

[0005] Currently, there is an unmet need for compositions and methods that can decrease and/or reverse T cell exhaustion/impairment and restore effector function after or during a chronic infection and for the treatment of cancer.

SUMMARY

[0006] Provided herein are compositions and methods for treating T cell exhaustion, or T cell impairment, in a subject, by administering a PTD-MYC fusion protein (e.g., an HIV TAT-MYC fusion protein) or immune cells isolated from a donor subject and treated with a PTD-MYC fusion protein. In some examples, the T cell exhaustion is associated with a chronic microbial infection (e.g. bacterial, viral, fungal, protozoan or parasitic) or cancer. In some examples, the T cell exhaustion, or T cell impairment, is associated with an acute viral infection (e.g. acute respiratory virus infections, such as infection by influenza virus, respiratory syncytial virus (RSV), pneumonia virus, respiratory vaccinia virus, parainfluenza virus, respiratory adenoviruses, severe acute respiratory syndrome corona virus (SARS-CoV), Middle East respiratory syndrome corona virus (MERS-CoV), or human metapneumovirus (HMPV)). In some examples, administration of the PTD-MYC fusion protein or PTD-MYC modified immune cells reduces T cell exhaustion, or T cell impairment, in the subject. For example, in some examples, administration of the PTD-MYC fusion protein or PTD-MYC modified immune cells reduces the number of exhausted cells (e.g., exhausted T cells) in the subject. In some examples, administration of the PTD-MYC fusion protein or PTD-MYC modified immune cells increases the immune response against a pathogen associated with a chronic microbial infection. In some examples, administration of the PTD-MYC fusion protein or PTD-MYC modified immune cells alleviate one or more symptoms of a chronic microbial infection.

[0006a] In one aspect, the present disclosure provides use of a composition comprising one or more modified immune cells in the manufacture of a medicament for treating a hepatitis B virus (HBV) infection in a subject in need thereof, wherein the one or more modified immune cells comprise a MYC fusion protein comprising (i) a protein transduction domain; and (ii) a MYC polypeptide sequence.

[0007] In another aspect, the present disclosure provides use of one or more modified immune cells in the manufacture of a medicament for treating T cell exhaustion in a subject in need thereof, wherein the one or more modified immune cells comprises a MYC fusion protein comprising (i) a protein transduction domain; and (ii) a MYC polypeptide sequence. Provided herein, in certain examples, are methods for treating T cell exhaustion, or T cell impairment, in a subject in need thereof, comprising administering an effective amount of one or more modified immune cells to the subject, wherein the one or more modified immune cells comprises a MYC fusion protein comprising (i) a protein transduction domain; and (ii) a MYC polypeptide sequence. In some examples, the subject is identified as having altered expression of at least one immune cell marker of T cell exhaustion, or T cell impairment, compared to expression of the at least one immune cell

marker in a healthy control. In some examples, the immune cell marker is an immune checkpoint protein. In some examples, the subject has a microbial infection. In some examples, the microbial infection is a chronic microbial infection. In some examples, the microbial infection is a bacterial infection, a viral infection, a fungal infection, a protozoan infection, or parasitic infection. In some examples, the microbial infection is caused by a pathogen selected from the group consisting of *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Mycobacterium bovis*, *Helicobacter pylori*, *Staphylococcus aureus*, *Salmonella Typhi*, *Treponema pallidum*, *Escherichia coli*, *Hemophilus influenza*, *Pseudomonas aeruginosa*, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, Human Immunodeficiency Virus (HIV), Herpesviruses, Herpes Simplex Virus (HSV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Measles Virus, Papovaviruses, Varicella-Zoster Virus, T-Cell Leukemia Viruses, Adenoviruses, Parvoviruses, Epstein-Barr Virus, Enterovirus, Mouse Hepatitis Virus (MHV), Cytomegalovirus (CMV), Papillomaviruses and Lymphocytic Choriomeningitis Virus (LCMV). In some examples, the T cell exhaustion, or T cell impairment, is associated with an acute viral infection, such as an acute respiratory virus infection, such as infection by influenza virus, respiratory syncytial virus (RSV), pneumonia virus, respiratory vaccinia virus, parainfluenza virus, respiratory adenoviruses, severe acute respiratory syndrome corona virus (SARS-CoV), Middle East respiratory syndrome corona virus (MERS-CoV), or human metapneumovirus (HMPV)). In some examples, the subject has cancer. In some examples, the cancer is melanoma. In some examples, the melanoma is relapsed refractory melanoma. In some examples, the one or more modified immune cells are derived from immune cells isolated from the subject. In some examples, the immune cells isolated from the subject are obtained from the peripheral blood of the subject. In some examples, the immune cells isolated from the subject are obtained from the lymph node, spleen, or tumor of the subject. In some examples, the one or more modified immune cells are prepared by contacting the immune cells *in vitro* with the MYC fusion protein. In some examples, the one or more modified immune cells are prepared by contacting a population of peripheral blood mononuclear cells from the subject *in vitro* with the MYC fusion protein. In some examples, the methods further comprise expanding the modified immune cells *in vitro* prior to and/or following contacting the modified immune cells with the MYC fusion protein. In some examples,

the protein transduction domain sequence is a TAT protein transduction domain sequence. In some examples, the MYC fusion protein comprises SEQ ID NO: 1. In some examples, the MYC fusion protein translocates to the nucleus of one or more modified immune cells. In some examples, the MYC fusion protein exhibits a biological activity of MYC. In some examples, the altered expression comprises an increase in the cell surface expression of one or more immune cell receptors. In some examples, the one or more cell surface receptors comprises PD-1, LAG-3, CD160, 2B4, or any combination thereof. In some examples, the one or more modified immune cells are administered intravenously, intraperitoneally, subcutaneously, intramuscularly, or intratumorally. In some examples, the subject is a human or a non-human animal. In some examples, the one or more modified immune cells comprises one or more T cells. In some examples, the one or more modified immune cells comprises one or more CD8⁺ T cells. In some examples, the one or more modified immune cells comprises one or more exhausted immune cells. In some examples, the one or more modified immune cells comprises one or more exhausted T cells. In some examples, the one or more modified immune cells comprises one or more exhausted CD8⁺ T cells.

[0008] In yet another aspect, the present disclosure provides use of one or more modified immune cells in the manufacture of a medicament for treating a chronic microbial infection in a subject in need thereof, wherein the one or more modified immune cells comprise a MYC fusion protein comprising (i) a protein transduction domain; and (ii) a MYC polypeptide sequence. Provided herein, in certain examples, are methods for treating a chronic microbial infection in a subject in need thereof, comprising administering an effective amount of one or more modified immune cells to the subject, wherein the one or more modified immune cells comprise a MYC fusion protein comprising (i) a protein transduction domain; and (ii) a MYC polypeptide sequence. In some examples, the subject is identified as having altered expression of at least one immune cell marker of T cell exhaustion, or T cell impairment, compared to expression of the at least one immune cell marker in a healthy control. In some examples, the immune cell marker is an immune checkpoint protein. In some examples, the microbial infection is a bacterial infection, a viral infection, a fungal infection, a protozoan infection, or parasitic infection. In some examples, the microbial infection is caused by a pathogen selected from the group consisting of *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Mycobacterium bovis*, *Helicobacter pylori*, *Staphylococcus aureus*, *Salmonella Typhi*, *Treponema pallidum*, *Escherichia coli*, *Hemophilus influenza*, *Pseudomonas aeruginosa*, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, Human Immunodeficiency Virus (HIV),

Herpesviruses, Herpes Simplex Virus (HSV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Measles Virus, Papovaviruses, Varicella-Zoster Virus, T-Cell Leukemia Viruses, Adenoviruses, Parvoviruses, Epstein-Barr Virus, Enterovirus, Mouse Hepatitis Virus (MHV), Cytomegalovirus (CMV), Papillomaviruses and Lymphocytic Choriomeningitis Virus (LCMV). In some examples, the subject was previously vaccinated against the pathogen. In some examples, the one or more modified immune cells are derived from immune cells isolated from the subject. In some examples, the immune cells isolated from the subject are obtained from the peripheral blood of the subject. In some examples, the immune cells isolated from the subject are obtained from the lymph node, spleen, or tumor of the subject. In some examples, the one or more modified immune cells are prepared by contacting the T cells *in vitro* with the MYC fusion protein. In some examples, the methods further comprise expanding the cells *in vitro* prior to and/or following contacting the cells with the MYC fusion protein. In some examples, the protein transduction domain sequence is a TAT protein transduction domain sequence. In some examples, the MYC fusion protein comprises SEQ ID NO: 1. In some examples, the MYC fusion protein translocates to the nucleus of one or more immune cells in the immune cell population. In some examples, the MYC fusion protein exhibits a biological activity of MYC. In some examples, the altered expression comprises an increase in the cell surface expression of one or more immune cell receptors. In some examples, the one or more cell surface receptors comprises PD-1, LAG-3, CD160, 2B4, or any combination thereof. In some examples, the one or more modified immune cells are administered intravenously, intraperitoneally, subcutaneously, intramuscularly, or intratumorally. In some examples, the subject is a human or a non-human animal. In some examples, the one or more modified immune cells comprises one or more T cells. In some examples, the one or more modified immune cells comprises one or more CD8⁺ T cells. In some examples, the one or more modified immune cells comprises one or more exhausted immune cells. In some examples, the one or more modified immune cells comprises one or more exhausted T cells. In some examples, the one or more modified immune cells comprises one or more exhausted CD8⁺ T cells.

[0009] In one aspect, the present disclosure provides use of one or more modified immune cells in the manufacture of a medicament for treating an acute respiratory viral infection associated with T cell impairment in a subject in need thereof, wherein the one or more modified immune cells comprise a MYC fusion protein comprising (i) a protein transduction domain; and (ii) a MYC polypeptide sequence. Provided herein, in certain examples, are methods for treating an acute respiratory infection associated with T cell impairment in a subject in need thereof, comprising administering an effective amount of one or more modified immune cells to the

subject, wherein the one or more modified immune cells comprise a MYC fusion protein comprising (i) a protein transduction domain; and (ii) a MYC polypeptide sequence. In some examples, the subject is identified as having altered expression of at least one immune cell marker of T cell exhaustion, or T cell impairment, compared to expression of the at least one immune cell marker in a healthy control. In some examples, the immune cell marker is an immune checkpoint protein. In some examples, the acute respiratory virus infection is caused by a pathogen selected from the group consisting of influenza virus, respiratory syncytial virus (RSV), pneumonia virus, respiratory vaccinia virus, parainfluenza virus, respiratory adenoviruses, severe acute respiratory syndrome corona virus (SARS-CoV), Middle East respiratory syndrome corona virus (MERS-CoV), and human metapneumovirus (HMPV)). In some examples, the subject was previously vaccinated against the pathogen. In some examples, the one or more modified immune cells are derived from immune cells isolated from the subject. In some examples, the immune cells isolated from the subject are obtained from the peripheral blood of the subject. In some examples, the immune cells isolated from the subject are obtained from the lymph node, spleen, or tumor of the subject. In some examples, the one or more modified immune cells are prepared by contacting the T cells *in vitro* with the MYC fusion protein. In some examples, the methods further comprise expanding the cells *in vitro* prior to and/or following contacting the cells with the MYC fusion protein. In some examples, the protein transduction domain sequence is a TAT protein transduction domain sequence. In some examples, the MYC fusion protein comprises SEQ ID NO: 1. In some examples, the MYC fusion protein translocates to the nucleus of one or more immune cells in the immune cell population. In some examples, the MYC fusion protein exhibits a biological activity of MYC. In some examples, the altered expression comprises an increase in the cell surface expression of one or more immune cell receptors. In some examples, the one or more cell surface receptors comprises PD-1, LAG-3, CD160, 2B4, or any combination thereof. In some examples, the one or more modified immune cells are administered intravenously, intraperitoneally, subcutaneously, intramuscularly, or intratumorally. In some examples, the subject is a human or a non-human animal. In some examples, the one or more modified immune cells comprises one or more T cells. In some examples, the one or more modified immune cells comprises one or more CD8⁺ T cells. In some examples, the one or more modified immune cells

comprises one or more exhausted immune cells. In some examples, the one or more modified immune cells comprises one or more exhausted T cells. In some examples, the one or more modified immune cells comprises one or more exhausted CD8⁺ T cells.

[0010] Also provided herein, in certain examples, are uses of one or more modified immune cells for treating T cell exhaustion, or T cell impairment, in a subject in need thereof, wherein the one or more modified immune cells comprise a MYC fusion protein comprising (i) a protein transduction domain; and (ii) a MYC polypeptide sequence.

[0011] Also provided herein, in certain examples, are uses of one or more modified immune cells for treating a chronic microbial infection or acute respiratory virus infection associated with T cell exhaustion, or T cell impairment, in a subject in need thereof, wherein the one or more modified immune cells comprise a MYC fusion protein comprising (i) a protein transduction domain; and (ii) a MYC polypeptide sequence.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] **FIGs. 1A-1C** illustrate the level of CD86 expression in populations of immune cells isolated from donor subjects, following pre-treatment with the PTD-MYC fusion polypeptide or vehicle control, and activation under various conditions.

[0013] **FIGs. 2A-2E** illustrate the level of CD279 (PD-1) expression (**FIGs. 2A-2C**) and CD152 (CTLA-4) expression (**FIGs. 2A** and **2D-2E**) in populations of immune cells isolated from donor subjects, following pre-treatment with the PTD-MYC fusion polypeptide or vehicle control, and activation under various conditions.

[0014] **FIGs. 3A-3E** illustrate the level of CD274 (PD-L1) expression (**FIGs. 3A-3C**) and CD25 (IL2RA) expression (**FIGs. 3A** and **3D-3E**) in populations of immune cells isolated from donor subjects, following pre-treatment with the PTD-MYC fusion polypeptide or vehicle control, and activation under various conditions.

[0015] **FIGs. 4A-4C** illustrate the level of CD279 (PD-1) and CD152 (CTLA-4) expression in peripheral blood mononuclear cells (PBMCs) isolated from patients enrolled in a relapsed refractory melanoma clinical study. **FIG. 4A** shows flow cytometry histograms of PBMC samples labeled with fluorescent antibodies to CD279 that were collected from two relapsed refractory melanoma patients (101 and 103) before and after a one-hour treatment

What is Claimed is:

1. Use of a composition comprising one or more modified immune cells in the manufacture of a medicament for treating a hepatitis B virus (HBV) infection in a subject in need thereof, wherein the one or more modified immune cells comprise a MYC fusion protein comprising (i) a protein transduction domain; and (ii) a MYC polypeptide sequence.
2. The use of claim 1, wherein the HBV infection is chronic HBV infection.
3. The use of claim 1 or claim 2, wherein the one or more modified immune cells are derived from immune cells isolated from the subject.
4. The use of claim 3, wherein the immune cells isolated from the subject are obtained from the peripheral blood of the subject.
5. The use of any one of claims 1-4, wherein the one or more modified immune cells are prepared by contacting the immune cells *in vitro* with the MYC fusion protein.
6. The use of any one of claims 1-5, further comprising expanding the cells *in vitro* prior to and/or following contacting the cells with the MYC fusion protein.
7. The use of any one of claims 1-6, wherein the protein transduction domain is a TAT protein transduction domain sequence.
8. The use of any one of claims 1-7, wherein the MYC fusion protein comprises SEQ ID NO: 1.
9. The use of any one of claims 1-8, wherein the MYC fusion protein translocates to the nucleus of one or more immune cells in the immune cell population.
10. The use of any one of claims 1-9, wherein the MYC fusion protein exhibits a biological activity of MYC.
11. The use of any one of claims 1-10, wherein the one or more modified immune cells are to be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly.
12. The use of any one of claims 1-11, wherein the subject is a human or a non-human animal.
13. The use of any one of claims 1-12, wherein the one or more modified immune cells comprises a T cell, a B cell, an NK cell, or any combination thereof.

14. The use of claim 13, wherein the T cell is selected from the group consisting of exhausted T cells, CD4+ T cells, CD8+ T cells, delta-gamma T cells, TILs, regulatory T cells, naïve T cells, memory T cells, activated T cells, tolerant T cells, chimeric T cells, and antigen-specific T cells.

15. The use of claim 13, wherein the B cell is selected from the group consisting of pre-B cells, progenitor B cells, early pro-B cells, late pro-B cells, large pre-B cells, small pre-B cells, immature B cells, mature B cells, naïve B cells, plasma B cells, activated B cells, exhausted B cells, tolerant B cells, chimeric B cells, antigen-specific B cells, memory B cell, B-1 cell, and B-2 cell populations.

16. The use of any one of claims 1-15, further comprising isolating the immune cells from the donor subject.

17. Use of one or more modified immune cells in the manufacture of a medicament for treating T cell exhaustion in a subject in need thereof, wherein the one or more modified immune cells comprises a MYC fusion protein comprising (i) a protein transduction domain; and (ii) a MYC polypeptide sequence.

18. The use of claim 17, wherein the subject is identified as having altered expression of at least one immune cell marker of T cell exhaustion compared to expression of the at least one immune cell marker in a healthy control, wherein optionally the immune cell marker is an immune checkpoint protein.

19. The use of claim 17 or 18, wherein the subject has a microbial infection,

wherein optionally the microbial infection is a bacterial infection, a viral infection, a fungal infection, a protozoan infection, or parasitic infection,

wherein optionally the microbial infection is caused by a pathogen selected from the group consisting of *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Mycobacterium bovis*, *Helicobacter pylori*, *Staphylococcus aureus*, *Salmonella Typhi*, *Treponema pallidum*, *Escherichia coli*, *Hemophilus influenza*, *Pseudomonas aeruginosa*, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, Human Immunodeficiency Virus (HIV), Herpesviruses, Herpes Simplex Virus (HSV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Measles Virus, Papovaviruses, Varicella-Zoster Virus, T-Cell Leukemia Viruses, Adenoviruses, Parvoviruses, Epstein-Barr Virus, Enterovirus, Mouse Hepatitis Virus (MHV), Cytomegalovirus (CMV), Papillomaviruses and Lymphocytic Choriomeningitis Virus (LCMV),

and wherein optionally the microbial infection is a chronic microbial infection.

20. The use of claim 17 or 18, wherein the subject has cancer, wherein optionally the cancer is melanoma, and wherein optionally the melanoma is relapsed refractory melanoma.

21. The use of any one of claims 17-20, wherein the one or more modified immune cells are derived from immune cells isolated from the subject, wherein optionally the immune cells isolated from the subject are obtained from the peripheral blood of the subject, or the lymph node, spleen, or tumor of the subject.

22. The use of any one of claims 17-21, wherein the one or more modified immune cells are prepared by contacting the immune cells *in vitro* with the MYC fusion protein, and/or contacting a population of peripheral blood mononuclear cells from the subject *in vitro* with the MYC fusion protein.

23. The use of claim 22, further comprising expanding the modified immune cells *in vitro* prior to and/or following contacting the modified immune cells with the MYC fusion protein.

24. The use of any one of claims 17-23, wherein the protein transduction domain sequence is a TAT protein transduction domain sequence,

wherein optionally the MYC fusion protein comprises SEQ ID NO: 1,

wherein optionally the MYC fusion protein translocates to the nucleus of one or more modified immune cells,

and wherein optionally the MYC fusion protein exhibits a biological activity of MYC.

25. The method of any one of claims 18-24, wherein the altered expression comprises an increase in the cell surface expression of one or more immune cell receptors, wherein optionally the one or more cell surface receptors comprises PD-1, LAG-3, CD160, 2B4, or any combination thereof.

26. The use of any one of claims 17-25, wherein the one or more modified immune cells are to be administered intravenously, intraperitoneally, subcutaneously, intramuscularly, or intratumorally,

wherein optionally the subject is a human or a non-human animal,

wherein optionally the one or more modified immune cells comprises one or more T cells,

wherein optionally the one or more modified immune cells comprises one or more CD8⁺ T cells,

wherein optionally the one or more modified immune cells comprises one or more exhausted immune cells,

wherein optionally the one or more modified immune cells comprises one or more exhausted T cells,

and wherein optionally the one or more modified immune cells comprises one or more exhausted CD8⁺ T cells.

27. Use of one or more modified immune cells in the manufacture of a medicament for treating a chronic microbial infection in a subject in need thereof, wherein the one or more modified immune cells comprise a MYC fusion protein comprising (i) a protein transduction domain; and (ii) a MYC polypeptide sequence.

28. The use of claim 27, wherein the subject is identified as having altered expression of at least one immune cell marker of T cell exhaustion compared to expression of the at least one immune cell marker in a healthy control, wherein optionally the immune cell marker is an immune checkpoint protein.

29. The use of claim 27 or 28, wherein the microbial infection is a bacterial infection, a viral infection, a fungal infection, or a protozoan infection,

wherein optionally the microbial infection is caused by a pathogen selected from the group consisting of *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Mycobacterium bovis*, *Helicobacter pylori*, *Staphylococcus aureus*, *Salmonella Typhi*, *Treponema pallidum*, *Escherichia coli*, *Hemophilus influenza*, *Pseudomonas aeruginosa*, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, Human Immunodeficiency Virus (HIV), Herpesviruses, Herpes Simplex Virus (HSV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Measles Virus, Papovaviruses, Varicella-Zoster Virus, T-Cell Leukemia Viruses, Adenoviruses, Parvoviruses, Epstein-Barr Virus, Enterovirus, Mouse Hepatitis Virus (MHV), Cytomegalovirus (CMV), Papillomaviruses and Lymphocytic Choriomeningitis Virus (LCMV),

and wherein optionally the subject was previously vaccinated against the pathogen.

30. The use of any one of claims 27-29, wherein the one or more modified immune cells are derived from immune cells isolated from the subject, wherein optionally the immune cells isolated from the subject are obtained from the peripheral blood of the subject, or the lymph node, or spleen of the subject, and wherein optionally the one or more modified immune cells are prepared by contacting the immune cells *in vitro* with the MYC fusion protein.

31. The use of any one of claims 27-30, further comprising expanding the cells *in vitro* prior to and/or following contacting the cells with the MYC fusion protein.

32. The use of any one of claims 27-31, wherein the protein transduction domain sequence is a TAT protein transduction domain sequence,

wherein optionally the MYC fusion protein comprises SEQ ID NO: 1,

wherein optionally the MYC fusion protein translocates to the nucleus of one or more immune cells in the immune cell population,

and wherein optionally the MYC fusion protein exhibits a biological activity of MYC.

33. The use of any one of claims 28-32 wherein the altered expression comprises an increase in the cell surface expression of one or more immune cell receptors, wherein optionally the one or more cell surface receptors comprises PD-1, LAG-3, CD160, 2B4, or any combination thereof.

34. The use of any one of claims 27-33, wherein the one or more modified immune cells are to be administered intravenously, intraperitoneally, subcutaneously, intramuscularly, or intratumorally,

wherein optionally the subject is a human or a non-human animal,

wherein optionally the one or more modified immune cells comprises one or more T cells,

wherein optionally the one or more modified immune cells comprises one or more CD8⁺ T cells,

wherein optionally the one or more modified immune cells comprises one or more exhausted immune cells,

wherein optionally the one or more modified immune cells comprises one or more exhausted T cells,

and wherein optionally the one or more modified immune cells comprises one or more exhausted CD8⁺ T cells.

35. Use of one or more modified immune cells in the manufacture of a medicament for treating an acute respiratory viral infection associated with T cell impairment in a subject in need thereof, wherein the one or more modified immune cells comprise a MYC fusion protein comprising (i) a protein transduction domain; and (ii) a MYC polypeptide sequence.

36. The use of claim 35, wherein the subject is identified as having altered expression of at least one immune cell marker of T cell exhaustion compared to expression of the at least one immune cell marker in a healthy control, wherein optionally the immune cell marker is an immune checkpoint protein.

37. The use of claim 35 or 36, wherein the acute respiratory viral infection is caused by a pathogen selected from the group consisting of influenza virus, respiratory syncytial virus (RSV), pneumonia virus, respiratory vaccinia virus, parainfluenza virus, respiratory adenoviruses, severe acute respiratory syndrome corona virus (SARS-CoV), Middle East respiratory syndrome corona virus (MERS-CoV), or human metapneumovirus (HMPV), wherein optionally the subject was previously vaccinated against the pathogen.

38. The use of any one of claims 35-37, wherein the one or more modified immune cells are derived from immune cells isolated from the subject, wherein optionally the immune cells isolated from the subject are obtained from the peripheral blood of the subject, or the lymph node or spleen of the subject, and wherein optionally the one or more modified immune cells are prepared by contacting the immune cells *in vitro* with the MYC fusion protein.

39. The use of any one of claims 35-38, further comprising expanding the cells *in vitro* prior to and/or following contacting the cells with the MYC fusion protein.

40. The use of any one of claims 35-39, wherein the protein transduction domain sequence is a TAT protein transduction domain sequence,

wherein optionally the MYC fusion protein comprises SEQ ID NO: 1,

wherein optionally the MYC fusion protein translocates to the nucleus of one or more immune cells in the immune cell population,

and wherein optionally the MYC fusion protein exhibits a biological activity of MYC.

41. The use of any one of claims 36-40, wherein the altered expression comprises an increase in the cell surface expression of one or more immune cell receptors, wherein optionally the one or more cell surface receptors comprises PD-1, LAG-3, CD160, 2B4, or any combination thereof.

42. The use of any one of claims 35-41, wherein the one or more modified immune cells are to be administered intravenously, intraperitoneally, subcutaneously, intramuscularly, or intratumorally,

wherein optionally the subject is a human or a non-human animal,

wherein optionally the one or more modified immune cells comprises one or more T cells,

wherein optionally the one or more modified immune cells comprises one or more CD8⁺ T cells,

wherein optionally the one or more modified immune cells comprises one or more exhausted immune cells,

wherein optionally the one or more modified immune cells comprises one or more exhausted T cells,

and wherein optionally the one or more modified immune cells comprises one or more exhausted CD8⁺ T cells.