG AAATCTTTGTACATAAACAATCTCTTAGTCTA ACATTC CCAAAATATCTAGAATACTCTCTTTCATTGATTAACAATCGGG AGGAAAATGATGTCTTCATCGAGTTGACCAA TGCAAGGGAAATGGAGGACAAAATCCTAAATAATTTCTTCTGCTCACCT TCCACTAAGCTGCTGAATGGCTGATGTCTAC AGATTTTCTCAAATTCCTTGTTAATAGTATATCTCATCACTGGTCTGTC AGAAACAAGTGCCTGAGCTAAAATCATCAAG CTATCCATATCAGGGTGTTTTATTAGTTTTTCCAGCTGTGACCAGAGAT CTTGATGAGAGTTCTTCAATGTTCTGGAACA CGCTTGAACCCACTTGGGGCTGGTCATCAATTTCTTCTTATTAGTTTA ATCGCTCCAGAATATCTAGAAGTCTGTCAT TGACTAACATTAACATTTGTCCAACAATATTCCCGCATTTCTTAACCT TACAATTGCATCATCATGCGTTTTTGAAAAGA TCACAAAGTAAATTGAGTAAAATAAGTCCAGAAACAGTAAAGTGTTTC TCCTGGTGTTGAAAACCTTTTAGACCTTTTAC TTTGTTACACACGGAAGGGCTTGAAGATAACACCTCTCTACAGCATCA ATAGATATAGAATTCTCATCTGACTGGCTTT CCATGTTGACTTCATCTATTGGATGCAATGCGATAGAGTAGACTACATC CATCAACTTGTTTGCACAAAAGGGCAGCTG
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		GGCACATCACTGTCTTTGTGGCTTCCTAATAAGATCAAGTCATTTATAA GCTTAGACTTTTGTGAAAATTTGAATTTCCC CAACTGCTTGTCAAAAATCTCCTTCTTAAACCAAAACCTTAACCTTTATG AGTTCTTCTCTTATGACAGATTCTCTAATGT CTCCTCTAACCCCAACAAAGAGGGATTTCATTTAACCTCTCATCATAACC CAAAGAATTCTTTTTCAAGCATTTCGATGTTT TCTAATCCCAAGCTCTGGTTTTTTGTGTTGGACAAACTATGGATCAATC GCTGGTATTCTTGTCTTCAATATTAATCTC TTGCATAAATTTTGATTTCTTTAGGATGTGATCAGCAACCACCGAACT CTTTCAACAACCCAATCAGCAAGGAATCTAT TGCTGTAGCTAGATCTGCCATCAACCACAGGAACCAACGTAATCCCTGC CCTTAGTAGGTCGGACTTTAGGTTTAAGAGC TTTGACATGTCACTCTTCCATTTTCTCTCAAACCTCATCAGGATTGACCC TAACAAAGGTTTCCAATAGGATGAGTGTTTT CCCTGTGAGTTTGAAGCCATCCGGAATGACTTTTGAAGGGTGGGACAT AGTATGCCATAGTCAGACAGGATCACATCAA CAAACCTCTGATCTGAATTGATCTGACAGGCGTGTGCCTCACAGGACTC AAGCTCTACTAACTTGACAGAAGTTTGAAC CCTTCCAACAACAGAGAGCTGGGGTGATGTTGAGATAAAAAGATGTCCC TTTGGTATGCTAGCTCCTGTCTTTCTGAAA ATGCTTTCTAATAAGGCTTTTTATTTCACTTTACTGATTCTCCATGCTC AAGTGCCGCTAGGATCCTCGGTGCG
11	Junin virus Candid#1 S segment	GCGCACCGGGGATCCTAGGCGATTTTGGTTACGCTATAATTGTAACGTG TTTCTGTTTGGACAACATCAAAAACATCCATTGCACAATGGGGCAGTTC ATTAGCTTCATGCAAGAAATACCAACCTTTTGCAGGAGGCTCTGAACA TTGCTCTTGTTGC AGTCAGTCTCATTGCCATCATTAAAGGGTATAGTGAACCTTGTACAAAAGT GGTTTATTCCAATTCTTTGTATTCTAGCGC TTGCAGGAAGATCCTGCACAGAAGAAGCTTTCAAAATCGGACTGCACAC TGAGTTCAGACTGTGTCCTTCTCAATGGTG GGTCTCTTTTCCAACAATCCACATGACCTACCTTTGTTGTGTACCTTAA ACAAGAGCCATCTTTACATTAAGGGGGGCAA TGCTTCATTTAGATCAGCTTTGATGATATTGCAGTATTGTTGCCACAG TATGATGTTATAATAACAACATCCAGCAGATA TGAGCTGGTGTTCAAAAGTGATGATCAAATTTGGTTGTCTCAGTGGTT CATGAATGCTGTGGGACATGATTGGCATCTA GACCCACCATTTCTGTGTAGGAACCGTGCAAAGACAGAAGGCTTCATCT TTCAAGTCAACACCTCCAAGACTGGTGTCAA TGGAATTATGCTAAGAAGTTTAAGACTGGCATGCATCATTTATATAGA GAATATCCTGACCCTTGCTTGAATGGCAAAC TGTGCTTAATGAAGGCACAACCTACCAGTTGGCCTCTCCAATGTCCACT CGACCACGTTAACACATTACACTTCCTTACA AGAGGTAAAAACATTCAACTTCCAAGGAGGTCCTTGAAAGCATTCTTCT CCTGGTCTTTGACAGACTCATCCGGCAAGGA TACCCCTGGAGGCTATTGTCTAGAAGAGTGGATGCTCGTAGCAGCCAAA ATGAAGTGTTTTGGCAATACTGCTGTAGCAA AATGCAATTTGAATCATGACTCTGAATTCTGTGACATGTTGAGGCTCTT TGATTACAACAAAATGCTATCAAAACCCTA AATGATGAACTAAGAAACAAGTAAATCTGATGGGGCAGACAATCAATG CCCTGATATCTGACAATTTATTGATGAAAAA CAAAATTAGGGAACGATGAGTGTCCCTTACTGCAATTACACAAAATTT TGGTATGTCAACCACACACTTTTCAAGACAAC ACTCATTACCAAGGTGCTGGTTAATAAAAAACAACAGCTATTTGAACAT CTCTGACTTCCGTAATGACTGGATATTAGAA

		AGTGACTTCTTAATTTCTGAAATGCTAAGCAAAGAGTATTCGGACAGGC AGGGTAAAACCTCTTTGACTTTAGTTGACAT CTGTATTTGGAGCACAGTATTCTTCACAGCGTCACTCTTCCTTCACTTG GTGGGTATACCCTCCACAGACACATCAGGG GCGAAGCATGCCCTTTGCCACACAGGTTGAACAGCTTGGGTGGTTGCAG ATGTGGTAAGTACCCCAATCTAAAGAAACCA ACAGTTTGGCGTAGAGGACACTAAGACCTCCTGAGGGTCCCCACCAGCC CGGGCACTGCCCGGGCTGGTGTGGCCCCCAGTCCGCGGCCTGGCCGCG GACTGGGGAGGCACTGCTTACAGTGCATAGGCTGCCTTCGGGAGGAACA GCAAGCTCGGTGGTAATAGAGGTGTAGGTTCTCCTCATAGAGCTTCCC ATCTAGCACTGACTGAAACATTATGCAGTCTAGCAGAGCACAGTGTGGT TCACTGGAGGCCAATTGAAGGGAGTATCCTTTTCCCTCTTTTCTTAT TGACAACCACTCCATTGTGATATTTG CATAAGTGACCATATTTCTCCCAGACCTGTTGATCAAACCTGCCTGGCTT GTTTCAGATGTGAGCTTAACATCAACCAGTTT AAGATCTCTTCTTCCATGGAGGTCAAACAACCTTCTGATGTCATCGGAT CCTTGAGTAGTCACAACCATGTCTGGAGGCA GCAAGCCGATCACGTAACCTAAGAACTCCTGGCATTGCATCTTCTATGTC CTTCATTAAGATGCCGTGAGAGTGTCTGCTA CCATTTTTTAAACCTTTCTCATCATGTGGTTTTTCTGAAGCAGTGAATGT ACTGCTTACCTGCAGGTTGGAATAATGCCAT CTCAACAGGGTCAGTGGCTGGTCTTCAATGTGAGCCAAAGGGTGTG GTGGGGTTCGAGTTTCCCCACTGCCTCTCTGA TGACAGCTTCTTGTATCTCTGTCAAGTTAGCCAATCTCAAATTCTGACC GTTTTTTTTCCGGCTGTCTAGGACCAGCAACT GGTTTCCTTGTGATCAATACTTGTGTTGTCCCATGACCTGCCTGTGA TTTGTGATCTAGAACCAATATAAGGCCAACC ATCGCCAGAAAGACAAAGTTTGTACAAAAGGTTTTTCATAAGGATTTCTA TTGCCTGGTTTTCTCATCAATAAACATGCCTT CTCTTCGTTTTAACCTGAATGGTTGATTTTATGAGGGAAGAGAAGTTTTCT TGGGGTGAAGTCTGATTGTTTTCCAACATGTTT CCACCATCAAGAATAGATGCTCCAGCCTTTACTGCAGCTGAAAGACTGA AGTTGTAACCAGAAATATTGATGGAGCTTTT ATCTTTAGTCACAATCTGAAGGCAGTCATGTTCTGAGTCAGTCTGTCA AGGTCACCTAAGTTTGGATACTTCACAGTGT ATAGAAGCCCAAGTGAGGTTAAAGCTTGTATGACACTGTTTATTGTCTC ACCTCCTTGAACAGTCATGCATGCAATTGTC AATGCAGGAACAGAGCCAACTGATTGTTTATGCTTTGAAGGGTCTTTAA CATCCCATATCCTCACCACACCATTTCCTCC AGTCCCTTGCTGTTGAAATCCCAGTGTCTCAATATCTCTGATCTTTTAA GCAAGTTGTGACTGGGACAAGTTACCCATGT AAACCCCTGAGAGCCTGTCTCTGCTCTTCTTATCTTGTGTTTTTAAATT CTCAAGGTCAGACGCCAACTCCATCAGTTCA TCCCTCCCCAGATCTCCCACCTTGAAAAGTGTGTTTCGTTGAACACTCC TCATGGACATGAGTCTGTCAACCTCTTTATT CAGGTCCCTCAACTTGTGAGGTCTTCTTCCCCCTTTTTAGTCTTTCTG AGTGCCCGCTGCACCTGTGCCACTTGGTTGA AGTCGATGCTGTGAGCAATTAGCTTGGCGTCCCTTCAAACATCTGACTT GACAGTCTGAGTGAATTGGCTCAAACCTCTC CTTAAGGACTGAGTCCATCTAAAGCTTGGAACTCCTTGGAGTGTGCCA TGCCAGAAGTTCTGGTGATTTTGTATCTAGAA TAGAGTTGCTCAGTGAAAGTGTTAGACACTATGCCTAGGATCCACTGTG CG
12	Amino acid sequence of the NP protein	MSLSKEVKSFQWTQALRRELQSFTSDVKA AVIKDATNLLNGLDFSEVSN VQRIMRKEKRDDKDLQRLRSLNQTVHSLVDLKSTSKKNVLKVGRLSABE

	of the Clone 13 strain of LCMV (GenBank Accession No. ABC96002.1; GI:86440166)	LMSLAADLEKLKAKIMRSERPQASGVYMGNLTTQQLDQRSQILQIVGMR KPQQGASGVVRVWDVKDSSLNNQFGTMPSLTMACMAKQSQTPLNDDVVQ ALTDLGLLYTVKYPNLNDLERLKDHPVLGVITEQQSSINISGYNFSLG AAVKAGAALLDGGNMLESILIKPSNSEDLLKAVLGAKRKLNMVSDQVG DRNPYENILYKVCLSGEGWPYIACRTSIVGRAWENTTIDLTSEKPAVNS PRPAPGAAGPPQVGLSYSQTMLLKDLMGGIDPNAPTWIDIEGRFNDPVE IAI FQPQNGQFIHFYREPVDQKQFKQDSKYSHGMDLADLFNAQPGLTSS VIGALPQGMVLSCQGSDDIRKLLDSQNRKDIKLIDVEMTREASREYEDK VWDKYGWLCKMHTGIVRDKKKKEITPHCALMDCIIFESASKARLPDLKT VHNILPHDLIFRGPNNVTL
13	Amino acid sequence of the GP protein of the Clone 13 strain of LCMV (GenBank Accession No. ABC96001.2; GI:116563462)	MGQIVTMFEALPHIIDEVINIVIIVLIVITGIKAVYNFATCGIFALISF LLLAGRSCGMGYLKGPDIIYKGVYQFKSVEFDMSHLNLTMPNACSANN SH HYISMGTSGLELTFTNDSIIISHNFCNLTSAFNKKTFDHTLMSIVSSLHL SIRGNSNYKAVSCDFNNGITIQYNLTFSDAQSAQSCRTFRGRVLDMFR TAFGGKYMRSWGWTGSDGKTTWCSQTSYQYLIIQNRTWENHCTYAGPF GMSRILLSQEKTKFLTRRLAGTFTWTLSOSSGVENPGGYCLTKWMILAA ELKCFGNTAVAKCNVNHDEEFCDMLRLIDYNKAALSFKFEDVESALHLF KTTVNSLISDQLLMRNHLRDLMGVPCNYSKFWYLEHAKTGETSVPKCW LVTNGSYLNETHFSDQIEQEADNMITEMLRKDYIKRQGSTPLALMDLLM FSTSAYLVSIFLHLVKIPTHRHIKGGSCPKPHRLTNKGICSCGAFKVP G VKTVWKR
14	amino acid sequence of the L protein of the Clone 13 strain of LCMV (GenBank Accession No. ABC96004.1; GI:86440169)	MDEIISELRELCLNYIEQDERLSRQKLNFLGQREPRMVLIIEGLKLLSRC IEIDSADKSGCTHNHDDKSVETILVESGIVCPGLPLIIPDGYKLIDNSL ILLECFVRSTPASFEKKFIEDTNKLACIREDLAVAGVTLVPIVDGRCDY DNSFMPEWANFKFRDLLFKLLEYSNQNEKVFEESYFRLCESLKTIDK RSGMDSMKILKDARSTHNDEIMRMCHEGINPNMSCDDVVFGINSLSFRF RRDLESGLKLRNFQKVNPEGLIKEFSELYENLADSDDILTLRSREAVESC PLMRFITAEETHGERGSETSTEYERLLSMLNKVSKLKLNLNTRRRQLNL DVLCSSLIKQSKFKGLKNDKHVWGCCYSSVNDRLVSFHSSTKEEFIRLL RNRKKSQVFRKVSFEELFRASISEFIAKIQKCLLVVGLSFEHYGLSEHL EQECHIPFTEFENFMKIGAHPIIMYYTKFEDYNFQPSTEQLKNIQSLRRL SSVCLALTNSMKTSSVARLRQNQIGSVRYQVVECKEVFCQVILKDSSEY HLLYQKTGESSRCYSIQGPDGHLISFYADPKRFFLPISFDEVLYNMIDI MISWIRSCPDLDCLTDIEVALRLLLLMLTNPTKRQKQVSVRYLVM AIVSDFSSTSLMDKLREDLITPAEKVVYKLLRFLIKTIFGTGEKVLLSA KFKFMLNVSYLCHLITKETPDRLTDQIKCFEKFFEPKSQFGFFVNPKEA ITPEEECVFYEQMKRFTSKEIDCQHTTPGVNLEAFSLMVSSFNNGTLIF KGEKKLNSLDPMTNNGCATALDLASNKSVVVKHLNGERLLEYDFNKL L VSAVSQITESFVRKQKYKLSHSDYEEKVSKLVSRVIGSKGEETGRSED NLAEICFDGEEETSFFKSLEEKVNTTIARYRRGRRANDKGDGEKLTNTK GLHHLQLILTGMMAHLRKVILSEISFHLVEDFDPSCLTNDMDKFI CEAV EGSTELSPLYFTSVIKDQCGLDEMAKNLCRKFFSENDWFSCMKMILLQM NANAYSGKYRHMQRQGLNFKFDWDKLEEDVRI SERESNSESLSKALSLT QCMSAALKNLCFYSEESPTSYSVGPDSGRLKFALSYKEQVGGNRELYI GDLRTKMFTRLIEDYFESFSSFFSGSCLNNDKEFENAILSMTINVREGF LNYSDHSHKSGPMMCPFLFLMFLQNLKLGDDQYVRSKGDHVSLLTWHM HKLVEVPFPVNVAMMKSIVKSKLKLRLGSETTVTERIFRQYFEMGIVPS HISSLIDMGQILHNASDFYGLLSERFINYCIGVIFGERPEAYTSSDDQ ITLFDRLSDLVSDPEEVLVLEFQSHLSGLLNKFI SPKSVAGRFAAE FKSRYFVWGEVPLLTKFVSAALHNKCKEPHQLCETIDTIADQAIANG VPVSLVNSIQRRTLDLLKYANFPLDPFLNLNTNDVKDWLDGSRGYRIQR LIEELCPNETKVVRLVRKLHHKLKNGEFNEEFFDLFNDRDKKEAILQL GDLLGLEEDLNQLADVNLNLNEMFPLRMVLRQKVVPVMTFQEEERIP SLIKTLQNKLCSEKFTGAQKLLSEAINKSAFQSCISSGFIGLCKTLGSR CVRNKNRENLYIKKLEDLTTDDHVTRVCNRDGITLYICDKQSHPEAHR

		DHICLLRPLLWDYICISLSNSFELGVWVLAEPKTKGKNNSENLTCLKHNP CDYVARKPESSRLLEDKVNLNQVIQSVRRLYPKIFEDQLLPFMSDMSSK NMRWSPRIKFLDLCLVIDINSESLSLISHVVKWKREHYTVLFSDLANS HQRSDSSLVDEFVSTRDVCKNFLKQVYFESFVREFVATTRTLGNFSWF PHKEMMPSEDGAEALGPFQSFVSKVVKNVERPMFRNDLQFGFGWFSYR MGDVVCNAAMLIRQGLTNPFAKSLKDLWDYMLNYTKGVLEFSISVDFT HNQNTDCLRKFSLI FLVRCQLQNPQVAELLSCSHLFKGEIDRRMLDEC LHLLRTDSVFKVNDGVFDIRSEEFEDYMEDPLILGDSLELELLGSKRIL DGIRSIDFERVGPWEPEVPLTVKMGALFEGRNLVQNIIVKLETKDMKVF LAGLEGYEKISDVLGNLFLHRFRTGEHLLGSEISVILQELCIDRSILLI PLSLLPDWFAFKDCRLCFSKSRSTLMYETVGGFRFLKGRSCDDWLGGSV AEDID
15	Amino acid sequence of the Z protein of the Clone 13 strain of LCMV (GenBank Accession No. ABC96003.1; GI:86440168)	MGQKKSREEKGTNSTNRAEILPDTTYLGPLSCKSCWQKFDLSVRCHDHY LCRHCLNLLLSVSDRCPLCKYPLPTRLKISTAPSSPPPYEE
16	Amino acid sequence of the GP protein of the WE strain of LCMV	MGQIVTMFEALPHIIDEVINIVIIIVLIIITSIKAVYNFATCGILALVSF LFLAGRSCGMYGLNGPDIYKGVYQFKSVEFDMSHLNLTMPNACSANNSH HYISMGSSGLELTFTNDSILNHNFCNLTSAFNKKTFDHTLMSIVSSLHL SIRGNSNHKAVSCDFNNGITIQYNLSFSDPQSAISQCRTFRGRVLDMFR TAFGGKYMRSWGWAGSDGKTTWCSQTSYQYLI IQNRTWENHCRYAGPF GMSRILFAQEKTFLTRRLAGTFTWTLSDSGVENPGGYCLTKWMILAA ELKCFGNTAVAKCNVNHDEEFCDMLRLIDYNKAALSKFKQDVESALHVF KTTVNSLISDQLLMRNHLRDLMGVPYCNYSKFWYLEHAKTGETSVPKCW LVTNGSYLNETHFSDQIEQEADNMITEMLRKDYIKRQGSTPLALMDLLM FSTSAYLISIFLHLVKIPTHRIKGGSCPKPHRLTNKGICSCGAFKVP VKTIWKRR
17	WE specific primer	5' AATCGTCTCTAAGGATGGGTGAGATTGTGACAATG-3'
18	WE specific fusion-primer carrying an overhang complementary to the WET-specific primer	5' AATCGTCTCTAAGGATGGGTGAGATTGTGACAATG-3'
19	WE specific primer	5' CTCGGTGATCATGTTATCTGCTTCTTGTTCGATTGA-3'
20	WE specific fusion-primer complementary to the WE-sequence	5' AATCGTCTCTTTCTTTATCTCCTCTTCCAGATGG-3'
21	Primer specific for LCMV NP	5' -GGCTCCCAGATCTGAAAAGTGT-3'
22	NP- and GP-specific primers; NP-specific: same as in RT reaction, GP-specific: 5'	5' -GCTGGCTTGCTACTAATGGCTC-3'

8. EXAMPLES

8.1 Example 1: Effect between r3LCMV treatment and chemotherapy

[00444] A potential synergistic effect between r3LCMV treatment and low-dose chemotherapy (cyclophosphamide treatment) was evaluated in the B16F10 mouse melanoma model.

[00445] 1×10^5 B16F10 tumor cells were implanted subcutaneously into C57BL/6 mice on day 0. Mice were subsequently left untreated (group 1), treated intraperitoneally with 2 mg cyclophosphamide on day 6 (group 2), injected intravenously with 2.1×10^5 PFU (in total) of a vector mix (7×10^4 PFU of each r3LCMV-GP100, r3LCMV-Trp1 and r3LCMV-Trp2) on day 7 (group 3), or treated with a combination of cyclophosphamide (day 6) and r3LCMV-vector mix (day 7) (group 4). The genomic organization of the r3LCMV constructs is essentially as shown for r3LCMV-GFP^{art} in **Fig. 2** except that in place of the GFP open reading frame the constructs have the open reading frame encoding for the antigen of interest, *i.e.* GP100, Trp1 and Trp2. Tumor growth after tumor challenge (**Fig. 3A**) as well as animal survival (**Fig. 3B** and **C**) were monitored. Symbols represent the mean $\pm$ SEM of three mice (groups 1 – 3) or four mice (group 4) per group. Treatment with the r3LCMV vector mix had a larger effect on tumor growth than chemotherapy alone. Best tumor control was achieved by combination of chemotherapy and treatment with the r3LCMV vector mix, indicating that the two combined treatments showed a synergistic effect.

[00446] T cell frequencies in the blood of test animals were analyzed by tetramer staining and flow cytometric analysis on days 15 and 22 of the experiment. Results indicate that considerably higher relative (**Fig. 4A**, left panel) and absolute (**Fig. 4A**, right panel) numbers of Trp2-specific CD8⁺ T cells were induced in mice treated with a combination of cyclophosphamide and r3LCMV-vectors compared to animals treated with r3LCMV vectors only. This synergistic effect could not be observed in this experiment for GP100-specific CD8⁺ T cells (**Fig. 4B**).

8.2 Example 2: Effect between r3LCMV treatment and chemotherapy in HCmel3 model

[00447] A potential synergistic effect between r3LCMV treatment and low-dose chemotherapy (cyclophosphamide treatment) is evaluated in the HCmel3 mouse melanoma model. HCmel3 tumor cells are derived from a primary Hgf-Cdk4^{R24C} melanoma.

[00448] HcMel3 tumor cells (4×10^5 cells) are implanted subcutaneously into C57BL/6 mice on day 0. On day 15, when all tumors are palpable, mice in groups 3 and 4 are treated intraperitoneally with 2 mg cyclophosphamide (CTX). On day 16 mice in groups 2 and 3 are injected intravenously with 7×10^4 RCV FFU r3LCMV-Trp2. Mice in group 4 are immunized intravenously with 1×10^5 RCV FFU r3PICV-Trp2.

[00449] The genomic organization of the r3LCMV constructs is essentially as shown for r3LCMV-GFP^{art} in **Fig. 2** except that in place of the GFP open reading frame the constructs have the open reading frame encoding for the antigen of interest, *i.e.* Trp2. Tumor growth after tumor challenge is monitored.

[00450] Trp2-specific CD8⁺ T cell frequencies in the blood of test animals are analyzed by tetramer staining.

8.3 Example 3: Effect between r3LCMV treatment and chemotherapy in HgfxCDK4^{R24C/R24C} mouse

[00451] The HgfxCDK4^{R24C/R24C} model is a syngeneic model where mice develop spontaneous tumors which show some similarities to human melanomas (Landsberg et al., Autochthonous primary and metastatic melanomas in Hgf-Cdk4 R24C mice evade T-cell-mediated immune surveillance. 2010; Bald et al., Immune cell-Poor Melanomas benefit from PD-1 Blockade after targeted type I IFN activation, 2014.).

[00452] A potential synergistic effect between r3LCMV treatment and low-dose chemotherapy (cyclophosphamide treatment) is evaluated in the HgfxCDK4^{R24C/R24C} mouse model. Mice are left untreated (group 1), treated intraperitoneally with 2 mg cyclophosphamide when tumors are palpable (around day 60) (group 2), injected intravenously with a vector mix (r3LCMV-GP100, r3LCMV-Trp1 and r3LCMV-Trp2) when tumors are palpable (around day 60) (group 3), or treated with a combination of cyclophosphamide and r3LCMV-vector mix (group 4). The genomic organization of the r3LCMV constructs is essentially as shown for r3LCMV-GFP^{art} in **Fig. 2** except that in place of the GFP open reading frame the constructs have the open reading frame encoding for the antigen of interest, *i.e.* GP100, Trp1 and Trp2. Tumor growth as well as animal survival are monitored.

[00453] T cell frequencies in the blood of test animals are analyzed by tetramer staining and flow cytometric analysis on days 15 and 22 of the experiment.

8.4 Example 4: Effect between r3LCMV treatment and chemotherapy with heterologous prime boost

[00454] The experiments in Examples 1 and 2 (both the B16F10 and HCrnel3 mouse models) are repeated to determine immune responses after heterologous prime boost vaccination using the following combinations of vectors with chemotherapy (cyclophosphamide): r3LCMV/r3LCMV, r3JUNV/r3LCMV, and r3PICV/r3LCMV.

8.5 Example 5: Heterologous prime boost

[00455] To investigate the immunogenicity of homologous versus heterologous prime-boost immunization, the induction of antigen-specific CD8⁺ T cell responses was compared between (i) mice treated with two administrations of r3LCMV-E7E6 (replication-competent LCMV vector expressing the antigens E7 and E6 from human papillomavirus type 16 (HPV16)) in a homologous prime-boost setting and (ii) animals primed with r3PICV-E7E6 (replication-competent Pichinde virus vector expressing E7 and E6 antigens) and boosted with r3LCMV-E7E6 in a heterologous prime-boost setting.

[00456] Results of this experiment are depicted in **Fig. 5**: C57BL/6 mice (5 mice per group) were immunized intravenously on day 0 with 10⁵ RCV FFU of r3LCMV-E7E6 (group 1) or 10⁵ RCV FFU of r3PICV-E7E6 (group 2) or were left untreated (group 3). The genomic organization of the r3LCMV constructs is essentially as shown for r3LCMV-GFP^{art} in **Fig. 2** except that in place of the GFP open reading frame the constructs have the open reading frame encoding for the antigen of interest, *i.e.* E7E6 (which is a fusion protein of the E6 and E7 proteins of HPV). On day 13 mice in groups 1 and 2 were boosted with 10⁵ RCV FFU of r3LCMV-E7E6. Mice of group 3 were again left untreated. E7-specific CD8⁺ T cell frequencies were subsequently analyzed by tetramer staining (Db-E7 (49-57)-Tetramer) on days 20 and 42 in the blood, and on day 51 in the spleen of test animals.

[00457] Respective results indicated that potent and durable, antigen-specific CD8⁺ T cell responses were induced in animals of test groups 1 and 2, treated with replication-competent arenavirus vectors expressing the E7 antigen. Significantly higher CD8⁺ T cell frequencies were induced by heterologous prime-boost combinations using r3PICV-E7E6 in combination with

r3LCMV-E7E6 (group 2) compared to homologous immunizations using r3LCMV-E7E6 only (group 1).

[00458] Homologous and heterologous prime-boost vaccination regimens were further analyzed and compared in regard to their anti-tumor efficacy in the TC-1 mouse tumor model (Lin *et al*, 1996, Cancer Res.;56(1):21-6). The level of tumor growth inhibition after administration of (i) two doses of r3LCMV-E7E6 (homologous prime-boost) or (ii) one dose of r3PICV-E7E6 followed by one dose of r3LCMV-E7E6 (heterologous prime-boost) was compared in TC-1 tumor bearing mice.

[00459] Results of these experiment are depicted in **Fig. 6**: On day 0 of the experiment female C57BL/6 mice (n=5 or n=3 animals per group for experimental groups and buffer group, respectively) were challenged subcutaneously with 1×10^5 TC-1 tumor cells, derived from mouse primary epithelial cells, co-transformed with HPV16 E6 and E7 and c-Ha-ras oncogenes. Ten days later (day 10 of the experiment) mice were immunized intravenously with either buffer (group 1) or 10^5 RCV FFU r3LCMV-E7E6 (group 2) or 10^5 RCV FFU r3PICV-E7E6 (group 3). 14 days post prime (day 24 of the experiment) mice in groups 2 and 3 received a boost administration of 10^5 RCV FFU r3LCMV-E7E6. Tumor growth was subsequently monitored over time. Arithmetic means $\pm$ SEM are shown. Arrows indicate time points of vaccination.

[00460] Respective results indicate that compared to the control group tumor growth was significantly delayed in all groups treated with replication-competent arenavirus vectors expressing the HPV E7 and E6 antigens. Higher levels of tumor growth control was observed in the test group treated with r3PICV-E7E6 in combination with r3LCMV-E7E6 in a heterologous prime-boost fashion.

8.6 Example 6: Effect between rLCMV treatment, chemotherapy and immune checkpoint inhibitor treatment in the B16F10 mouse melanoma model

[00461] A potential synergistic effect between rLCMV treatment, low-dose chemotherapy (cyclophosphamide treatment) and immune checkpoint inhibitor (anti PD-1) treatment is evaluated in the B16F10 mouse melanoma model.

[00462] Results of the experiment are depicted in **Fig. 7**. 1×10^5 B16F10 tumor cells were implanted subcutaneously into C57BL/6 mice on day 0. Mice were subsequently left untreated (group 1), treated intraperitoneally with 2 mg cyclophosphamide (CTX) on day 6 and 200 μ g

each of anti PD-1 and anti-CTLA-4 on days 10, 13, 16, 19 and 22 (group 2), treated intraperitoneally with 2 mg cyclophosphamide on day 6 and injected intravenously with 1.2x10⁵ FFU (in total) of a r3LCMV vector mix (r3LCMV-GP100, r3LCMV-Trp1 and r3LCMV-Trp2) on day 7 (group 3), or treated with cyclophosphamide on day 6, an r3LCMV-vector mix on day 7 and anti PD-1 and anti-CTLA-4 on days 10, 13, 16, 19 and 22 (group 4).

[00463] Respective results indicated that no additional effect on tumor growth inhibition could be achieved by combining the checkpoint inhibitor treatment with the combination of chemotherapy and r3LCMV.

[00464] The term “comprise” and variants of the term such as “comprises” or “comprising” are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

[00465] Any reference to publications cited in this specification is not an admission that the disclosures constitute common general knowledge in Australia.

WHAT IS CLAIMED IS:

1. Use of an arenavirus particle or a pharmaceutical composition thereof for the manufacture of a medicament for the treatment of a neoplastic disease in a subject in combination with a chemotherapeutic agent, wherein the arenavirus particle is a tri-segmented arenavirus particle comprising one L segment and two S segments, and wherein the arenavirus particle is engineered to contain an arenavirus genomic segment comprising:
 - (i) a nucleotide sequence encoding a human papillomavirus (HPV)-associated antigen or an antigenic fragment thereof; and
 - (ii) at least one arenavirus open reading frame ("ORF") in a position other than the wild-type position of the ORF, wherein the ORF encodes the glycoprotein ("GP"), the nucleoprotein ("NP"), the matrix protein Z ("Z protein") or the RNA dependent RNA polymerase L ("L protein") of the arenavirus particle.
2. A method for treating a neoplastic disease in a subject in need thereof, wherein the method comprises administering to the subject in need thereof an arenavirus particle or a pharmaceutical composition thereof, and a chemotherapeutic agent, wherein the arenavirus particle is a tri-segmented arenavirus particle comprising one L segment and two S segments, and wherein the arenavirus particle is engineered to contain an arenavirus genomic segment comprising:
 - (i) a nucleotide sequence encoding a human papillomavirus (HPV)-associated antigen or an antigenic fragment thereof; and
 - (ii) at least one arenavirus open reading frame ("ORF") in a position other than the wild-type position of the ORF, wherein the ORF encodes the glycoprotein ("GP"), the nucleoprotein ("NP"), the matrix protein Z ("Z protein") or the RNA dependent RNA polymerase L ("L protein") of the arenavirus particle.

3. A kit comprising two or more containers and instructions for use, wherein one of the containers comprises an arenavirus particle or a pharmaceutical composition thereof and another of the containers comprises a chemotherapeutic agent, wherein the arenavirus particle is a tri-segmented arenavirus particle comprising one L segment and two S segments, and wherein the arenavirus particle is engineered to contain an arenavirus genomic segment comprising:
 - (i) a nucleotide sequence encoding a human papillomavirus (HPV)-associated antigen or an antigenic fragment thereof; and
 - (ii) at least one arenavirus open reading frame (“ORF”) in a position other than the wild-type position of the ORF, wherein the ORF encodes the glycoprotein (“GP”), the nucleoprotein (“NP”), the matrix protein Z (“Z protein”) or the RNA dependent RNA polymerase L (“L protein”) of the arenavirus particle.
4. Use of the kit of claim 3, for the manufacture of a medicament for the treatment of a neoplastic disease in a subject.
5. A method for treating a neoplastic disease in a subject in need thereof, wherein the method comprises administering to the subject in need thereof the arenavirus particle or a pharmaceutical composition thereof and the chemotherapeutic agent of the kit of claim 3.
6. The use of claim 1 or 4, the method of claim 2 or 5, or the kit of claim 3, wherein the chemotherapeutic agent is a platinum-based chemotherapy, a taxane, or a combination thereof.
7. The use of any one of claims 1, 4, and 6, or the method of any one of claims 2, 5, and 6, wherein the neoplastic disease is a human papillomavirus (HPV) induced cancer.
8. The use of any one of claims 1, 4, and 6, or the method of any one of claims 2, 5, and 6, wherein the neoplastic disease is selected from the group consisting of anal cancer;

- cervical cancer; head and neck cancer; mouth cancer; oral cancer; oral cavity cancer; penile cancer; throat cancer; vaginal cancer; vulvar cancer, or a combination thereof.
9. The use of any one of claims 1, 4, and 6-8, the method of any one of claims 2 and 5-8, or the kit of claim 3 or 6, wherein the HPV-associated antigen is selected from the group consisting of HPV E7 and E6 fusion protein, HPV E6, or HPV E7.
 10. The use of any one of claims 1, 4, and 6-9, or the method of any one of claims 2 and 5-9, wherein
 - (i) the arenavirus particle or the pharmaceutical composition thereof and the chemotherapeutic agent are co-administered simultaneously;
 - (ii) the arenavirus particle or the pharmaceutical composition thereof is administered prior to administration of the chemotherapeutic agent, or the arenavirus particle or the pharmaceutical composition thereof is administered after administration of the chemotherapeutic agent, optionally wherein the interval between administration of the arenavirus particle and the chemotherapeutic agent is about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, or more; or
 - (iii) the arenavirus particle or the pharmaceutical composition thereof and the chemotherapeutic agent are administered in a therapeutically effective amount.
 11. The use of any one of claims 1, 4, and 6-9, or the method of any one of claims 2 and 5-9, wherein the arenavirus particle or the pharmaceutical composition thereof and the chemotherapeutic agent are administered on the same day.

12. The use of any one of claims 1, 4, and 6-11, or the method of any one of claims 2, and 5-11, wherein the method or the use comprises administering to the subject the arenavirus particle (a first arenavirus particle) or the pharmaceutical composition thereof, and administering to the subject, after a period of time, a second arenavirus particle or a pharmaceutical composition thereof.
13. The use or the method of claim 12, wherein the second arenavirus particle is derived from a different arenavirus species as the arenavirus particle, and the second arenavirus particle is engineered to contain an arenavirus genomic segment comprising the same HPV-associated antigen or antigenic fragment thereof as those in the arenavirus particle.
14. The use or the method of claim 13, wherein the second arenavirus particle is derived from lymphocytic choriomeningitis virus ("LCMV") and the arenavirus particle is derived from Pichinde virus ("PICV").
15. The use of any one of claims 1, 4, and 6-14, the method of any one of claims 2, and 5-14, or the kit of any one of claims 3, 6, and 9, wherein one of the two S segments is selected from the group consisting of:
 - (i) an S segment, wherein the ORF encoding the NP is under control of an arenavirus 5' UTR;
 - (ii) an S segment, wherein the ORF encoding the Z protein is under control of an arenavirus 5' UTR;
 - (iii) an S segment, wherein the ORF encoding the L protein is under control of an arenavirus 5' UTR;
 - (iv) an S segment, wherein the ORF encoding the GP is under control of an arenavirus 3' UTR;
 - (v) an S segment, wherein the ORF encoding the L protein is under control of an arenavirus 3' UTR; and

- (vi) an S segment, wherein the ORF encoding the Z protein is under control of an arenavirus 3' UTR.
- 16. The use of any one of claims 1, 4, and 6-15, the method of any one of claims 2, and 5-15, or the kit of any one of claims 3, 6, 9, and 15, wherein the ORF encoding the GP is under control of an arenavirus 3' UTR.
- 17. The use of any one of claims 1, 4, and 6-16, the method of any one of claims 2, and 5-16, or the kit of any one of claims 3, 6, 9, 15, and 16, wherein each of the two S segments comprises a nucleotide sequence encoding the HPV-associated antigen or antigenic fragment thereof.
- 18. The use of any one of claims 1, 4, and 6-17, the method of any one of claims 2, and 5-17, or the kit of any one of claims 3, 6, 9, and 15-17, wherein the arenavirus particle is derived from lymphocytic choriomeningitis virus ("LCMV") or Pichinde virus ("PICV"), optionally wherein:
 - (i) the LCMV is MP strain, WE strain, Armstrong strain, or Armstrong Clone 13 strain; or
 - (ii) the PICV is strain Munchique CoAn4763 isolate P18, or P2 strain.
- 19. The use of any one of claims 1, 4, and 6-18, the method of any one of claims 2, and 5-18, or the kit of any one of claims 3, 6, 9, and 15-18, wherein the method or the use further comprises administering an immune checkpoint inhibitor to the subject, or the kit further comprises an immune checkpoint inhibitor, optionally wherein the immune checkpoint inhibitor is an anti-PD-1 antibody.
- 20. A method for treating a human papillomavirus (HPV) induced cancer in a subject in need thereof, wherein the method comprises administering to the subject an arenavirus particle or a pharmaceutical composition thereof, and a chemotherapeutic agent, wherein the

chemotherapeutic agent is a platinum-based chemotherapy, a taxane, or a combination thereof, wherein the arenavirus particle is derived from lymphocytic choriomeningitis virus ("LCMV") or Pichinde virus ("PICV") and is a tri-segmented arenavirus particle comprising one L segment, a first S segment, and a second S segment, and wherein:

- (i) the first S segment comprises an open reading frame encoding the arenaviral glycoprotein GP in a position under control of a genomic 3' untranslated region and an open reading frame encoding a HPV E7 and E6 fusion protein in a position under control of a genomic 5' untranslated region;
- (ii) the second S segment comprises an open reading frame encoding the arenaviral nucleoprotein NP in a position under control of a genomic 3' untranslated region and an open reading frame encoding a HPV E7 and E6 fusion protein in a position under control of a genomic 5' untranslated region; and
- (iii) the L segment comprises an open reading frame encoding ribonucleic acid (RNA) dependent RNA polymerase L in a position under control of a genomic 3' untranslated region and an open reading frame encoding the matrix protein Z in a position under control of a genomic 5' untranslated region.

21. Use of an arenavirus particle or a pharmaceutical composition thereof for the manufacture of a medicament for the treatment of a human papillomavirus (HPV) induced cancer in a subject in combination with a chemotherapeutic agent, wherein the chemotherapeutic agent is a platinum-based chemotherapy, a taxane, or a combination thereof, wherein the arenavirus particle is derived from lymphocytic choriomeningitis virus ("LCMV") or Pichinde virus ("PICV") and is a tri-segmented arenavirus particle comprising one L segment, a first S segment, and a second S segment, and wherein:
- (i) the first S segment comprises an open reading frame encoding the arenaviral glycoprotein GP in a position under control of a genomic 3' untranslated region and an open reading frame encoding a HPV E7 and E6 fusion protein in a position under control of a genomic 5' untranslated region;

- (ii) the second S segment comprises an open reading frame encoding the arenaviral nucleoprotein NP in a position under control of a genomic 3' untranslated region and an open reading frame encoding a HPV E7 and E6 fusion protein in a position under control of a genomic 5' untranslated region; and
 - (iii) the L segment comprises an open reading frame encoding ribonucleic acid (RNA) dependent RNA polymerase L in a position under control of a genomic 3' untranslated region and an open reading frame encoding the matrix protein Z in a position under control of a genomic 5' untranslated region.
- 22. A kit comprising two or more containers and instructions for use, wherein one of the containers comprises an arenavirus particle or a pharmaceutical composition thereof and another of the containers comprises a chemotherapeutic agent, wherein the chemotherapeutic agent is a platinum-based chemotherapy, a taxane, or a combination thereof, wherein the arenavirus particle is derived from lymphocytic choriomeningitis virus ("LCMV") or Pichinde virus ("PICV") and is a tri-segmented arenavirus particle comprising one L segment, a first S segment, and a second S segment, and wherein:
 - (i) the first S segment comprises an open reading frame encoding the arenaviral glycoprotein GP in a position under control of a genomic 3' untranslated region and an open reading frame encoding a HPV E7 and E6 fusion protein in a position under control of a genomic 5' untranslated region;
 - (ii) the second S segment comprises an open reading frame encoding the arenaviral nucleoprotein NP in a position under control of a genomic 3' untranslated region and an open reading frame encoding a HPV E7 and E6 fusion protein in a position under control of a genomic 5' untranslated region; and
 - (iii) the L segment comprises an open reading frame encoding ribonucleic acid (RNA) dependent RNA polymerase L in a position under control of a genomic 3' untranslated region and an open reading frame encoding the matrix protein Z in a position under control of a genomic 5' untranslated region.

23. Use of the kit of claim 22 for the manufacture of a medicament for the treatment of a neoplastic disease in a subject.
24. A method for treating a neoplastic disease in a subject in need thereof, wherein the method comprises administering to the subject in need thereof the arenavirus particle or a pharmaceutical composition thereof and the chemotherapeutic agent of the kit of claim 22.

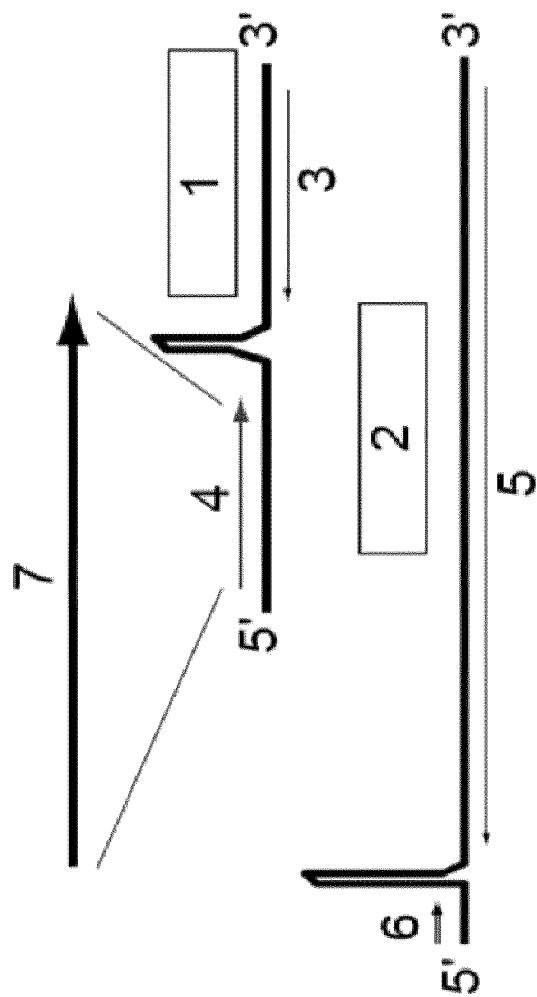


Fig. 1

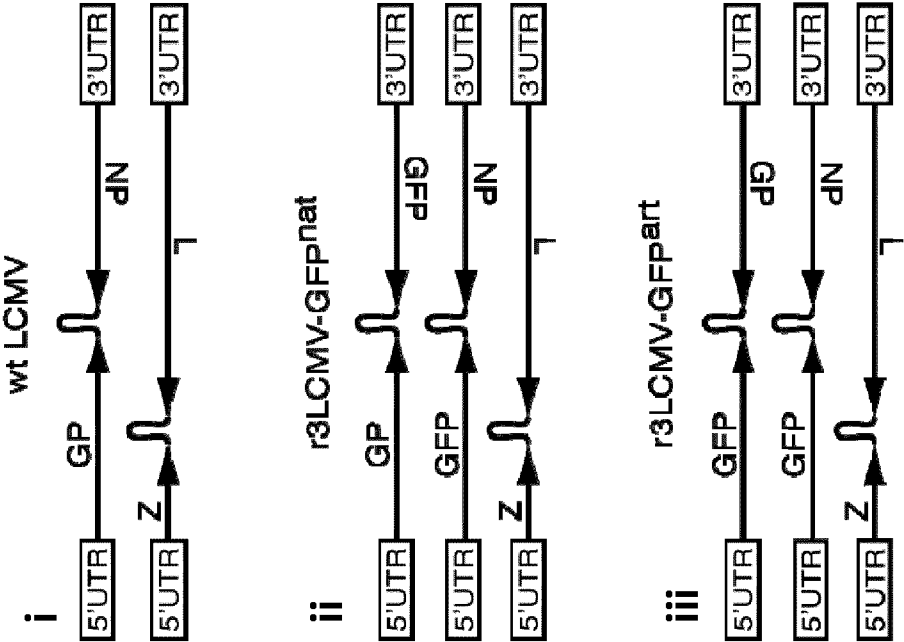


Fig. 2

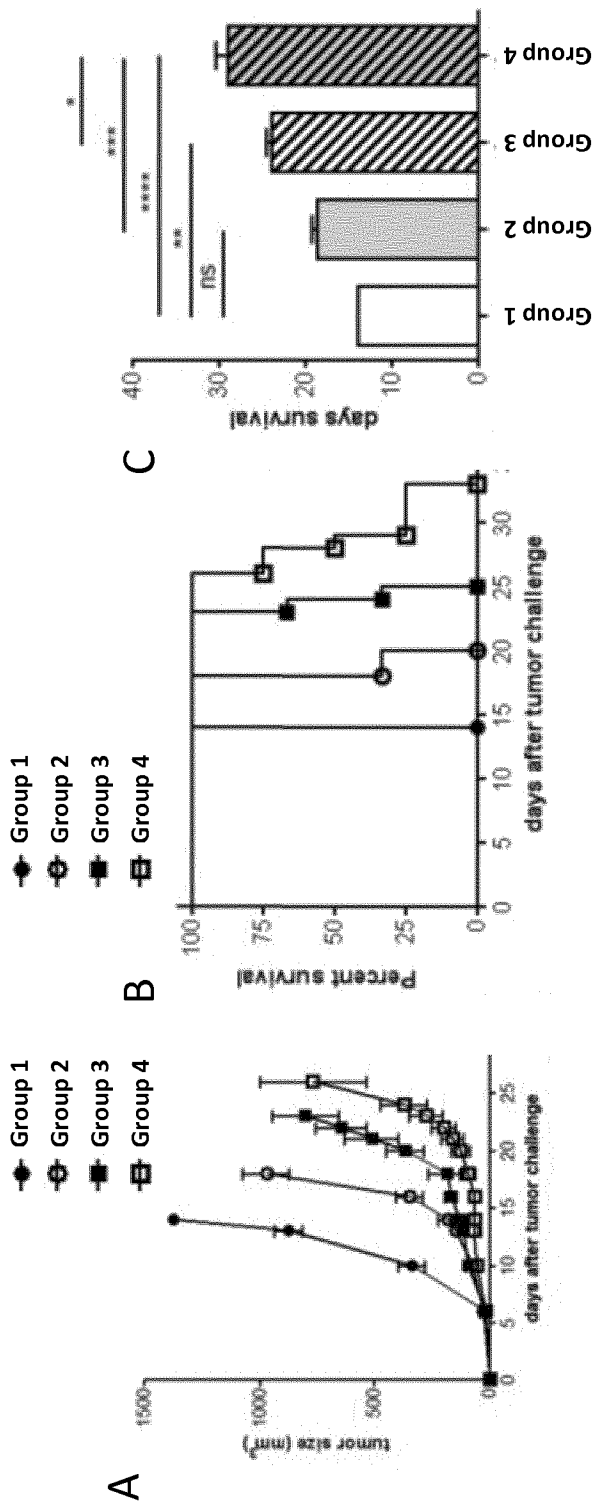


Fig. 3A-C

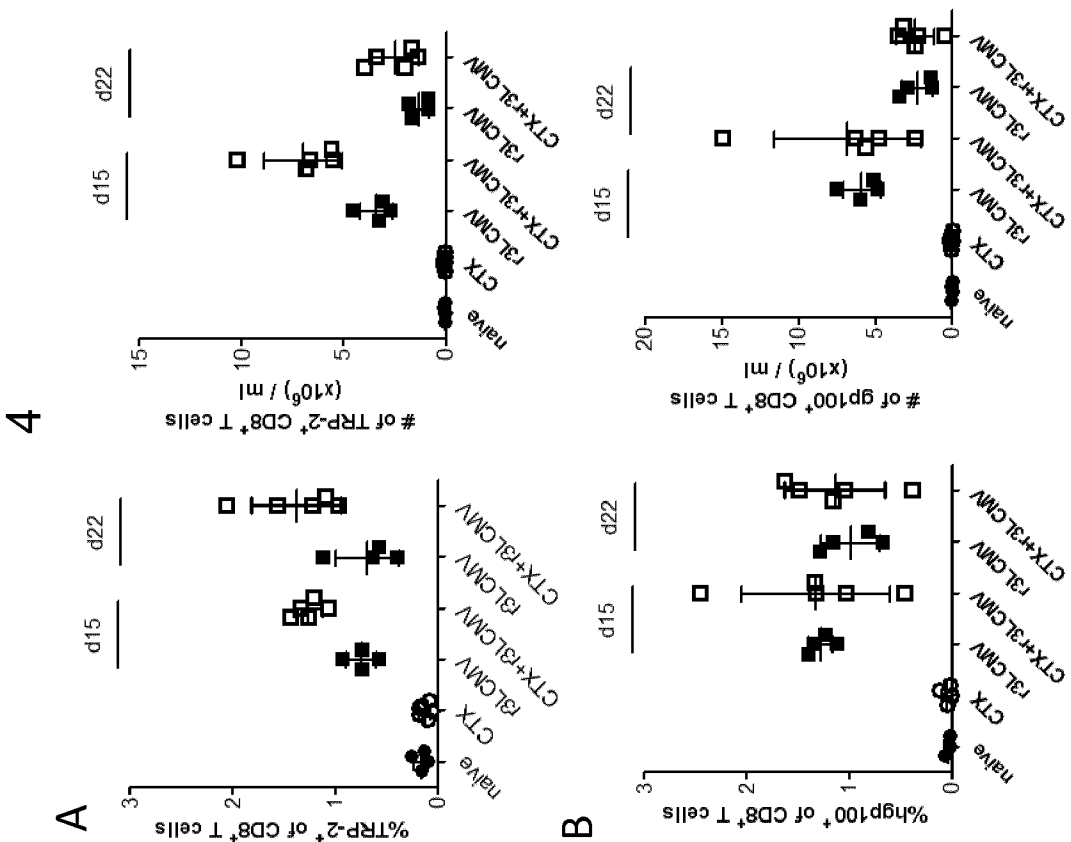


Fig. 4A-B

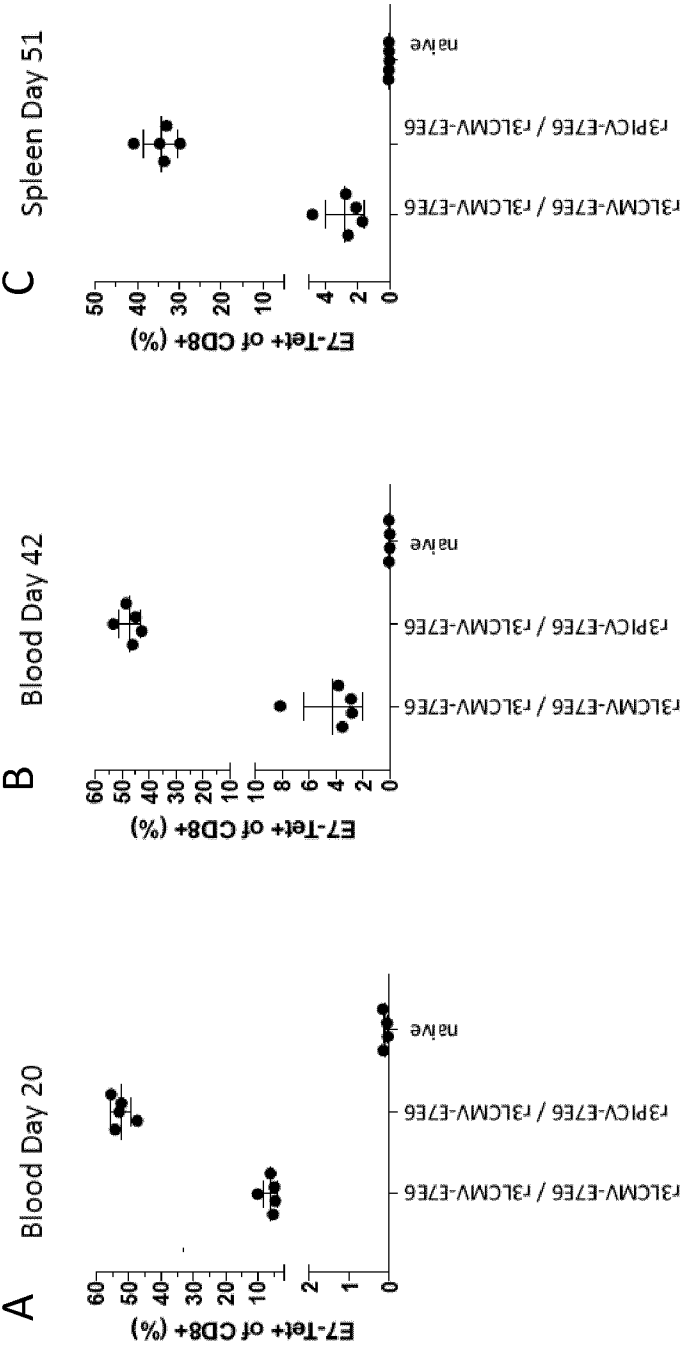


Fig. 5A-C

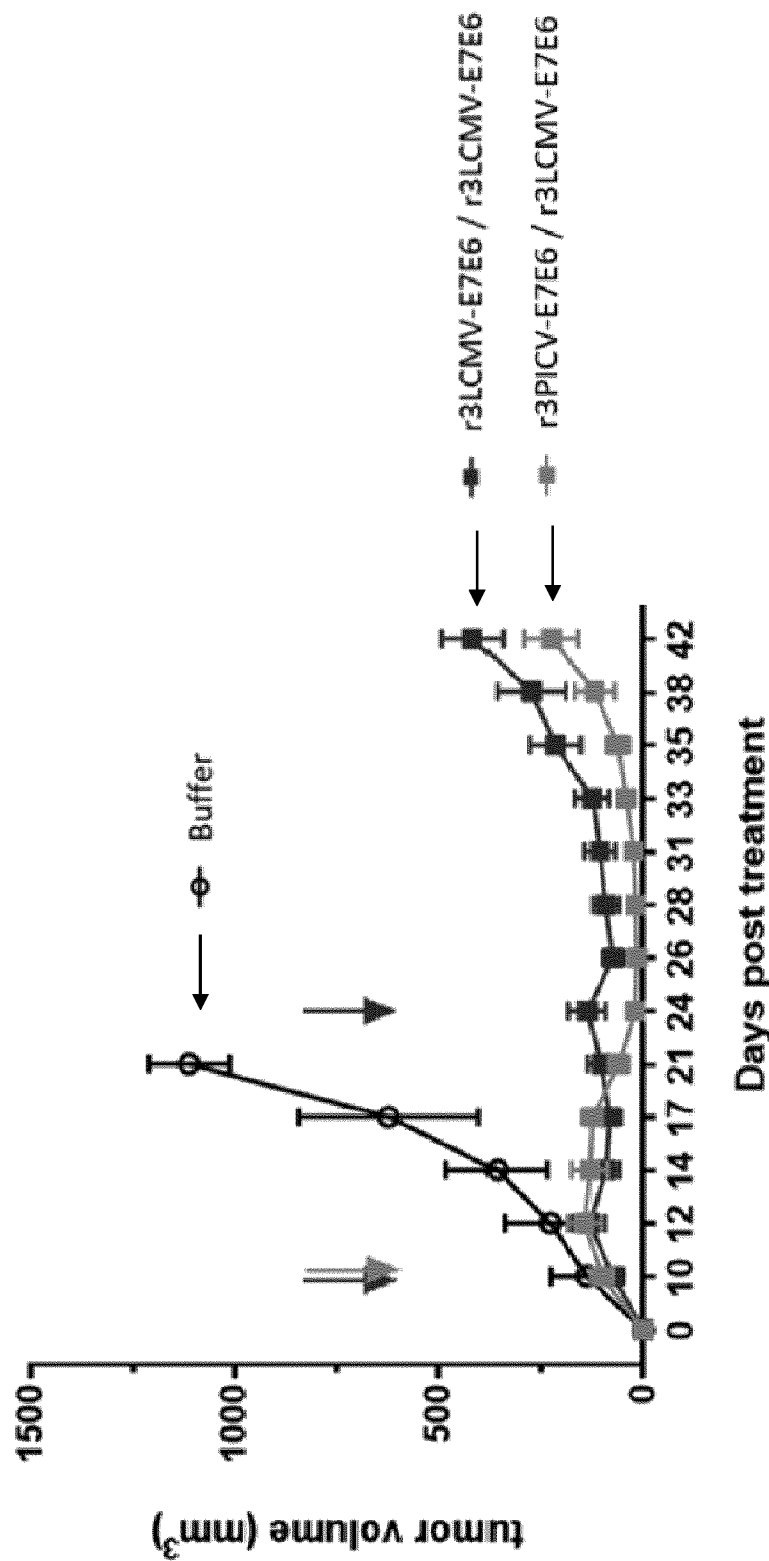


Fig. 6

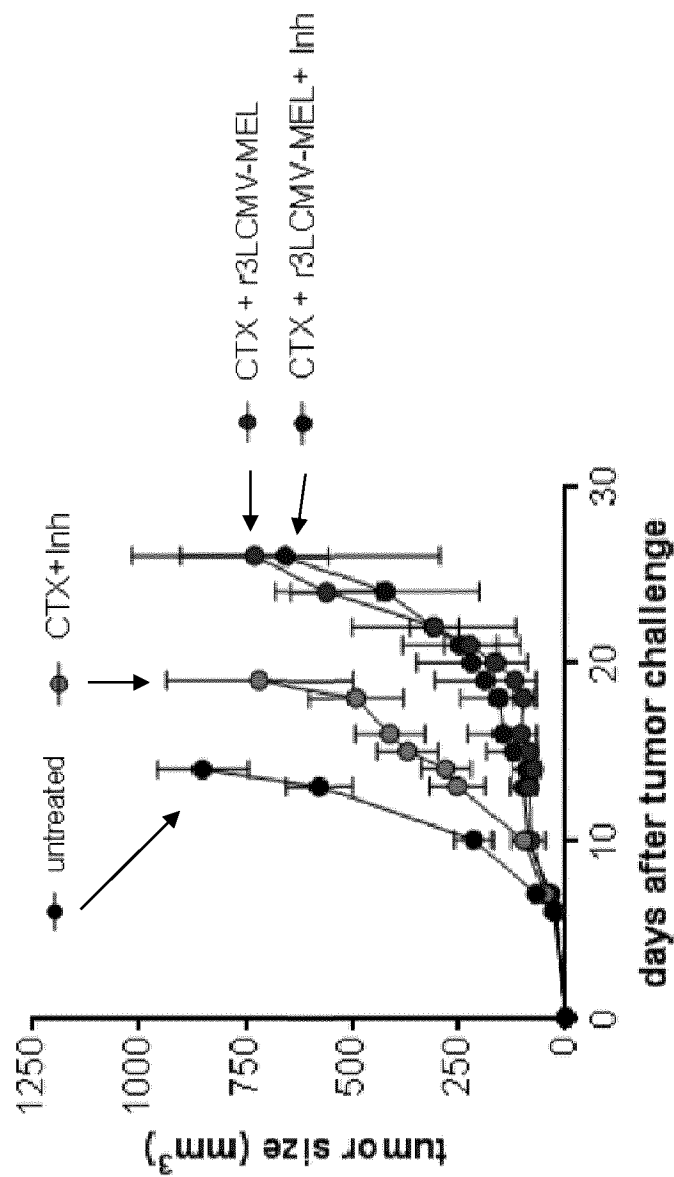


Fig. 7A

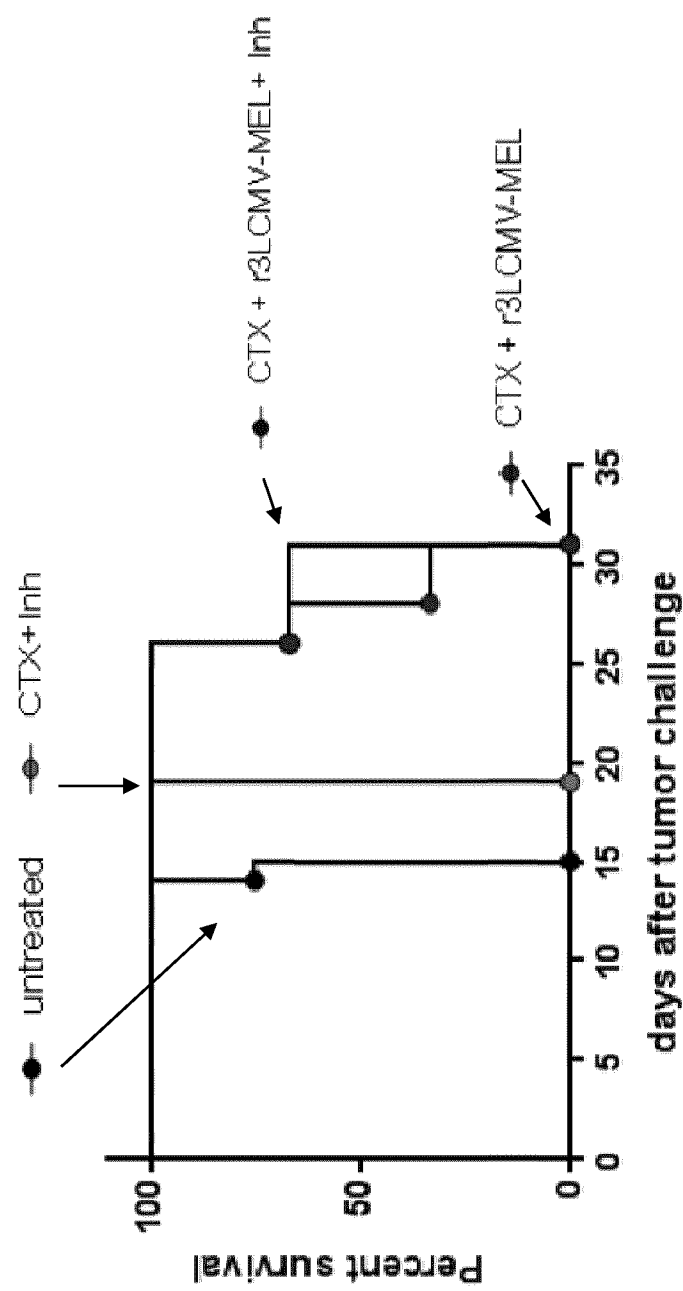


Fig. 7B

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eolf-seql.txt

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eolf-seql.txt

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eolf-seql.txt

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eolf-seql.txt

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eolf-seql.txt

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gtcatcagat ccctgacaac ttaggacct tccctgtgga agagcaccta ttactgaaga	1980
tgtcagccca ggttgtgcat tgaagaggtc agcaagggtc atgccatgtg agtatttggg	2040
gtcctgcttg aattgttttt gatcagtggg ttctctatag aaatgtatgt actgcccatt	2100
ctgtggctga aatattgcta tttctaccgg gtcattaaat ctgccctcaa tgtcaatcca	2160
tgtaggagcg ttaggggtcaa tacctcccat gaggtccttc agcaacattg tttggctgta	2220
gcttaagccc acctgaggtg ggcccgctgc ccagggcgt ggtttgggtg agttggccat	2280
aggcctctca tttgtcagat caattgttgt gttctcccat gctctcccta caactgatgt	2340
tctacaagct atgtatggcc acccctcccc tgaaagacag actttgtaga ggatgttctc	2400
gtaaggattc ctgtctccaa cctgatcaga aacaaacatg ttgagtttct tcttggcccc	2460
aagaactgct ttcaggagat cctcactgtt gcttggctta attaagatgg attccaacat	2520
gttaccacca tctaacaagg ctgcccctgc tttcacagca gcaccgagac tgaaattgta	2580
gccagatatg ttgatgctag actgctgctc agtgatgact cccaagactg ggtgcttgtc	2640
tttcagcctt tcaagggtcac ttaggttcgg gtacttgact gtgtaaagca gcccaaggtc	2700
tgtgagtgtg tgcacaacgt cattgagtga ggtttgtgat tgtttggcca tacaagccat	2760
tgtaagctt ggcattgtgc cgaattgatt gttcagaagt gatgagtcct tcacatccca	2820
gaccctcacc acaccatttg cactctgctg aggtctcctc attccaacca tttgcagaat	2880
ctgagatctt tgggtcaagct gttgtgctgt taagttcccc atgtagactc cagaagttag	2940
aggcctttca gacctcatga ttttagcctt cagtttttca aggtcagctg caaggacat	3000

eolf-seql.txt

```

cagttcttct gcactaagcc tccttacttt tagaacattc ttttttgatg ttgactttag      3060
gtccacaagg gaatacacag tttggttgag gcttctgagt ctctgtaaat ctttgtcatc      3120
cctcttctct ttcctcatga tcctctgaac attgctcacc tcagagaagt ctaatccatt      3180
cagaaggctg gtggcatcct tgatcacagc agctttcaca tctgatgtga agccttgaag      3240
ctctctcctc aatgcctggg tccattgaaa gcttttaact tctttggaca gagacatttt      3300
gtcactcagt ggatttccaa gtcaaatgcg caatcaaaaat gcctaggatc cactgtgcg      3359

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<210> 6

<211> 558

<212> PRT

<213> Artificial Sequence

<220>

<223> NP protein of the MP strain of LCMV

<400> 6

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1           5           10           15

```

```

Arg Arg Glu Leu Gln Gly Phe Thr Ser Asp Val Lys Ala Ala Val Ile
          20           25           30

```

```

Lys Asp Ala Thr Ser Leu Leu Asn Gly Leu Asp Phe Ser Glu Val Ser
          35           40           45

```

```

Asn Val Gln Arg Ile Met Arg Lys Glu Lys Arg Asp Asp Lys Asp Leu
          50           55           60

```

```

Gln Arg Leu Arg Ser Leu Asn Gln Thr Val Tyr Ser Leu Val Asp Leu
65           70           75           80

```

```

Lys Ser Thr Ser Lys Lys Asn Val Leu Lys Val Gly Arg Leu Ser Ala
          85           90           95

```

```

Glu Glu Leu Met Ser Leu Ala Ala Asp Leu Glu Lys Leu Lys Ala Lys
          100          105          110

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eolf-seql.txt

Ile Met Arg Ser Glu Arg Pro Leu Thr Ser Gly Val Tyr Met Gly Asn
115 120 125

Leu Thr Ala Gln Gln Leu Asp Gln Arg Ser Gln Ile Leu Gln Met Val
130 135 140

Gly Met Arg Arg Pro Gln Gln Ser Ala Asn Gly Val Val Arg Val Trp
145 150 155 160

Asp Val Lys Asp Ser Ser Leu Leu Asn Asn Gln Phe Gly Thr Met Pro
165 170 175

Ser Leu Thr Met Ala Cys Met Ala Lys Gln Ser Gln Thr Ser Leu Asn
180 185 190

Asp Val Val Gln Ala Leu Thr Asp Leu Gly Leu Leu Tyr Thr Val Lys
195 200 205

Tyr Pro Asn Leu Ser Asp Leu Glu Arg Leu Lys Asp Lys His Pro Val
210 215 220

Leu Gly Val Ile Thr Glu Gln Gln Ser Ser Ile Asn Ile Ser Gly Tyr
225 230 235 240

Asn Phe Ser Leu Gly Ala Ala Val Lys Ala Gly Ala Ala Leu Leu Asp
245 250 255

Gly Gly Asn Met Leu Glu Ser Ile Leu Ile Lys Pro Ser Asn Ser Glu
260 265 270

Asp Leu Leu Lys Ala Val Leu Gly Ala Lys Lys Lys Leu Asn Met Phe
275 280 285

Val Ser Asp Gln Val Gly Asp Arg Asn Pro Tyr Glu Asn Ile Leu Tyr
290 295 300

Lys Val Cys Leu Ser Gly Glu Gly Trp Pro Tyr Ile Ala Cys Arg Thr
305 310 315 320

eolf-seql.txt

Ser Val Val Gly Arg Ala Trp Glu Asn Thr Thr Ile Asp Leu Thr Asn
325 330 335

Glu Arg Pro Met Ala Asn Ser Pro Lys Pro Ala Pro Gly Ala Ala Gly
340 345 350

Pro Pro Gln Val Gly Leu Ser Tyr Ser Gln Thr Met Leu Leu Lys Asp
355 360 365

Leu Met Gly Gly Ile Asp Pro Asn Ala Pro Thr Trp Ile Asp Ile Glu
370 375 380

Gly Arg Phe Asn Asp Pro Val Glu Ile Ala Ile Phe Gln Pro Gln Asn
385 390 395 400

Gly Gln Tyr Ile His Phe Tyr Arg Glu Pro Thr Asp Gln Lys Gln Phe
405 410 415

Lys Gln Asp Ser Lys Tyr Ser His Gly Met Asp Leu Ala Asp Leu Phe
420 425 430

Asn Ala Gln Pro Gly Leu Thr Ser Ser Val Ile Gly Ala Leu Pro Gln
435 440 445

Gly Met Val Leu Ser Cys Gln Gly Ser Asp Asp Ile Arg Lys Leu Leu
450 455 460

Asp Ser Gln Asn Arg Arg Asp Ile Lys Leu Ile Asp Val Glu Met Thr
465 470 475 480

Lys Glu Ala Ser Arg Glu Tyr Glu Asp Lys Val Trp Asp Lys Tyr Gly
485 490 495

Trp Leu Cys Lys Met His Thr Gly Ile Val Arg Asp Lys Lys Lys Lys
500 505 510

Glu Val Thr Pro His Cys Ala Leu Met Asp Cys Ile Ile Phe Glu Ser
515 520 525

eolf-seql.txt

Ala Ser Lys Ala Arg Leu Pro Asp Leu Lys Thr Val His Asn Ile Leu
530 535 540

Pro His Asp Leu Ile Phe Arg Gly Pro Asn Val Val Thr Leu
545 550 555

<210> 7

<211> 498

<212> PRT

<213> Artificial Sequence

<220>

<223> GP protein of the MP strain of LCMV

<400> 7

Met Gly Gln Ile Val Thr Met Phe Glu Ala Leu Pro His Ile Ile Asp
1 5 10 15

Glu Val Ile Asn Ile Val Ile Ile Val Leu Ile Ile Ile Thr Ser Ile
20 25 30

Lys Ala Val Tyr Asn Phe Ala Thr Cys Gly Ile Leu Ala Leu Ile Ser
35 40 45

Phe Leu Phe Leu Ala Gly Arg Ser Cys Gly Met Tyr Gly Leu Asp Gly
50 55 60

Pro Asp Ile Tyr Lys Gly Val Tyr Arg Phe Lys Ser Val Glu Phe Asp
65 70 75 80

Met Ser Tyr Leu Asn Leu Thr Met Pro Asn Ala Cys Ser Ala Asn Asn
85 90 95

Ser His His Tyr Ile Ser Met Gly Thr Ser Gly Leu Glu Leu Thr Phe
100 105 110

Thr Asn Asp Ser Ile Ile Thr His Asn Phe Cys Asn Leu Thr Ser Ala
115 120 125

Leu Asn Lys Arg Thr Phe Asp His Thr Leu Met Ser Ile Val Ser Ser
130 135 140

eolf-seql.txt

Leu His Leu Ser Ile Arg Gly Val Pro Ser Tyr Lys Ala Val Ser Cys
145 150 155 160

Asp Phe Asn Asn Gly Ile Thr Ile Gln Tyr Asn Leu Ser Phe Ser Asn
165 170 175

Ala Gln Ser Ala Leu Ser Gln Cys Lys Thr Phe Arg Gly Arg Val Leu
180 185 190

Asp Met Phe Arg Thr Ala Phe Gly Gly Lys Tyr Met Arg Ser Gly Trp
195 200 205

Gly Trp Thr Gly Ser Asp Gly Lys Thr Thr Trp Cys Ser Gln Thr Asn
210 215 220

Tyr Gln Tyr Leu Ile Ile Gln Asn Arg Thr Trp Glu Asn His Cys Arg
225 230 235 240

Tyr Ala Gly Pro Phe Gly Met Ser Arg Ile Leu Phe Ala Gln Glu Lys
245 250 255

Thr Arg Phe Leu Thr Arg Arg Leu Ala Gly Thr Phe Thr Trp Thr Leu
260 265 270

Ser Asp Ser Ser Gly Val Glu Asn Pro Gly Gly Tyr Cys Leu Thr Lys
275 280 285

Trp Met Ile Leu Ala Ala Glu Leu Lys Cys Phe Gly Asn Thr Ala Val
290 295 300

Ala Lys Cys Asn Val Asn His Asp Glu Glu Phe Cys Asp Met Leu Arg
305 310 315 320

Leu Ile Asp Tyr Asn Lys Ala Ala Leu Ser Lys Phe Lys Glu Asp Val
325 330 335

Glu Ser Ala Leu His Leu Phe Lys Thr Thr Val Asn Ser Leu Ile Ser
340 345 350

eolf-seql.txt

Asp Gln Leu Leu Met Arg Asn His Leu Arg Asp Leu Met Gly Val Pro
 355 360 365

Tyr Cys Asn Tyr Ser Lys Phe Trp Tyr Leu Glu His Ala Lys Thr Gly
 370 375 380

Glu Thr Ser Val Pro Lys Cys Trp Leu Val Ser Asn Gly Ser Tyr Leu
 385 390 395 400

Asn Glu Thr His Phe Ser Asp Gln Ile Glu Gln Glu Ala Asp Asn Met
 405 410 415

Ile Thr Glu Met Leu Arg Lys Asp Tyr Ile Lys Arg Gln Gly Ser Thr
 420 425 430

Pro Leu Ala Leu Met Asp Leu Leu Met Phe Ser Thr Ser Ala Tyr Leu
 435 440 445

Ile Ser Ile Phe Leu His Leu Val Arg Ile Pro Thr His Arg His Ile
 450 455 460

Lys Gly Gly Ser Cys Pro Lys Pro His Arg Leu Thr Ser Lys Gly Ile
 465 470 475 480

Cys Ser Cys Gly Ala Phe Lys Val Pro Gly Val Glu Thr Thr Trp Lys
 485 490 495

Arg Arg

<210> 8
 <211> 2209
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> L protein of the MP strain of LCMV

<400> 8

eolf-seql.txt

Met Asp Glu Ala Ile Ser Glu Leu Arg Glu Leu Cys Leu Asn His Ile
1 5 10 15

Glu Gln Asp Glu Arg Leu Ser Arg Gln Lys Leu Asn Phe Leu Gly Gln
20 25 30

Arg Glu Pro Arg Met Val Leu Ile Glu Gly Leu Lys Leu Leu Ser Arg
35 40 45

Cys Ile Glu Ile Asp Ser Ala Asp Lys Ser Gly Cys Ile His Asn His
50 55 60

Asp Asp Lys Ser Val Glu Ala Ile Leu Ile Glu Ser Gly Ile Val Cys
65 70 75 80

Pro Gly Leu Pro Leu Ile Ile Pro Asp Gly Tyr Lys Leu Ile Asp Asn
85 90 95

Ser Leu Ile Leu Leu Glu Cys Phe Val Arg Ser Thr Pro Ala Ser Phe
100 105 110

Glu Lys Lys Phe Ile Glu Asp Thr Asn Lys Leu Ala Cys Ile Lys Glu
115 120 125

Asp Leu Ala Ile Ala Gly Ile Thr Leu Val Pro Ile Val Asp Gly Arg
130 135 140

Cys Asp Tyr Asp Asn Ser Phe Met Pro Glu Trp Val Asn Phe Lys Phe
145 150 155 160

Arg Asp Leu Leu Phe Lys Leu Leu Glu Tyr Ser Ser Gln Asp Glu Lys
165 170 175

Val Phe Glu Glu Ser Glu Tyr Phe Arg Leu Cys Glu Ser Leu Lys Thr
180 185 190

Thr Val Asp Lys Arg Ser Gly Ile Asp Ser Met Lys Ile Leu Lys Asp
195 200 205

eolf-seql.txt

Ala Arg Ser Phe His Asn Asp Glu Ile Met Lys Met Cys His Asp Gly
210 215 220

Val Asn Pro Asn Met Asn Cys Asp Asp Val Val Leu Gly Ile Asn Ser
225 230 235 240

Leu Tyr Ser Arg Phe Arg Arg Asp Leu Glu Thr Gly Lys Leu Lys Arg
245 250 255

Ser Phe Gln Lys Ile Asn Pro Gly Asn Leu Ile Lys Glu Phe Ser Glu
260 265 270

Leu Tyr Glu Thr Leu Ala Asp Ser Asp Asp Ile Ser Ala Leu Ser Lys
275 280 285

Glu Ala Val Glu Ser Cys Pro Leu Met Arg Phe Ile Thr Ala Asp Thr
290 295 300

His Gly Tyr Glu Arg Gly Ser Glu Thr Ser Thr Glu Tyr Glu Arg Leu
305 310 315 320

Leu Ser Met Leu Asn Lys Val Lys Ser Leu Lys Leu Leu Asn Thr Arg
325 330 335

Arg Arg Gln Leu Leu Asn Leu Asp Val Leu Cys Leu Ser Ser Leu Ile
340 345 350

Lys Gln Ser Lys Leu Lys Gly Ser Lys Asn Asp Lys His Trp Val Gly
355 360 365

Cys Cys Tyr Gly Ser Val Asn Asp Arg Leu Val Ser Phe His Ser Thr
370 375 380

Lys Glu Glu Phe Ile Arg Leu Leu Arg Asn Arg Arg Lys Ser Lys Ala
385 390 395 400

Tyr Arg Lys Val Ser Leu Glu Asp Leu Phe Arg Thr Ser Ile Asn Glu
405 410 415

eolf-seql.txt

Phe Ile Leu Lys Val Gln Arg Cys Leu Ser Val Val Gly Leu Ser Phe
420 425 430

Gly His Tyr Gly Leu Ser Glu His Leu Glu His Glu Cys His Ile Pro
435 440 445

Phe Ile Glu Phe Glu Asn Phe Met Arg Ser Gly Thr His Pro Ile Met
450 455 460

Tyr Tyr Thr Lys Phe Glu Asp Tyr Asp Phe Gln Pro Asn Thr Glu Gln
465 470 475 480

Leu Arg Asn Met His Ser Leu Lys Arg Leu Ser Ser Val Cys Leu Ala
485 490 495

Leu Thr Asn Ser Met Lys Thr Ser Ser Val Ala Arg Leu Arg Gln Asn
500 505 510

Gln Leu Gly Ser Val Arg Tyr Gln Val Val Glu Cys Lys Glu Val Phe
515 520 525

Cys Gln Val Ile Lys Leu Asp Ser Glu Glu Tyr His Leu Leu Tyr Gln
530 535 540

Lys Thr Gly Glu Ser Ser Arg Cys Tyr Ser Ile Gln Gly Pro Asn Gly
545 550 555 560

His Leu Ile Ser Phe Tyr Ala Asp Pro Lys Arg Phe Phe Leu Pro Ile
565 570 575

Phe Ser Asp Glu Val Leu His Asn Met Ile Asp Thr Met Ile Ser Trp
580 585 590

Ile Arg Ser Cys Pro Asp Leu Lys Asp Ser Ile Asp Asp Val Glu Ile
595 600 605

Ala Leu Arg Thr Leu Leu Leu Leu Met Leu Thr Asn Pro Thr Lys Arg
610 615 620

eolf-seql.txt

Asn Gln Lys Gln Val Gln Asn Ile Arg Tyr Leu Val Met Ala Ile Val
625 630 635 640

Ser Asp Phe Ser Ser Thr Ser Leu Met Asp Lys Leu Lys Glu Asp Leu
645 650 655

Ile Thr Pro Ala Glu Lys Val Val Tyr Lys Leu Leu Arg Phe Leu Ile
660 665 670

Lys Thr Val Phe Gly Thr Gly Glu Lys Val Leu Leu Ser Ala Lys Phe
675 680 685

Lys Phe Met Leu Asn Val Ser Tyr Leu Cys His Leu Ile Thr Lys Glu
690 695 700

Thr Pro Asp Arg Leu Thr Asp Gln Ile Lys Cys Phe Glu Lys Phe Phe
705 710 715 720

Glu Pro Lys Ser Glu Phe Gly Phe Phe Val Asn Pro Lys Glu Ser Ile
725 730 735

Thr Pro Glu Glu Glu Cys Val Phe Tyr Asp Gln Met Lys Lys Phe Thr
740 745 750

Gly Lys Glu Val Asp Cys Gln Arg Thr Thr Pro Gly Val Asn Leu Glu
755 760 765

Ala Phe Ser Met Met Val Ser Ser Phe Asn Asn Gly Thr Leu Ile Phe
770 775 780

Lys Gly Glu Lys Arg Leu Asn Ser Leu Asp Pro Met Thr Asn Ser Gly
785 790 795 800

Cys Ala Thr Ala Leu Asp Leu Ala Ser Asn Lys Ser Val Val Val Asn
805 810 815

Lys His Leu Asn Gly Glu Arg Leu Leu Glu Tyr Asp Phe Asn Lys Leu
820 825 830

eolf-seql.txt

Leu Val Ser Ala Val Ser Gln Ile Thr Glu Ser Phe Met Arg Lys Gln
835 840 845

Lys Tyr Lys Leu Asn His Ser Asp Tyr Glu Tyr Lys Val Ser Lys Leu
850 855 860

Val Ser Arg Leu Val Ile Gly Ser Lys Glu Thr Glu Ala Gly Lys Leu
865 870 875 880

Glu Gly Asp Ser Ala Asp Ile Cys Phe Asp Gly Glu Glu Glu Thr Ser
885 890 895

Phe Phe Lys Asn Leu Glu Asp Lys Val Asn Ser Thr Ile Lys Arg Tyr
900 905 910

Glu Arg Ser Lys Lys Thr Asn Glu Gly Glu Asn Glu Val Gly Phe Glu
915 920 925

Asn Thr Lys Gly Leu His His Leu Gln Thr Ile Leu Ser Gly Lys Met
930 935 940

Ala Tyr Leu Arg Lys Val Ile Leu Ser Glu Ile Ser Phe His Leu Val
945 950 955 960

Glu Asp Phe Asp Pro Ser Cys Leu Thr Asn Asp Asp Met Lys Phe Ile
965 970 975

Cys Glu Ala Ile Glu Thr Ser Thr Glu Leu Ser Pro Leu Tyr Phe Thr
980 985 990

Ser Ala Val Lys Glu Gln Cys Gly Leu Asp Glu Met Ala Lys Asn Leu
995 1000 1005

Cys Arg Lys Phe Phe Ser Glu Gly Asp Trp Phe Ser Cys Met Lys
1010 1015 1020

Met Ile Leu Leu Gln Met Asn Ala Asn Ala Tyr Ser Gly Lys Tyr
1025 1030 1035

eolf-seql.txt

Arg	His	Met	Gln	Arg	Gln	Gly	Leu	Asn	Phe	Lys	Phe	Asp	Trp	Asp
1040						1045					1050			
Lys	Leu	Glu	Glu	Asp	Val	Arg	Ile	Ser	Glu	Arg	Glu	Ser	Asn	Ser
1055						1060					1065			
Glu	Ser	Leu	Ser	Lys	Ala	Leu	Ser	Leu	Thr	Lys	Cys	Met	Ser	Ala
1070						1075					1080			
Ala	Leu	Lys	Asn	Leu	Cys	Phe	Tyr	Ser	Glu	Glu	Ser	Pro	Thr	Ser
1085						1090					1095			
Tyr	Thr	Ser	Val	Gly	Pro	Asp	Ser	Gly	Arg	Leu	Lys	Phe	Ala	Leu
1100						1105					1110			
Ser	Tyr	Lys	Glu	Gln	Val	Gly	Gly	Asn	Arg	Glu	Leu	Tyr	Ile	Gly
1115						1120					1125			
Asp	Leu	Arg	Thr	Lys	Met	Phe	Thr	Arg	Leu	Ile	Glu	Asp	Tyr	Phe
1130						1135					1140			
Glu	Ser	Phe	Ser	Ser	Phe	Phe	Ser	Gly	Ser	Cys	Leu	Asn	Asn	Asp
1145						1150					1155			
Lys	Glu	Phe	Glu	Asn	Ala	Ile	Leu	Ser	Met	Thr	Ile	Asn	Val	Arg
1160						1165					1170			
Glu	Gly	Leu	Leu	Asn	Tyr	Ser	Met	Asp	His	Ser	Lys	Trp	Gly	Pro
1175						1180					1185			
Met	Met	Cys	Pro	Phe	Leu	Phe	Leu	Met	Leu	Leu	Gln	Asn	Leu	Lys
1190						1195					1200			
Leu	Gly	Asp	Asp	Gln	Tyr	Val	Arg	Ser	Gly	Lys	Asp	His	Ile	Ser
1205						1210					1215			
Thr	Leu	Leu	Thr	Trp	His	Met	His	Lys	Leu	Val	Glu	Val	Pro	Phe
1220						1225					1230			

eolf-seql.txt

Pro	Val	Val	Asn	Ala	Met	Met	Lys	Ser	Tyr	Ile	Lys	Ser	Lys	Leu
1235						1240					1245			
Lys	Leu	Leu	Arg	Gly	Ser	Glu	Thr	Thr	Val	Thr	Glu	Arg	Ile	Phe
1250						1255					1260			
Arg	Glu	Tyr	Phe	Glu	Leu	Gly	Ile	Val	Pro	Ser	His	Ile	Ser	Ser
1265						1270					1275			
Leu	Ile	Asp	Met	Gly	Gln	Gly	Ile	Leu	His	Asn	Ala	Ser	Asp	Phe
1280						1285					1290			
Tyr	Gly	Leu	Ile	Ser	Glu	Arg	Phe	Ile	Asn	Tyr	Cys	Ile	Gly	Val
1295						1300					1305			
Ile	Phe	Gly	Glu	Arg	Pro	Glu	Ser	Tyr	Thr	Ser	Ser	Asp	Asp	Gln
1310						1315					1320			
Ile	Thr	Leu	Phe	Asp	Arg	Arg	Leu	Ser	Glu	Leu	Val	Asp	Ser	Asp
1325						1330					1335			
Pro	Glu	Glu	Val	Leu	Val	Leu	Leu	Glu	Phe	His	Ser	His	Leu	Ser
1340						1345					1350			
Gly	Leu	Leu	Asn	Lys	Phe	Ile	Ser	Pro	Lys	Ser	Val	Val	Gly	Arg
1355						1360					1365			
Phe	Ala	Ala	Glu	Phe	Lys	Ser	Arg	Phe	Tyr	Val	Trp	Gly	Glu	Glu
1370						1375					1380			
Val	Pro	Leu	Leu	Thr	Lys	Phe	Val	Ser	Ala	Ala	Leu	His	Asn	Val
1385						1390					1395			
Lys	Cys	Lys	Glu	Pro	His	Gln	Leu	Cys	Glu	Thr	Ile	Asp	Thr	Ile
1400						1405					1410			
Ala	Asp	Gln	Ala	Val	Ala	Asn	Gly	Val	Pro	Val	Ser	Leu	Val	Asn
1415						1420					1425			

eolf-seql.txt

Cys	Ile	Gln	Lys	Arg	Thr	Leu	Asp	Leu	Leu	Lys	Tyr	Ala	Asn	Phe
1430						1435					1440			
Pro	Leu	Asp	Pro	Phe	Leu	Leu	Asn	Thr	Asn	Thr	Asp	Val	Lys	Asp
1445						1450					1455			
Trp	Leu	Asp	Gly	Ser	Arg	Gly	Tyr	Arg	Ile	Gln	Arg	Leu	Ile	Glu
1460						1465					1470			
Glu	Leu	Cys	Pro	Ser	Glu	Thr	Lys	Val	Met	Arg	Arg	Leu	Val	Arg
1475						1480					1485			
Arg	Leu	His	His	Lys	Leu	Lys	Asn	Gly	Glu	Phe	Asn	Glu	Glu	Phe
1490						1495					1500			
Phe	Leu	Asp	Leu	Phe	Asn	Arg	Asp	Lys	Lys	Glu	Ala	Ile	Leu	Gln
1505						1510					1515			
Leu	Gly	Asn	Ile	Leu	Gly	Leu	Glu	Glu	Asp	Leu	Ser	Gln	Leu	Ala
1520						1525					1530			
Asn	Ile	Asn	Trp	Leu	Asn	Leu	Asn	Glu	Leu	Phe	Pro	Leu	Arg	Met
1535						1540					1545			
Val	Leu	Arg	Gln	Lys	Val	Val	Tyr	Pro	Ser	Val	Met	Thr	Phe	Gln
1550						1555					1560			
Glu	Glu	Arg	Ile	Pro	Ser	Leu	Ile	Lys	Thr	Leu	Gln	Asn	Lys	Leu
1565						1570					1575			
Cys	Ser	Lys	Phe	Thr	Arg	Gly	Ala	Gln	Lys	Leu	Leu	Ser	Glu	Ala
1580						1585					1590			
Ile	Asn	Lys	Ser	Ala	Phe	Gln	Ser	Cys	Ile	Ser	Ser	Gly	Phe	Ile
1595						1600					1605			
Gly	Leu	Cys	Lys	Thr	Leu	Gly	Ser	Arg	Cys	Val	Arg	Asn	Lys	Asn
1610						1615					1620			

eolf-seql.txt

Arg	Asp	Asn	Leu	Tyr	Ile	Arg	Lys	Val	Leu	Glu	Asp	Leu	Ala	Met
1625						1630					1635			
Asp	Ala	His	Val	Thr	Ala	Ile	His	Arg	His	Asp	Gly	Ile	Met	Leu
1640						1645					1650			
Tyr	Ile	Cys	Asp	Arg	Gln	Ser	His	Pro	Glu	Ala	His	Cys	Asp	His
1655						1660					1665			
Ile	Ser	Leu	Leu	Arg	Pro	Leu	Leu	Trp	Asp	Tyr	Ile	Cys	Ile	Ser
1670						1675					1680			
Leu	Ser	Asn	Ser	Phe	Glu	Leu	Gly	Val	Trp	Val	Leu	Ala	Glu	Pro
1685						1690					1695			
Val	Lys	Gly	Lys	Asn	Glu	Gly	Ser	Ser	Ser	Leu	Lys	His	Leu	Asn
1700						1705					1710			
Pro	Cys	Asp	Tyr	Val	Ala	Arg	Lys	Pro	Glu	Ser	Ser	Arg	Leu	Leu
1715						1720					1725			
Glu	Asp	Lys	Ile	Ser	Leu	Asn	His	Val	Ile	Gln	Ser	Val	Arg	Arg
1730						1735					1740			
Leu	Tyr	Pro	Lys	Ile	Tyr	Glu	Asp	Gln	Leu	Leu	Pro	Phe	Met	Ser
1745						1750					1755			
Asp	Met	Ser	Ser	Lys	Asn	Met	Arg	Trp	Ser	Pro	Arg	Ile	Lys	Phe
1760						1765					1770			
Leu	Asp	Leu	Cys	Val	Leu	Ile	Asp	Ile	Asn	Ser	Glu	Ser	Leu	Ser
1775						1780					1785			
Leu	Ile	Ser	His	Val	Val	Lys	Trp	Lys	Arg	Asp	Glu	His	Tyr	Thr
1790						1795					1800			
Val	Leu	Phe	Ser	Asp	Leu	Val	Asn	Ser	His	Gln	Arg	Ser	Asp	Ser
1805						1810					1815			

eolf-seql.txt

Ser Leu Val Asp Glu Phe Val Val Ser Thr Arg Asp Val Cys Lys
1820 1825 1830

Asn Phe Leu Lys Gln Val Tyr Phe Glu Ser Phe Val Arg Glu Phe
1835 1840 1845

Val Ala Thr Ser Arg Thr Leu Gly Ser Phe Ser Trp Phe Pro His
1850 1855 1860

Lys Asp Met Met Pro Ser Glu Asp Gly Ala Glu Ala Leu Gly Pro
1865 1870 1875

Phe Gln Ser Phe Ile Leu Lys Val Val Asn Lys Asn Met Glu Arg
1880 1885 1890

Pro Met Phe Arg Asn Asp Leu Gln Phe Gly Phe Gly Trp Phe Ser
1895 1900 1905

Tyr Arg Leu Gly Asp Ile Val Cys Asn Ala Ala Met Leu Ile Lys
1910 1915 1920

Gln Gly Leu Thr Asn Pro Lys Ala Phe Lys Ser Leu Arg Asn Leu
1925 1930 1935

Trp Asp Tyr Met Ile Asn Asn Thr Glu Gly Val Leu Glu Phe Ser
1940 1945 1950

Ile Thr Val Asp Phe Thr His Asn Gln Asn Asn Thr Asp Cys Leu
1955 1960 1965

Arg Lys Phe Ser Leu Ile Phe Leu Val Lys Cys Gln Leu Gln Gly
1970 1975 1980

Pro Gly Val Ala Glu Phe Leu Ser Cys Ser His Leu Phe Lys Gly
1985 1990 1995

Glu Val Asp Arg Arg Phe Leu Asp Glu Cys Leu His Leu Leu Arg
2000 2005 2010

eolf-seql.txt

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 35 40 45

Tyr Leu Cys Arg His Cys Leu Asn Leu Leu Leu Ser Val Ser Asp Arg
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Cys Pro Leu Cys Lys His Pro Leu Pro Thr Lys Leu Lys Ile Ser Thr
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eolf-seql.txt

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eolf-seql.txt

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eolf-seql.txt

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eolf-seql.txt

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eolf-seql.txt

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<211> 3411

<212> DNA

<213> Artificial Sequence

<220>

<223> Junin virus Candid#1 S segment

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eolf-seql.txt

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eolf-seql.txt

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<210> 12

<211> 558

<212> PRT

<213> Artificial Sequence

<220>

eolf-seql.txt

<223> NP protein of the Clone 13 strain of LCMV
(GenBank Accession No. ABC96002.1; GI:86440166)

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20 25 30

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35 40 45

Asn Val Gln Arg Ile Met Arg Lys Glu Lys Arg Asp Asp Lys Asp Leu
50 55 60

Gln Arg Leu Arg Ser Leu Asn Gln Thr Val His Ser Leu Val Asp Leu
65 70 75 80

Lys Ser Thr Ser Lys Lys Asn Val Leu Lys Val Gly Arg Leu Ser Ala
85 90 95

Glu Glu Leu Met Ser Leu Ala Ala Asp Leu Glu Lys Leu Lys Ala Lys
100 105 110

Ile Met Arg Ser Glu Arg Pro Gln Ala Ser Gly Val Tyr Met Gly Asn
115 120 125

Leu Thr Thr Gln Gln Leu Asp Gln Arg Ser Gln Ile Leu Gln Ile Val
130 135 140

Gly Met Arg Lys Pro Gln Gln Gly Ala Ser Gly Val Val Arg Val Trp
145 150 155 160

Asp Val Lys Asp Ser Ser Leu Leu Asn Asn Gln Phe Gly Thr Met Pro
165 170 175

Ser Leu Thr Met Ala Cys Met Ala Lys Gln Ser Gln Thr Pro Leu Asn
180 185 190

eolf-seql.txt

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Tyr Pro Asn Leu Asn Asp Leu Glu Arg Leu Lys Asp Lys His Pro Val
210 215 220

Leu Gly Val Ile Thr Glu Gln Gln Ser Ser Ile Asn Ile Ser Gly Tyr
225 230 235 240

Asn Phe Ser Leu Gly Ala Ala Val Lys Ala Gly Ala Ala Leu Leu Asp
245 250 255

Gly Gly Asn Met Leu Glu Ser Ile Leu Ile Lys Pro Ser Asn Ser Glu
260 265 270

Asp Leu Leu Lys Ala Val Leu Gly Ala Lys Arg Lys Leu Asn Met Phe
275 280 285

Val Ser Asp Gln Val Gly Asp Arg Asn Pro Tyr Glu Asn Ile Leu Tyr
290 295 300

Lys Val Cys Leu Ser Gly Glu Gly Trp Pro Tyr Ile Ala Cys Arg Thr
305 310 315 320

Ser Ile Val Gly Arg Ala Trp Glu Asn Thr Thr Ile Asp Leu Thr Ser
325 330 335

Glu Lys Pro Ala Val Asn Ser Pro Arg Pro Ala Pro Gly Ala Ala Gly
340 345 350

Pro Pro Gln Val Gly Leu Ser Tyr Ser Gln Thr Met Leu Leu Lys Asp
355 360 365

Leu Met Gly Gly Ile Asp Pro Asn Ala Pro Thr Trp Ile Asp Ile Glu
370 375 380

Gly Arg Phe Asn Asp Pro Val Glu Ile Ala Ile Phe Gln Pro Gln Asn
385 390 395 400

eolf-seql.txt

Gly Gln Phe Ile His Phe Tyr Arg Glu Pro Val Asp Gln Lys Gln Phe
405 410 415

Lys Gln Asp Ser Lys Tyr Ser His Gly Met Asp Leu Ala Asp Leu Phe
420 425 430

Asn Ala Gln Pro Gly Leu Thr Ser Ser Val Ile Gly Ala Leu Pro Gln
435 440 445

Gly Met Val Leu Ser Cys Gln Gly Ser Asp Asp Ile Arg Lys Leu Leu
450 455 460

Asp Ser Gln Asn Arg Lys Asp Ile Lys Leu Ile Asp Val Glu Met Thr
465 470 475 480

Arg Glu Ala Ser Arg Glu Tyr Glu Asp Lys Val Trp Asp Lys Tyr Gly
485 490 495

Trp Leu Cys Lys Met His Thr Gly Ile Val Arg Asp Lys Lys Lys Lys
500 505 510

Glu Ile Thr Pro His Cys Ala Leu Met Asp Cys Ile Ile Phe Glu Ser
515 520 525

Ala Ser Lys Ala Arg Leu Pro Asp Leu Lys Thr Val His Asn Ile Leu
530 535 540

Pro His Asp Leu Ile Phe Arg Gly Pro Asn Val Val Thr Leu
545 550 555

<210> 13

<211> 498

<212> PRT

<213> Artificial Sequence

<220>

<223> GP protein of the Clone 13 strain of LCMV
(GenBank Accession No. ABC96001.2; GI:116563462)

<400> 13

eolf-seql.txt

Met Gly Gln Ile Val Thr Met Phe Glu Ala Leu Pro His Ile Ile Asp
1 5 10 15

Glu Val Ile Asn Ile Val Ile Ile Val Leu Ile Val Ile Thr Gly Ile
20 25 30

Lys Ala Val Tyr Asn Phe Ala Thr Cys Gly Ile Phe Ala Leu Ile Ser
35 40 45

Phe Leu Leu Leu Ala Gly Arg Ser Cys Gly Met Tyr Gly Leu Lys Gly
50 55 60

Pro Asp Ile Tyr Lys Gly Val Tyr Gln Phe Lys Ser Val Glu Phe Asp
65 70 75 80

Met Ser His Leu Asn Leu Thr Met Pro Asn Ala Cys Ser Ala Asn Asn
85 90 95

Ser His His Tyr Ile Ser Met Gly Thr Ser Gly Leu Glu Leu Thr Phe
100 105 110

Thr Asn Asp Ser Ile Ile Ser His Asn Phe Cys Asn Leu Thr Ser Ala
115 120 125

Phe Asn Lys Lys Thr Phe Asp His Thr Leu Met Ser Ile Val Ser Ser
130 135 140

Leu His Leu Ser Ile Arg Gly Asn Ser Asn Tyr Lys Ala Val Ser Cys
145 150 155 160

Asp Phe Asn Asn Gly Ile Thr Ile Gln Tyr Asn Leu Thr Phe Ser Asp
165 170 175

Ala Gln Ser Ala Gln Ser Gln Cys Arg Thr Phe Arg Gly Arg Val Leu
180 185 190

Asp Met Phe Arg Thr Ala Phe Gly Gly Lys Tyr Met Arg Ser Gly Trp
195 200 205

eolf-seql.txt

Gly Trp Thr Gly Ser Asp Gly Lys Thr Thr Trp Cys Ser Gln Thr Ser
210 215 220

Tyr Gln Tyr Leu Ile Ile Gln Asn Arg Thr Trp Glu Asn His Cys Thr
225 230 235 240

Tyr Ala Gly Pro Phe Gly Met Ser Arg Ile Leu Leu Ser Gln Glu Lys
245 250 255

Thr Lys Phe Leu Thr Arg Arg Leu Ala Gly Thr Phe Thr Trp Thr Leu
260 265 270

Ser Asp Ser Ser Gly Val Glu Asn Pro Gly Gly Tyr Cys Leu Thr Lys
275 280 285

Trp Met Ile Leu Ala Ala Glu Leu Lys Cys Phe Gly Asn Thr Ala Val
290 295 300

Ala Lys Cys Asn Val Asn His Asp Glu Glu Phe Cys Asp Met Leu Arg
305 310 315 320

Leu Ile Asp Tyr Asn Lys Ala Ala Leu Ser Lys Phe Lys Glu Asp Val
325 330 335

Glu Ser Ala Leu His Leu Phe Lys Thr Thr Val Asn Ser Leu Ile Ser
340 345 350

Asp Gln Leu Leu Met Arg Asn His Leu Arg Asp Leu Met Gly Val Pro
355 360 365

Tyr Cys Asn Tyr Ser Lys Phe Trp Tyr Leu Glu His Ala Lys Thr Gly
370 375 380

Glu Thr Ser Val Pro Lys Cys Trp Leu Val Thr Asn Gly Ser Tyr Leu
385 390 395 400

Asn Glu Thr His Phe Ser Asp Gln Ile Glu Gln Glu Ala Asp Asn Met
405 410 415

eolf-seql.txt

Ile Thr Glu Met Leu Arg Lys Asp Tyr Ile Lys Arg Gln Gly Ser Thr
420 425 430

Pro Leu Ala Leu Met Asp Leu Leu Met Phe Ser Thr Ser Ala Tyr Leu
435 440 445

Val Ser Ile Phe Leu His Leu Val Lys Ile Pro Thr His Arg His Ile
450 455 460

Lys Gly Gly Ser Cys Pro Lys Pro His Arg Leu Thr Asn Lys Gly Ile
465 470 475 480

Cys Ser Cys Gly Ala Phe Lys Val Pro Gly Val Lys Thr Val Trp Lys
485 490 495

Arg Arg

<210> 14
<211> 2210
<212> PRT
<213> Artificial Sequence

<220>
<223> L protein of the Clone 13 strain of LCMV
(GenBank Accession No. ABC96004.1; GI:86440169)

<400> 14

Met Asp Glu Ile Ile Ser Glu Leu Arg Glu Leu Cys Leu Asn Tyr Ile
1 5 10 15

Glu Gln Asp Glu Arg Leu Ser Arg Gln Lys Leu Asn Phe Leu Gly Gln
20 25 30

Arg Glu Pro Arg Met Val Leu Ile Glu Gly Leu Lys Leu Leu Ser Arg
35 40 45

Cys Ile Glu Ile Asp Ser Ala Asp Lys Ser Gly Cys Thr His Asn His
50 55 60

Asp Asp Lys Ser Val Glu Thr Ile Leu Val Glu Ser Gly Ile Val Cys

eolf-seql.txt

```

65              70              75              80

Pro Gly Leu Pro Leu Ile Ile Pro Asp Gly Tyr Lys Leu Ile Asp Asn
      85              90              95

Ser Leu Ile Leu Leu Glu Cys Phe Val Arg Ser Thr Pro Ala Ser Phe
      100             105             110

Glu Lys Lys Phe Ile Glu Asp Thr Asn Lys Leu Ala Cys Ile Arg Glu
      115             120             125

Asp Leu Ala Val Ala Gly Val Thr Leu Val Pro Ile Val Asp Gly Arg
      130             135             140

Cys Asp Tyr Asp Asn Ser Phe Met Pro Glu Trp Ala Asn Phe Lys Phe
      145             150             155             160

Arg Asp Leu Leu Phe Lys Leu Leu Glu Tyr Ser Asn Gln Asn Glu Lys
      165             170             175

Val Phe Glu Glu Ser Glu Tyr Phe Arg Leu Cys Glu Ser Leu Lys Thr
      180             185             190

Thr Ile Asp Lys Arg Ser Gly Met Asp Ser Met Lys Ile Leu Lys Asp
      195             200             205

Ala Arg Ser Thr His Asn Asp Glu Ile Met Arg Met Cys His Glu Gly
      210             215             220

Ile Asn Pro Asn Met Ser Cys Asp Asp Val Val Phe Gly Ile Asn Ser
      225             230             235             240

Leu Phe Ser Arg Phe Arg Arg Asp Leu Glu Ser Gly Lys Leu Lys Arg
      245             250             255

Asn Phe Gln Lys Val Asn Pro Glu Gly Leu Ile Lys Glu Phe Ser Glu
      260             265             270

Leu Tyr Glu Asn Leu Ala Asp Ser Asp Asp Ile Leu Thr Leu Ser Arg

```

eolf-seql.txt

275

280

285

Glu Ala Val Glu Ser Cys Pro Leu Met Arg Phe Ile Thr Ala Glu Thr
 290 295 300

His Gly His Glu Arg Gly Ser Glu Thr Ser Thr Glu Tyr Glu Arg Leu
 305 310 315 320

Leu Ser Met Leu Asn Lys Val Lys Ser Leu Lys Leu Leu Asn Thr Arg
 325 330 335

Arg Arg Gln Leu Leu Asn Leu Asp Val Leu Cys Leu Ser Ser Leu Ile
 340 345 350

Lys Gln Ser Lys Phe Lys Gly Leu Lys Asn Asp Lys His Trp Val Gly
 355 360 365

Cys Cys Tyr Ser Ser Val Asn Asp Arg Leu Val Ser Phe His Ser Thr
 370 375 380

Lys Glu Glu Phe Ile Arg Leu Leu Arg Asn Arg Lys Lys Ser Lys Val
 385 390 395 400

Phe Arg Lys Val Ser Phe Glu Glu Leu Phe Arg Ala Ser Ile Ser Glu
 405 410 415

Phe Ile Ala Lys Ile Gln Lys Cys Leu Leu Val Val Gly Leu Ser Phe
 420 425 430

Glu His Tyr Gly Leu Ser Glu His Leu Glu Gln Glu Cys His Ile Pro
 435 440 445

Phe Thr Glu Phe Glu Asn Phe Met Lys Ile Gly Ala His Pro Ile Met
 450 455 460

Tyr Tyr Thr Lys Phe Glu Asp Tyr Asn Phe Gln Pro Ser Thr Glu Gln
 465 470 475 480

Leu Lys Asn Ile Gln Ser Leu Arg Arg Leu Ser Ser Val Cys Leu Ala

eolf-seql.txt

485

490

495

Leu Thr Asn Ser Met Lys Thr Ser Ser Val Ala Arg Leu Arg Gln Asn
 500 505 510

Gln Ile Gly Ser Val Arg Tyr Gln Val Val Glu Cys Lys Glu Val Phe
 515 520 525

Cys Gln Val Ile Lys Leu Asp Ser Glu Glu Tyr His Leu Leu Tyr Gln
 530 535 540

Lys Thr Gly Glu Ser Ser Arg Cys Tyr Ser Ile Gln Gly Pro Asp Gly
 545 550 555 560

His Leu Ile Ser Phe Tyr Ala Asp Pro Lys Arg Phe Phe Leu Pro Ile
 565 570 575

Phe Ser Asp Glu Val Leu Tyr Asn Met Ile Asp Ile Met Ile Ser Trp
 580 585 590

Ile Arg Ser Cys Pro Asp Leu Lys Asp Cys Leu Thr Asp Ile Glu Val
 595 600 605

Ala Leu Arg Thr Leu Leu Leu Leu Met Leu Thr Asn Pro Thr Lys Arg
 610 615 620

Asn Gln Lys Gln Val Gln Ser Val Arg Tyr Leu Val Met Ala Ile Val
 625 630 635 640

Ser Asp Phe Ser Ser Thr Ser Leu Met Asp Lys Leu Arg Glu Asp Leu
 645 650 655

Ile Thr Pro Ala Glu Lys Val Val Tyr Lys Leu Leu Arg Phe Leu Ile
 660 665 670

Lys Thr Ile Phe Gly Thr Gly Glu Lys Val Leu Leu Ser Ala Lys Phe
 675 680 685

Lys Phe Met Leu Asn Val Ser Tyr Leu Cys His Leu Ile Thr Lys Glu

eolf-seql.txt

690

695

700

Thr Pro Asp Arg Leu Thr Asp Gln Ile Lys Cys Phe Glu Lys Phe Phe
 705 710 715 720

Glu Pro Lys Ser Gln Phe Gly Phe Phe Val Asn Pro Lys Glu Ala Ile
 725 730 735

Thr Pro Glu Glu Glu Cys Val Phe Tyr Glu Gln Met Lys Arg Phe Thr
 740 745 750

Ser Lys Glu Ile Asp Cys Gln His Thr Thr Pro Gly Val Asn Leu Glu
 755 760 765

Ala Phe Ser Leu Met Val Ser Ser Phe Asn Asn Gly Thr Leu Ile Phe
 770 775 780

Lys Gly Glu Lys Lys Leu Asn Ser Leu Asp Pro Met Thr Asn Ser Gly
 785 790 795 800

Cys Ala Thr Ala Leu Asp Leu Ala Ser Asn Lys Ser Val Val Val Asn
 805 810 815

Lys His Leu Asn Gly Glu Arg Leu Leu Glu Tyr Asp Phe Asn Lys Leu
 820 825 830

Leu Val Ser Ala Val Ser Gln Ile Thr Glu Ser Phe Val Arg Lys Gln
 835 840 845

Lys Tyr Lys Leu Ser His Ser Asp Tyr Glu Tyr Lys Val Ser Lys Leu
 850 855 860

Val Ser Arg Leu Val Ile Gly Ser Lys Gly Glu Glu Thr Gly Arg Ser
 865 870 875 880

Glu Asp Asn Leu Ala Glu Ile Cys Phe Asp Gly Glu Glu Glu Thr Ser
 885 890 895

Phe Phe Lys Ser Leu Glu Glu Lys Val Asn Thr Thr Ile Ala Arg Tyr

eolf-seql.txt

900

905

910

Arg Arg Gly Arg Arg Ala Asn Asp Lys Gly Asp Gly Glu Lys Leu Thr
 915 920 925

Asn Thr Lys Gly Leu His His Leu Gln Leu Ile Leu Thr Gly Lys Met
 930 935 940

Ala His Leu Arg Lys Val Ile Leu Ser Glu Ile Ser Phe His Leu Val
 945 950 955 960

Glu Asp Phe Asp Pro Ser Cys Leu Thr Asn Asp Asp Met Lys Phe Ile
 965 970 975

Cys Glu Ala Val Glu Gly Ser Thr Glu Leu Ser Pro Leu Tyr Phe Thr
 980 985 990

Ser Val Ile Lys Asp Gln Cys Gly Leu Asp Glu Met Ala Lys Asn Leu
 995 1000 1005

Cys Arg Lys Phe Phe Ser Glu Asn Asp Trp Phe Ser Cys Met Lys
 1010 1015 1020

Met Ile Leu Leu Gln Met Asn Ala Asn Ala Tyr Ser Gly Lys Tyr
 1025 1030 1035

Arg His Met Gln Arg Gln Gly Leu Asn Phe Lys Phe Asp Trp Asp
 1040 1045 1050

Lys Leu Glu Glu Asp Val Arg Ile Ser Glu Arg Glu Ser Asn Ser
 1055 1060 1065

Glu Ser Leu Ser Lys Ala Leu Ser Leu Thr Gln Cys Met Ser Ala
 1070 1075 1080

Ala Leu Lys Asn Leu Cys Phe Tyr Ser Glu Glu Ser Pro Thr Ser
 1085 1090 1095

Tyr Thr Ser Val Gly Pro Asp Ser Gly Arg Leu Lys Phe Ala Leu

eolf-seql.txt

1100

1105

1110

Ser Tyr Lys Glu Gln Val Gly Gly Asn Arg Glu Leu Tyr Ile Gly
 1115 1120 1125

Asp Leu Arg Thr Lys Met Phe Thr Arg Leu Ile Glu Asp Tyr Phe
 1130 1135 1140

Glu Ser Phe Ser Ser Phe Phe Ser Gly Ser Cys Leu Asn Asn Asp
 1145 1150 1155

Lys Glu Phe Glu Asn Ala Ile Leu Ser Met Thr Ile Asn Val Arg
 1160 1165 1170

Glu Gly Phe Leu Asn Tyr Ser Met Asp His Ser Lys Trp Gly Pro
 1175 1180 1185

Met Met Cys Pro Phe Leu Phe Leu Met Phe Leu Gln Asn Leu Lys
 1190 1195 1200

Leu Gly Asp Asp Gln Tyr Val Arg Ser Gly Lys Asp His Val Ser
 1205 1210 1215

Thr Leu Leu Thr Trp His Met His Lys Leu Val Glu Val Pro Phe
 1220 1225 1230

Pro Val Val Asn Ala Met Met Lys Ser Tyr Val Lys Ser Lys Leu
 1235 1240 1245

Lys Leu Leu Arg Gly Ser Glu Thr Thr Val Thr Glu Arg Ile Phe
 1250 1255 1260

Arg Gln Tyr Phe Glu Met Gly Ile Val Pro Ser His Ile Ser Ser
 1265 1270 1275

Leu Ile Asp Met Gly Gln Gly Ile Leu His Asn Ala Ser Asp Phe
 1280 1285 1290

Tyr Gly Leu Leu Ser Glu Arg Phe Ile Asn Tyr Cys Ile Gly Val

eolf-seql.txt

1295

1300

1305

Ile Phe Gly Glu Arg Pro Glu Ala Tyr Thr Ser Ser Asp Asp Gln
 1310 1315 1320

Ile Thr Leu Phe Asp Arg Arg Leu Ser Asp Leu Val Val Ser Asp
 1325 1330 1335

Pro Glu Glu Val Leu Val Leu Leu Glu Phe Gln Ser His Leu Ser
 1340 1345 1350

Gly Leu Leu Asn Lys Phe Ile Ser Pro Lys Ser Val Ala Gly Arg
 1355 1360 1365

Phe Ala Ala Glu Phe Lys Ser Arg Phe Tyr Val Trp Gly Glu Glu
 1370 1375 1380

Val Pro Leu Leu Thr Lys Phe Val Ser Ala Ala Leu His Asn Val
 1385 1390 1395

Lys Cys Lys Glu Pro His Gln Leu Cys Glu Thr Ile Asp Thr Ile
 1400 1405 1410

Ala Asp Gln Ala Ile Ala Asn Gly Val Pro Val Ser Leu Val Asn
 1415 1420 1425

Ser Ile Gln Arg Arg Thr Leu Asp Leu Leu Lys Tyr Ala Asn Phe
 1430 1435 1440

Pro Leu Asp Pro Phe Leu Leu Asn Thr Asn Thr Asp Val Lys Asp
 1445 1450 1455

Trp Leu Asp Gly Ser Arg Gly Tyr Arg Ile Gln Arg Leu Ile Glu
 1460 1465 1470

Glu Leu Cys Pro Asn Glu Thr Lys Val Val Arg Lys Leu Val Arg
 1475 1480 1485

Lys Leu His His Lys Leu Lys Asn Gly Glu Phe Asn Glu Glu Phe

eolf-seql.txt

1490

1495

1500

Phe Leu Asp Leu Phe Asn Arg Asp Lys Lys Glu Ala Ile Leu Gln
 1505 1510 1515

Leu Gly Asp Leu Leu Gly Leu Glu Glu Asp Leu Asn Gln Leu Ala
 1520 1525 1530

Asp Val Asn Trp Leu Asn Leu Asn Glu Met Phe Pro Leu Arg Met
 1535 1540 1545

Val Leu Arg Gln Lys Val Val Tyr Pro Ser Val Met Thr Phe Gln
 1550 1555 1560

Glu Glu Arg Ile Pro Ser Leu Ile Lys Thr Leu Gln Asn Lys Leu
 1565 1570 1575

Cys Ser Lys Phe Thr Arg Gly Ala Gln Lys Leu Leu Ser Glu Ala
 1580 1585 1590

Ile Asn Lys Ser Ala Phe Gln Ser Cys Ile Ser Ser Gly Phe Ile
 1595 1600 1605

Gly Leu Cys Lys Thr Leu Gly Ser Arg Cys Val Arg Asn Lys Asn
 1610 1615 1620

Arg Glu Asn Leu Tyr Ile Lys Lys Leu Leu Glu Asp Leu Thr Thr
 1625 1630 1635

Asp Asp His Val Thr Arg Val Cys Asn Arg Asp Gly Ile Thr Leu
 1640 1645 1650

Tyr Ile Cys Asp Lys Gln Ser His Pro Glu Ala His Arg Asp His
 1655 1660 1665

Ile Cys Leu Leu Arg Pro Leu Leu Trp Asp Tyr Ile Cys Ile Ser
 1670 1675 1680

Leu Ser Asn Ser Phe Glu Leu Gly Val Trp Val Leu Ala Glu Pro

eolf-seql.txt

1685

1690

1695

Thr Lys Gly Lys Asn Asn Ser Glu Asn Leu Thr Leu Lys His Leu
 1700 1705 1710

Asn Pro Cys Asp Tyr Val Ala Arg Lys Pro Glu Ser Ser Arg Leu
 1715 1720 1725

Leu Glu Asp Lys Val Asn Leu Asn Gln Val Ile Gln Ser Val Arg
 1730 1735 1740

Arg Leu Tyr Pro Lys Ile Phe Glu Asp Gln Leu Leu Pro Phe Met
 1745 1750 1755

Ser Asp Met Ser Ser Lys Asn Met Arg Trp Ser Pro Arg Ile Lys
 1760 1765 1770

Phe Leu Asp Leu Cys Val Leu Ile Asp Ile Asn Ser Glu Ser Leu
 1775 1780 1785

Ser Leu Ile Ser His Val Val Lys Trp Lys Arg Asp Glu His Tyr
 1790 1795 1800

Thr Val Leu Phe Ser Asp Leu Ala Asn Ser His Gln Arg Ser Asp
 1805 1810 1815

Ser Ser Leu Val Asp Glu Phe Val Val Ser Thr Arg Asp Val Cys
 1820 1825 1830

Lys Asn Phe Leu Lys Gln Val Tyr Phe Glu Ser Phe Val Arg Glu
 1835 1840 1845

Phe Val Ala Thr Thr Arg Thr Leu Gly Asn Phe Ser Trp Phe Pro
 1850 1855 1860

His Lys Glu Met Met Pro Ser Glu Asp Gly Ala Glu Ala Leu Gly
 1865 1870 1875

Pro Phe Gln Ser Phe Val Ser Lys Val Val Asn Lys Asn Val Glu

eolf-seql.txt

1880						1885						1890			
Arg	Pro	Met	Phe	Arg	Asn	Asp	Leu	Gln	Phe	Gly	Phe	Gly	Trp	Phe	
	1895					1900					1905				
Ser	Tyr	Arg	Met	Gly	Asp	Val	Val	Cys	Asn	Ala	Ala	Met	Leu	Ile	
	1910					1915					1920				
Arg	Gln	Gly	Leu	Thr	Asn	Pro	Lys	Ala	Phe	Lys	Ser	Leu	Lys	Asp	
	1925					1930					1935				
Leu	Trp	Asp	Tyr	Met	Leu	Asn	Tyr	Thr	Lys	Gly	Val	Leu	Glu	Phe	
	1940					1945					1950				
Ser	Ile	Ser	Val	Asp	Phe	Thr	His	Asn	Gln	Asn	Asn	Thr	Asp	Cys	
	1955					1960					1965				
Leu	Arg	Lys	Phe	Ser	Leu	Ile	Phe	Leu	Val	Arg	Cys	Gln	Leu	Gln	
	1970					1975					1980				
Asn	Pro	Gly	Val	Ala	Glu	Leu	Leu	Ser	Cys	Ser	His	Leu	Phe	Lys	
	1985					1990					1995				
Gly	Glu	Ile	Asp	Arg	Arg	Met	Leu	Asp	Glu	Cys	Leu	His	Leu	Leu	
	2000					2005					2010				
Arg	Thr	Asp	Ser	Val	Phe	Lys	Val	Asn	Asp	Gly	Val	Phe	Asp	Ile	
	2015					2020					2025				
Arg	Ser	Glu	Glu	Phe	Glu	Asp	Tyr	Met	Glu	Asp	Pro	Leu	Ile	Leu	
	2030					2035					2040				
Gly	Asp	Ser	Leu	Glu	Leu	Glu	Leu	Leu	Gly	Ser	Lys	Arg	Ile	Leu	
	2045					2050					2055				
Asp	Gly	Ile	Arg	Ser	Ile	Asp	Phe	Glu	Arg	Val	Gly	Pro	Glu	Trp	
	2060					2065					2070				
Glu	Pro	Val	Pro	Leu	Thr	Val	Lys	Met	Gly	Ala	Leu	Phe	Glu	Gly	

eolf-seql.txt

2075

2080

2085

Arg Asn Leu Val Gln Asn Ile Ile Val Lys Leu Glu Thr Lys Asp
2090 2095 2100

Met Lys Val Phe Leu Ala Gly Leu Glu Gly Tyr Glu Lys Ile Ser
2105 2110 2115

Asp Val Leu Gly Asn Leu Phe Leu His Arg Phe Arg Thr Gly Glu
2120 2125 2130

His Leu Leu Gly Ser Glu Ile Ser Val Ile Leu Gln Glu Leu Cys
2135 2140 2145

Ile Asp Arg Ser Ile Leu Leu Ile Pro Leu Ser Leu Leu Pro Asp
2150 2155 2160

Trp Phe Ala Phe Lys Asp Cys Arg Leu Cys Phe Ser Lys Ser Arg
2165 2170 2175

Ser Thr Leu Met Tyr Glu Thr Val Gly Gly Arg Phe Arg Leu Lys
2180 2185 2190

Gly Arg Ser Cys Asp Asp Trp Leu Gly Gly Ser Val Ala Glu Asp
2195 2200 2205

Ile Asp
2210

<210> 15

<211> 90

<212> PRT

<213> Artificial Sequence

<220>

<223> Z protein of the Clone 13 strain of LCMV
(GenBank Accession No. ABC96003.1; GI:86440168)

<400> 15

Met Gly Gln Gly Lys Ser Arg Glu Glu Lys Gly Thr Asn Ser Thr Asn
1 5 10 15

eolf-seql.txt

Arg Ala Glu Ile Leu Pro Asp Thr Thr Tyr Leu Gly Pro Leu Ser Cys
20 25 30

Lys Ser Cys Trp Gln Lys Phe Asp Ser Leu Val Arg Cys His Asp His
35 40 45

Tyr Leu Cys Arg His Cys Leu Asn Leu Leu Leu Ser Val Ser Asp Arg
50 55 60

Cys Pro Leu Cys Lys Tyr Pro Leu Pro Thr Arg Leu Lys Ile Ser Thr
65 70 75 80

Ala Pro Ser Ser Pro Pro Pro Tyr Glu Glu
85 90

<210> 16
<211> 498
<212> PRT
<213> Artificial Sequence

<220>
<223> GP protein of the WE strain of LCMV

<400> 16

Met Gly Gln Ile Val Thr Met Phe Glu Ala Leu Pro His Ile Ile Asp
1 5 10 15

Glu Val Ile Asn Ile Val Ile Ile Val Leu Ile Ile Ile Thr Ser Ile
20 25 30

Lys Ala Val Tyr Asn Phe Ala Thr Cys Gly Ile Leu Ala Leu Val Ser
35 40 45

Phe Leu Phe Leu Ala Gly Arg Ser Cys Gly Met Tyr Gly Leu Asn Gly
50 55 60

Pro Asp Ile Tyr Lys Gly Val Tyr Gln Phe Lys Ser Val Glu Phe Asp
65 70 75 80

eolf-seql.txt

Met Ser His Leu Asn Leu Thr Met Pro Asn Ala Cys Ser Ala Asn Asn
85 90 95

Ser His His Tyr Ile Ser Met Gly Ser Ser Gly Leu Glu Leu Thr Phe
100 105 110

Thr Asn Asp Ser Ile Leu Asn His Asn Phe Cys Asn Leu Thr Ser Ala
115 120 125

Phe Asn Lys Lys Thr Phe Asp His Thr Leu Met Ser Ile Val Ser Ser
130 135 140

Leu His Leu Ser Ile Arg Gly Asn Ser Asn His Lys Ala Val Ser Cys
145 150 155 160

Asp Phe Asn Asn Gly Ile Thr Ile Gln Tyr Asn Leu Ser Phe Ser Asp
165 170 175

Pro Gln Ser Ala Ile Ser Gln Cys Arg Thr Phe Arg Gly Arg Val Leu
180 185 190

Asp Met Phe Arg Thr Ala Phe Gly Gly Lys Tyr Met Arg Ser Gly Trp
195 200 205

Gly Trp Ala Gly Ser Asp Gly Lys Thr Thr Trp Cys Ser Gln Thr Ser
210 215 220

Tyr Gln Tyr Leu Ile Ile Gln Asn Arg Thr Trp Glu Asn His Cys Arg
225 230 235 240

Tyr Ala Gly Pro Phe Gly Met Ser Arg Ile Leu Phe Ala Gln Glu Lys
245 250 255

Thr Lys Phe Leu Thr Arg Arg Leu Ala Gly Thr Phe Thr Trp Thr Leu
260 265 270

Ser Asp Ser Ser Gly Val Glu Asn Pro Gly Gly Tyr Cys Leu Thr Lys
275 280 285

eolf-seql.txt

Trp Met Ile Leu Ala Ala Glu Leu Lys Cys Phe Gly Asn Thr Ala Val
290 295 300

Ala Lys Cys Asn Val Asn His Asp Glu Glu Phe Cys Asp Met Leu Arg
305 310 315 320

Leu Ile Asp Tyr Asn Lys Ala Ala Leu Ser Lys Phe Lys Gln Asp Val
325 330 335

Glu Ser Ala Leu His Val Phe Lys Thr Thr Val Asn Ser Leu Ile Ser
340 345 350

Asp Gln Leu Leu Met Arg Asn His Leu Arg Asp Leu Met Gly Val Pro
355 360 365

Tyr Cys Asn Tyr Ser Lys Phe Trp Tyr Leu Glu His Ala Lys Thr Gly
370 375 380

Glu Thr Ser Val Pro Lys Cys Trp Leu Val Thr Asn Gly Ser Tyr Leu
385 390 395 400

Asn Glu Thr His Phe Ser Asp Gln Ile Glu Gln Glu Ala Asp Asn Met
405 410 415

Ile Thr Glu Met Leu Arg Lys Asp Tyr Ile Lys Arg Gln Gly Ser Thr
420 425 430

Pro Leu Ala Leu Met Asp Leu Leu Met Phe Ser Thr Ser Ala Tyr Leu
435 440 445

Ile Ser Ile Phe Leu His Leu Val Lys Ile Pro Thr His Arg His Ile
450 455 460

Lys Gly Gly Ser Cys Pro Lys Pro His Arg Leu Thr Asn Lys Gly Ile
465 470 475 480

Cys Ser Cys Gly Ala Phe Lys Val Pro Gly Val Lys Thr Ile Trp Lys
485 490 495

Arg Arg

<210> 17
 <211> 35
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> WE specific primer

<400> 17
 aatcgtctct aaggatgggt cagattgtga caatg 35

<210> 18
 <211> 35
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> WE specific fusion-primer carrying an overhang
 complementary to the WET-specific primer

<400> 18
 aatcgtctct aaggatgggt cagattgtga caatg 35

<210> 19
 <211> 37
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> WE specific primer

<400> 19
 ctcggtgatc atgttatctg cttcttggtc gatttga 37

<210> 20
 <211> 34
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> WE specific fusion-primer complementary to the
 WE-sequence

<400> 20
 aatcgtctct ttctttatct cctcttccag atgg 34

<210> 21
 <211> 23
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Primer specific for LCMV NP

<400> 21
 ggctcccaga tctgaaaact gtt 23

<210> 22
 <211> 22
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> NP- and GP-specific primers

<400> 22
 gctggcttgt cactaatggc tc 22