Summary ~~of the invention~~

[0005] The present ~~invention~~disclosure addresses the above needs by providing a recombinant rhabdovirus, such as a vesicular stomatitis virus, which encodes in its genome a CD80 extracellular domain Fc-fusion protein or a functional variant thereof, preferably a human CD80 extracellular domain.

[0006] It is to be understood that any ~~embodiment~~ example relating to a specific aspect might also be combined with another ~~embodiment~~ example also relating to that specific aspect, even in multiple tiers and combinations comprising several ~~embodiments~~examples to that specific aspect.

[0007] ~~In a first aspect, the~~The present ~~invention~~disclosure relates to a recombinant rhabdovirus encoding in its genome at least one CD80 extracellular domain Fc-fusion protein or a functional variant thereof, wherein the CD80 extracellular domain Fc-fusion protein comprises the extracellular domain of CD80 and further comprises the Fc domain of an IgG.

[0008] In one ~~embodiment~~ example~~relating to the first aspect~~, the CD80 extracellular domain Fc-fusion protein or functional variant thereof is selected from the group comprising: (i) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, (ii) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1, (iii) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2, (iv) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1 and the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2, (v) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain consists of amino acids 1-207 of SEQ ID NO:4 or has at least 80% identity to amino acids 1-207 of SEQ ID NO:4 and the Fc domain consists of amino acids 208-433 of SEQ ID NO:4 or has at least 80% identity to amino acids 208-433 of SEQ ID NO:4, (vi) a CD80 extracellular domain Fc-fusion

protein according to any of (i)-(v) further comprising a signal peptide sequence, (vii) a CD80 extracellular domain Fc-fusion protein, comprising SEQ ID NO:3 or having at least 80% identity to SEQ ID NO:3.

[0009] In one ~~embodiment~~example ~~relating to the first aspect~~, the recombinant rhabdovirus is a vesiculovirus.

[0010] In one ~~embodiment~~example ~~relating to the first aspect~~, the vesiculovirus is selected from the group comprising: vesicular stomatitis alagoas virus (VSAV), carajás virus (CJSV), chandipura virus (CHPV), cocal virus (COCV), vesicular stomatitis Indiana virus (VSIV), isfahan virus (ISFV), maraba virus (MARAV), vesicular stomatitis New Jersey virus (VSNJV), or piry virus (PIRYV), preferably a vesicular stomatitis Indiana virus (VSIV) or preferably a vesicular stomatitis New Jersey virus (VSNJV).

[0011] In one ~~embodiment~~example ~~relating to the first aspect~~, the recombinant rhabdovirus is replication-competent.

[0012] In one ~~embodiment~~example ~~relating to the first aspect~~, the CD80 extracellular domain is human CD80 extracellular domain.

[0013] In one ~~embodiment~~example ~~relating to the first aspect~~, the recombinant rhabdovirus lacks a functional gene coding for glycoprotein G, and/or lacks a functional glycoprotein G; or, the gene coding for the glycoprotein G is replaced by the gene coding for the glycoprotein GP of another virus, and/or the glycoprotein G is replaced by the glycoprotein GP of another virus; or, the gene coding for the glycoprotein G is replaced by the gene coding for the glycoprotein GP of an arenavirus, and/or the glycoprotein G is replaced by the glycoprotein GP of an arenavirus. In a further preferred ~~embodiment~~example, the gene coding for the glycoprotein G is replaced by the gene coding for the glycoprotein GP of Dandenong virus or Mopeia virus, and/or the glycoprotein G is replaced by the glycoprotein GP of Dandenong virus or Mopeia virus. Even more preferred, the gene coding for the glycoprotein G is replaced by the gene coding for the glycoprotein GP of lymphocyte choriomeningitis virus (LCMV), and/or the glycoprotein G is replaced by the glycoprotein GP of LCMV.

[0014] In a preferred ~~embodiment~~example ~~relating to the first aspect~~, the ~~invention~~disclosure provides a recombinant vesicular stomatitis virus encoding in its genome at least one CD80 extracellular domain Fc-fusion protein or a functional variant thereof, wherein the CD80 extracellular domain Fc-fusion protein comprises the extracellular domain of

CD80 and further comprises the Fc domain of an IgG. In a related ~~embodiment~~example, the CD80 extracellular domain Fc-fusion protein is selected from the group comprising: (i) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, (ii) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1, (iii) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2, (iv) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1 and the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2, (v) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain consists of amino acids 1-207 of SEQ ID NO:4 or has at least 80% identity to amino acids 1-207 of SEQ ID NO:4 and the Fc domain consists of amino acids 208-433 of SEQ ID NO:4 or has at least 80% identity to amino acids 208-433 of SEQ ID NO:4, (vi) a CD80 extracellular domain Fc-fusion protein according to any of (i)-(v) further comprising a signal peptide sequence, or (vii) a CD80 extracellular domain Fc-fusion protein, comprising SEQ ID NO:3 or having at least 80% identity to SEQ ID NO:3; and wherein the gene coding for the glycoprotein G of the recombinant vesicular stomatitis virus is replaced by the gene coding for the glycoprotein GP of lymphocyte choriomeningitis virus (LCMV), and/or the glycoprotein G is replaced by the glycoprotein GP of LCMV.

[0015] ~~In a second aspect, the~~The present ~~invention~~disclosure relates to a recombinant vesicular stomatitis virus, encoding in its genome at least for a vesicular stomatitis virus nucleoprotein (N), large protein (L), phosphoprotein (P), matrix protein (M), glycoprotein (G) and at least one CD80 extracellular domain Fc-fusion protein or a functional variant thereof, wherein the CD80 extracellular domain Fc-fusion protein comprises the extracellular domain of CD80 and further comprises the Fc domain of an IgG.

[0015a] In one aspect, the present disclosure relates to a recombinant vesicular stomatitis virus encoding in its genome at least one CD80 extracellular domain Fc-fusion protein or a functional variant thereof, wherein the CD80 extracellular domain Fc-fusion protein comprises the extracellular domain of CD80 and further comprises the Fc domain of an IgG, wherein the gene coding for the glycoprotein G of the recombinant vesicular stomatitis virus is replaced by the gene coding for the glycoprotein GP of Lymphocyte choriomeningitis virus (LCMV), and/or the glycoprotein G is replaced by the glycoprotein GP of LCMV.

[0015b] In another aspect, the present disclosure relates to a recombinant vesicular stomatitis virus, encoding in its genome at least for a vesicular stomatitis virus nucleoprotein (N), large protein (L), phosphoprotein (P), matrix protein (M), glycoprotein (G) and at least one CD80 extracellular domain Fc-fusion protein or a functional variant thereof, wherein the CD80 extracellular domain Fc-fusion protein comprises the extracellular domain of CD80 and further comprises the Fc domain of an IgG, wherein the gene coding for the glycoprotein G of the recombinant vesicular stomatitis virus is replaced by the gene coding for the glycoprotein GP of Lymphocyte choriomeningitis virus (LCMV), and/or the glycoprotein G is replaced by the glycoprotein GP of LCMV.

[0015c] In another aspect, the present disclosure relates to a recombinant vesicular stomatitis virus encoding in its genome a vesicular stomatitis virus nucleoprotein (N), large protein (L), phosphoprotein (P), matrix protein (M), glycoprotein (G) and at least one CD80 extracellular domain Fc-fusion protein or a functional variant thereof, wherein the CD80 extracellular domain Fc-fusion protein comprises the extracellular domain of CD80 and further comprises the Fc domain of an IgG and is selected from the group comprising:

(i) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1,

(ii) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1,

(iii) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2,

(iv) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1 and the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2,

(v) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain consists of amino acids 1-207 of SEQ ID NO:4 or has at least 80% identity to amino acids 1-207 of SEQ ID NO:4 and the Fc domain consists of amino acids 208-433 of SEQ ID NO:4 or has at least 80% identity to amino acids 208-433 of SEQ ID NO:4,

(vi) a CD80 extracellular domain Fc-fusion protein according to any of (i)-(v) further comprising a signal peptide sequence, and

(vii) a CD80 extracellular domain Fc-fusion protein, comprising SEQ ID NO:3 or having at least 80% identity to SEQ ID NO:3,

wherein, the gene coding for the glycoprotein G of the vesicular stomatitis virus is replaced by the gene coding for the glycoprotein GP of lymphocyte choriomeningitis virus (LCMV), and/or the glycoprotein G is replaced by the glycoprotein GP of LCMV, and wherein

- the nucleoprotein (N) comprises an amino acid as set forth in SEQ ID NO:7 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:7,
- the phosphoprotein (P) comprises an amino acid as set forth in SEQ ID NO:8 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:8,
- the large protein (L) comprises an amino acid as set forth in SEQ ID NO:9 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:9, and
- the matrix protein (M) comprises an amino acid as set forth in SEQ ID NO:10 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:10.

[0016] In one ~~embodiment~~example ~~relating to the second aspect~~, the nucleoprotein (N) comprises an amino acid sequence as set forth in SEQ ID NO:7 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:7.

[0017] In one ~~embodiment~~example ~~relating to the second aspect~~, the phosphoprotein (P) comprises an amino acid sequence as set forth in SEQ ID NO:8 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:8.

[0018] In one ~~embodiment~~example ~~relating to the second aspect~~, the large protein (L) comprises an amino acid sequence as set forth in SEQ ID NO:9 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:9.

[0019] In one ~~embodiment~~example ~~relating to the second aspect~~, the matrix protein (M) comprises an amino acid sequence as set forth in SEQ ID NO:10 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:10.

[0020] In a preferred ~~embodiment~~example ~~relating to the second aspect~~, the nucleoprotein (N) comprises an amino acid sequence as set forth in SEQ ID NO:7 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:7, the phosphoprotein (P) comprises an amino acid sequence as set forth in SEQ ID NO:8 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:8, the large protein (L) comprises an amino acid sequence as set forth in SEQ ID NO:9 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:9, and the matrix protein (M) comprises an amino acid sequence as set forth in SEQ ID NO:10 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:10.

[0021] In one ~~embodiment~~example ~~relating to the second aspect~~, the recombinant vesicular stomatitis virus is replication-competent.

[0022] In one ~~embodiment~~example ~~relating to the second aspect~~, the recombinant vesicular stomatitis virus lacks a functional gene coding for glycoprotein G, and/or lacks a functional glycoprotein G; or, the gene coding for the glycoprotein G is replaced by the gene coding for the glycoprotein GP of another virus, and/or the glycoprotein G is replaced by the glycoprotein GP of another virus; or, the gene coding for the glycoprotein G is replaced by the gene coding for the glycoprotein GP of lymphocyte choriomeningitis virus (LCMV), and/or the glycoprotein G is replaced by the glycoprotein GP of LCMV.

[0023] In one ~~embodiment~~example ~~relating to the second aspect~~, the CD80 extracellular domain Fc-fusion protein is selected from the group comprising: (i) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, (ii) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1, (iii) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2, (iv) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1 and the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2, (v) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain consists of amino acids 1-207 of SEQ ID NO:4 or has at least 80% identity to amino acids 1-207 of SEQ ID NO:4 and the Fc domain consists of amino acids 208-433 of SEQ ID NO:4 or has at least 80% identity to amino acids 208-433 of SEQ ID NO:4, (vi) a CD80 extracellular domain Fc-fusion protein according to any of (i)-(v) further comprising a signal peptide sequence, or (vii) a CD80 extracellular domain Fc-fusion protein, comprising SEQ ID NO:3 or having at least 80% identity to SEQ ID NO:3.

[0024] In a preferred ~~embodiment~~example ~~relating to the second aspect~~, the ~~invention~~disclosure provides a recombinant vesicular stomatitis virus encoding in its genome a vesicular stomatitis virus nucleoprotein (N), large protein (L), phosphoprotein (P), matrix protein

87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:9, and the matrix protein (M) comprises an amino acid as set forth in SEQ ID NO:10 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:10.

[0024a] In another aspect, the present disclosure provides a recombinant vesicular stomatitis virus encoding in its RNA genome at least one CD80 extracellular domain Fc-fusion protein or a functional variant thereof, wherein the CD80 extracellular domain Fc-fusion protein comprises the extracellular domain of CD80 and further comprises the Fc domain of an IgG, wherein the RNA genome of the recombinant rhabdovirus comprises or consists of a coding sequence identical or at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 24.

[0025] ~~In a third aspect, the~~The present ~~invention~~disclosure provides for a pharmaceutical composition, characterized in that the composition comprises a recombinant rhabdovirus according to the ~~first aspect~~disclosure or any of its ~~embodiments~~examples, or a recombinant vesicular stomatitis virus according ~~the second aspect~~to the disclosure or any of its ~~embodiments~~examples.

[0025a] In another aspect, the present disclosure provides a pharmaceutical composition, characterized in that the composition comprises a recombinant vesicular stomatitis virus as described herein.

[0026] ~~In a fourth aspect, the~~The present ~~invention~~disclosure provides for a recombinant rhabdovirus according to the ~~first aspect~~disclosure or any of its ~~embodiments~~examples, or a recombinant vesicular stomatitis virus according ~~the second aspect~~to the disclosure or any of its ~~embodiments~~examples, or a pharmaceutical composition according to the ~~third aspect~~disclosure or any of its ~~embodiments~~examples, for use as a medicament.

[0026a] In another aspect, the present disclosure provides a recombinant vesicular stomatitis virus as described herein or a pharmaceutical composition as described herein for use as a medicament.

[0027] In one ~~embodiment~~example ~~relating to the fourth aspect~~, the ~~invention~~disclosure provides a recombinant rhabdovirus, a recombinant vesicular stomatitis virus, or a pharmaceutical composition for the use in the treatment of cancer, preferably solid cancers. In a preferred ~~embodiment~~example, the solid cancer is selected from the list comprising: reproductive tumor, an ovarian tumor, a pancreatic tumor, a testicular tumor, an endocrine tumor, a gastrointestinal tumor, a liver tumor, a kidney tumor, a colon tumor, a colorectal tumor, a bladder tumor, a prostate tumor, a skin tumor, melanoma, a respiratory tumor, a lung tumor, a breast tumor, a head & neck tumor, a head and neck squamous-cell carcinoma (HNSCC), and a bone tumor.

[0027a] In another aspect, the present disclosure provides a recombinant vesicular stomatitis virus as described herein or a pharmaceutical composition as described herein for use in the treatment of cancer, preferably solid cancers.

[0027a] In another aspect, the present disclosure provides use of a recombinant vesicular stomatitis virus as described herein or a pharmaceutical composition as described herein in the manufacture of a medicament for the treatment of cancer, preferably solid cancers.

[0028] In one ~~embodiment~~example ~~relating to the fourth aspect~~, the recombinant rhabdovirus, the recombinant vesicular stomatitis virus, or the pharmaceutical composition is to be administered intratumorally or intravenously. In another related ~~embodiment~~example, the recombinant rhabdovirus, the recombinant vesicular stomatitis virus or the pharmaceutical composition is to be administered at least once intratumorally and subsequently intravenously. In a further related ~~embodiment~~example, the subsequent intravenous administration of the recombinant rhabdovirus, recombinant vesicular stomatitis virus or the pharmaceutical composition is given 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23

days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days or 31 days after the initial intratumoral administration.

[0029] ~~In a fifth aspect, the~~The present ~~invention~~disclosure provides for a composition comprising a recombinant rhabdovirus according to the ~~first aspect~~disclosure or any of its ~~embodiments~~examples, or a recombinant vesicular stomatitis virus according ~~the second aspect~~to the disclosure or any of its ~~embodiments~~examples and further an inhibitor, wherein the inhibitor is a PD-1 pathway inhibitor or a SMAC mimetic.

[0029a] In another aspect, the present disclosure provides a composition comprising a recombinant vesicular stomatitis virus as described herein and further a PD-1 pathway inhibitor or a SMAC mimetic.

[0030] In one ~~embodiment~~example ~~relating to the fifth aspect~~, the PD-1 pathway inhibitor is an antagonistic antibody, which is directed against PD-1 or PD-L1. In a further related ~~embodiment~~example, the SMAC mimetic is selected from the group consisting of any of compounds 1 to 26 from table 2 or a pharmaceutically acceptable salt of one of these compounds. In another related ~~embodiment~~example, the PD-1 pathway inhibitor is an antagonist selected from the group consisting of pembrolizumab, nivolumab, pidilizumab, atezolizumab, avelumab, durvalumab, PDR-001, PD1-1, PD1-2, PD1-3, PD1-4 and PD1-5 (as shown in Table 1). In a most preferred ~~embodiment~~example, the PD-1 pathway inhibitor is BI-754091.

[0031] ~~In a sixth aspect, the~~The present ~~invention~~disclosure provides a kit of parts comprising: a recombinant rhabdovirus, a recombinant vesicular stomatitis virus or a pharmaceutical composition as defined ~~in any of the first to third aspects~~herein or any of their ~~embodiments~~examples, and a PD-1 pathway inhibitor or SMAC mimetic as defined in any of the ~~embodiments~~examples ~~relating to the fifth aspect~~.

[0031a] In another aspect, the present disclosure provides a kit of parts comprising:

a) a recombinant vesicular stomatitis virus as described herein or a pharmaceutical composition as described herein, and

b) a PD-1 pathway inhibitor or SMAC mimetic as described herein.

[0032] ~~In a seventh aspect, the~~The present ~~invention~~disclosure provides for a combination treatment comprising: a) a recombinant rhabdovirus according to the ~~first aspect~~disclosure or any of its ~~embodiments~~examples, or a recombinant vesicular stomatitis virus according ~~the second aspect~~to the disclosure or any of its ~~embodiments~~examples, or a pharmaceutical composition according to the ~~third aspect~~disclosure or any of its ~~embodiments~~examples, and b) a PD-1 pathway inhibitor or a SMAC mimetic. In one ~~embodiment~~example ~~relating to the seventh aspect~~ a) and b) may be administered concomitantly, sequentially or alternately. In a related ~~embodiment~~example, a) and b) are administered via different administration routes. In a further related ~~embodiment~~example, a) is administered intratumorally b) is administered intravenously.

[0033] In one ~~embodiment~~example ~~relating to the seventh aspect~~, the PD-1 pathway inhibitor is an antagonistic antibody, which is directed against PD-1 or PD-L1. In a related ~~embodiment~~example the PD-1 pathway inhibitor is selected from the group consisting

of pembrolizumab, nivolumab, pidilizumab, atezolizumab, avelumab, durvalumab, PDR-001, PD1-1, PD1-2, PD1-3, PD1-4 and PD1-5 (see Table 1). In a further related ~~embodiment~~example the SMAC mimetic is selected from the group consisting of any one of compounds 1 to 26 according to table 2 or a pharmaceutically acceptable salt of one of these compounds.

[0034] ~~In an eight aspect, the invention~~The disclosure provides for a virus producing cell, characterized in that the cell produces a recombinant rhabdovirus according to the ~~first aspect~~disclosure or any of its ~~embodiments~~examples, or a recombinant vesicular stomatitis virus according ~~the second aspect~~to the disclosure or any of its ~~embodiments~~examples.

[0034a] In another aspect, the present disclosure provides a virus producing cell, characterized in that the cell produces a recombinant vesicular stomatitis virus as described herein.

[0035] In one ~~embodiment~~example ~~relating to the eight aspect~~, the virus producing cell is a Vero cell, a HEK cell, a HEK293 cell, a Chinese hamster ovary cell (CHO), or a baby hamster kidney (BHK) cell.

[0036] ~~In a ninth aspect, the invention~~The disclosure provides for a method of producing a recombinant rhabdovirus in a cell culture:

(i) Infecting a host cell with a recombinant rhabdovirus, preferably a vesicular stomatitis virus,

(ii) Culturing the host cell under conditions allowing replication of the recombinant rhabdovirus,

(iii) Harvesting the recombinant rhabdovirus from the cell culture,

(iv) Optionally, enzyme treatment of the virus harvest, preferably with benzonase,

(v) Capturing the rhabdovirus harvest by loading on a cation exchange monolith membrane adsorber or resin followed by elution,

(vi) Polish rhabdovirus by subjecting the eluate of step (v) to size exclusion, multi modal size exclusion/ion exchange or tangential flow filtration,

(vii) Buffer change of polished rhabdovirus by ultrafiltration/diafiltration,

(viii) Sterile filtration of rhabdovirus.

[0037] In one ~~embodiment~~example ~~relating to the ninth aspect~~, the host cell is a HEK293 cell.

[0038] In one ~~embodiment~~example ~~relating to the ninth aspect~~, the host cell is cultured in suspension.

[0039] In one ~~embodiment~~example ~~relating to the ninth aspect~~, the recombinant rhabdovirus is formulated into a pharmaceutical composition. In a preferred ~~embodiment~~example, the recombinant rhabdovirus according to the ~~first aspect~~disclosure or any of its ~~embodiments~~examples, or a recombinant vesicular stomatitis virus according ~~the second aspect~~to the disclosure or any of its ~~embodiments~~examples is formulated into a pharmaceutical composition.

Brief description of the drawings

[0040] **FIG.1:** A schematic representation of an immunological synapse and components between an Antigen Presenting Cell (APC) and a T-cell. CD80 is a key co-stimulatory molecule during T-cell activation. Efficient T-cell stimulation requires two converging molecular signals within the immunological synapse. Signal 1: Antigen-specific (TCR:MHC/Peptide) and Signal 2. Antigen-independent (CD28:CD80).

[0041] **FIG.2:** Cartoon of CD80 extracellular domain (ECD) Fc-fusion protein (bivalent). The fusion protein is expressed in the transduced tumor cells following viral infection. The two CD80 extracellular domain Fc-fusion monomers are covalently linked together by disulfide bonds formed between cysteine residues in each monomer, thereby forming the CD80 extracellular domain Fc-fusion protein dimer.

[0042] **FIG.3A-B** Replication (A) and Viability (B) of VSV-GP-CD80-Fc relative to the parental virus VSV-GP were compared. HEK293F cells were infected with either VSV-GP or VSV-GP-CD80-Fc. Y-axis shows cell viability in percent or genome copies per ml. Both cell viability and replication were monitored for up to 48h after infection (x-axis: hours post infection).

[0043] **FIG.4** Soluble CD80-Fc detection by ELISA in tissue culture supernatants from HEK293 cells infected with VSV-GP or VSV-GP-CD80-Fc each with a mulplicity of infection of 1 (MOI 1). CD80-Fc expression (y-axis in µg/ml) was determined for different time points after infection for up to 48hours (x-axis).

[0044] **FIG.5A-B** In vivo efficacy (A) and body weight development (B) of mice treated with VSV-GP-CD80-Fc compared to the parental virus VSV-GP using the CT26.CL25-IFNARKO tumor model (i.v.). (A) Mice were treated on day 0 & 3 with a low viral dose of $2x10^7$ $TCID_{50}$. X-axis shows the time (in days) and y-axis the percentage of mice that survived. (B) Body weight development of the same treated