

CLAIMS

What is claimed is:

1. ~~Use of A method of preventing or treating a virus-induced organ injury or failure in an individual, comprising administering to the individual~~ an effective amount of an IL-22 dimer, in the manufacture of a medicament for:

- ~~(a) preventing or treating a virus-induced organ injury or failure in an individual;~~
- ~~(b) protecting an organ from virus-induced organ injury or failure in an individual;~~
- ~~(c) promoting regeneration of injured tissue or organ due to virus infection in an individual;~~
- ~~(d) treating or preventing endothelial dysfunction in an injured tissue or organ due to virus infection in an individual; or~~
- ~~(e) reducing inflammation due to virus infection in an individual.~~

2. The ~~method-use~~ of claim 1, wherein the virus-induced organ injury or failure is

- ~~(a) virus-induced lung injury or failure; or~~
- ~~(b) virus-induced sepsis, septic shock, or multiple organ dysfunction syndrome (MODS).~~

3. The ~~method-use~~ of claim 2, wherein the virus-induced lung injury or failure is pulmonary fibrosis, pneumonia, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), Severe Acute Respiratory Syndrome coronavirus (SARS), Middle East Respiratory Syndrome coronavirus (MERS), Coronavirus disease 2019 (COVID-19), Influenza A virus subtype H1N1 (H1N1) swine flu, or Influenza A virus subtype H5N1 (H5N1) bird flu.

~~4. The method of claim 1, wherein the virus-induced organ injury or failure is virus-induced sepsis, septic shock, or multiple organ dysfunction syndrome (MODS).~~

~~45.~~ The ~~method-use~~ of any one of claims 1-~~34~~, wherein the virus-induced organ injury or failure is caused by a virus of any one of the *Orthomyxoviridae*, *Filoviridae*, *Flaviviridae*, *Coronaviridae*, and *Poxviridae* families.

~~56.~~ The ~~method-use~~ of claim ~~45~~,

- ~~(a) wherein the virus is an *Orthomyxoviridae* virus selected from the group consisting of Influenza A virus, Influenza B virus, Influenza C virus, and any subtype or reassortant thereof;~~
- ~~(b) wherein the virus is a *Coronaviridae* virus selected from the group consisting of alpha coronaviruses 229E (HCoV-229E), New Haven coronavirus NL63 (HCoV-NL63), beta coronaviruses OC43 (HCoV-OC43), coronavirus HKU1 (HCoV-HKU1), Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), Middle East Respiratory Syndrome coronavirus~~

(MERS-CoV), and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2);

(c) wherein the virus is a *Filoviridae* virus selected from Ebola virus (EBOV) and Marburg virus (MARV); or

(d) wherein the virus is a *Flaviviridae* virus selected from the group consisting of Zika virus (ZIKV), West Nile virus (WNV), Dengue virus (DENV), and Yellow Fever virus (YFV).

~~7. The method of claim 6, wherein the virus is an Influenza A virus or any subtype or reassortant thereof.~~

~~68. The method-use of claim ~~57~~, wherein the virus is~~

~~(a) Influenza A virus subtype H1N1 (H1N1) or Influenza A virus subtype H5N1 (H5N1);~~
~~or~~

~~(b) SARS-CoV-2 or variant thereof.~~

~~9. The method of claim 5, wherein the virus is a *Coronaviridae* virus selected from the group consisting of alpha-coronaviruses 229E (HCoV-229E), New Haven coronavirus NL63 (HCoV-NL63), beta-coronaviruses OC43 (HCoV-OC43), coronavirus HKU1 (HCoV-HKU1), Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), Middle East Respiratory Syndrome coronavirus (MERS-CoV), and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).~~

~~10. The method of claim 5, wherein the virus is a *Filoviridae* virus selected from Ebola virus (EBOV) and Marburg virus (MARV).~~

~~11. The method of claim 5, wherein the virus is a *Flaviviridae* virus selected from the group consisting of Zika virus (ZIKV), West Nile virus (WNV), Dengue virus (DENV), and Yellow Fever virus (YFV).~~

~~712. The method-use of any one of claims 1-~~611~~, wherein further comprising administering to the individual an effective amount of another therapeutic agent is to be further administered to the individual.~~

~~813. The method-use of claim ~~712~~, wherein the other therapeutic agent is selected from the group consisting of a corticosteroid, an anti-inflammatory signal transduction modulator, a β 2-adrenoreceptor agonist bronchodilator, an anticholinergic, a mucolytic agent, an antiviral agent, an anti-fibrotic agent, hypertonic saline, an antibody, a vaccine, ~~or and~~ mixtures thereof.~~

~~914. The method-use of claim ~~813~~,~~

~~(a) wherein the antiviral agent is selected from the group consisting of remdesivir,~~

lopinavir/ritonavir, IFN- α , lopinavir, ritonavir, penciclovir, galidesivir, disulfiram, darunavir, cobicistat, ASC09F, disulfiram, nafamostat, griffithsin, alisporivir, chloroquine, nitazoxanide, baloxavir marboxil, oseltamivir, zanamivir, peramivir, amantadine, rimantadine, favipiravir, laninamivir, ribavirin, umifenovir, and any combinations thereof; or

(b) the anti-fibrotic agent is selected from the group consisting of nintedanib, pirfenidone, and N-Acetylcysteine (NAC).

1015. The ~~method-use~~ of claim 914, wherein:

(a) the other therapeutic agent is i) remdesivir, or ii) lopinavir/ritonavir and IFN α , and the virus-induced organ injury or failure is induced by SARS-CoV-2; or

(b) the other therapeutic agent is selected from the group consisting of oseltamivir, zanamivir, peramivir, lopinavir/ritonavir, IFN α , and any combinations thereof, and the virus-induced organ injury or failure is induced by H1N1 or H5N1.

~~16.— The method of claim 14, wherein the other therapeutic agent is selected from the group consisting of oseltamivir, zanamivir, peramivir, lopinavir/ritonavir, IFN α , and any combinations thereof, and the virus induced organ injury or failure is induced by H1N1 or H5N1.~~

~~17.— The method of claim 13, wherein the anti-fibrotic agent is selected from the group consisting of nintedanib, pirfenidone, and N-Acetylcysteine (NAC).~~

~~18.— The method of any one of claims 12-17, wherein the IL 22 dimer is administered simultaneously or sequentially with the other therapeutic agent.~~

~~19.— A method of protecting an organ from virus induced organ injury or failure in an individual, comprising administering to the individual an effective amount of an IL 22 dimer.~~

1120. The ~~method-use~~ of any one of claims 1-1019,

(a) wherein the virus-induced organ injury or failure comprises endothelial cell injury, dysfunction, or death; and/or

(b) wherein the injured tissue or organ comprises injured or dysfunctional endothelial cells.

~~21.— A method of promoting regeneration of injured tissue or organ due to virus infection in an individual, comprising administering to the individual an effective amount of an IL 22 dimer.~~

~~22.— The method of claim 21, wherein the injured tissue or organ comprises injured or dysfunctional endothelial cells.~~

1223. The ~~method-use~~ of any one of claims 1-11~~claim 20 or 22~~, wherein endothelial dysfunction comprises endothelial glycocalyx degradation.

~~24. A method of treating or preventing endothelial dysfunction in an injured tissue or organ due to virus infection in an individual, comprising administering to the individual an effective amount of an IL-22 dimer.~~

1325. The method-use of any one of claims 120-1224, wherein the method-use comprises preventing and/or reducing endothelial glycocalyx degradation, down-regulating Toll-like Receptor 4 (TLR4) signaling, and/or regenerating endothelial glycocalyx.

1426. The method-use of any one of claims 11-1320 and 22-25, wherein the endothelial cell is a pulmonary endothelial cell.

~~27. A method of reducing inflammation due to virus infection in an individual, comprising administering to the individual an effective amount of an IL-22 dimer.~~

1528. The method-use of any one of claims 1-1427, wherein the IL-22 dimer comprises two monomeric subunits, and wherein each monomeric subunit comprises an IL-22 monomer and a dimerization domain.

1629. The method-use of claim 1528, wherein the IL-22 monomer is connected to the dimerization domain via an optional linker.

1730. The method-use of claim 1629, wherein the linker:

(a) comprises the sequence of any one of SEQ ID NOs: 1-20 and 32;

(b) is about 6 to about 30 amino acids in length; and/or

(c) comprises the sequence of SEQ ID NO: 1 or 10.

~~31. The method of claim 29 or 30, wherein the linker is about 6 to about 30 amino acids in length.~~

~~32. The method of any one of claims 29-31, wherein the linker comprises the sequence of SEQ ID NO: 1 or 10.~~

1833. The method-use of any one of claims 1528-1732, wherein the dimerization domain comprises:

(a) at least two cysteines capable of forming intermolecular disulfide bonds; and/or

(b) at least a portion of an Fc fragment.

~~34. The method of any one of claims 28-33, wherein the dimerization domain comprises at least a portion of an Fc fragment.~~

1935. The method-use of claim 1834, wherein the Fc fragment comprises:

(a) CH2 and CH3 domains; and/or

(b) the sequence of SEQ ID NO: 22 or 23.

~~36. The method of claim 34 or 35, wherein the Fe fragment comprises the sequence of SEQ ID NO: 22 or 23.~~

2037. The method-use of any one of claims ~~1528-1936~~, wherein the IL-22 monomer comprises the sequence of SEQ ID NO: 21.

2138. The method-use of any one of claims ~~1528-2037~~,

 (a) wherein the IL-22 monomer is N-terminal to the dimerization domain; or

 (b) wherein the IL-22 monomer is C-terminal to the dimerization domain.

~~39. The method of any one of claims 28-37, wherein the IL-22 monomer is C-terminal to the dimerization domain.~~

2240. The method-use of any one of claims ~~1528-2139~~,

 (a) wherein each monomeric subunit comprises the sequence of any of SEQ ID NOs: 24-27; and/or

 (b) wherein each monomeric subunit comprises the sequence of SEQ ID NO: 24.

~~41. The method of any one of claims 28-38 and 40, wherein each monomeric subunit comprises the sequence of SEQ ID NO: 24.~~

2342. The method-use of any one of claims 1-~~2241~~, wherein the effective amount of the IL-22 dimer is:

 (a) about 2 µg/kg to about 200 µg /kg;

 (b) about 5 µg/kg to about 80 µg/kg;

 (c) about 10 µg/kg to about 45 µg/kg; or

 (d) about 30 µg/kg to about 45 µg/kg.

~~43. The method of any one of claims 1-42, wherein the effective amount of the IL-22 dimer is about 5 µg/kg to about 80 µg/kg.~~

~~44. The method of any one of claims 1-43, wherein the effective amount of the IL-22 dimer is about 10 µg/kg to about 45 µg/kg.~~

~~45. The method of any one of claims 1-44, wherein the effective amount of the IL-22 dimer is about 30 µg/kg to about 45 µg/kg.~~

2446. The method-use of any one of claims 1-~~2345~~, wherein:

 (a) the IL-22 dimer is to be administered intravenously, intrapulmonarily, ~~or~~ via inhalation, or via insufflation;

(b) the IL-22 dimer is to be administered at least once a week; and/or

(c) the IL-22 dimer is to be administered on day 1 and day 6 of a 10-day treatment cycle, or day 1 and day 8 of a 14-day treatment cycle.

~~47. The method of any one of claims 1-46, wherein the IL-22 dimer is administered at least once a week.~~

~~48. The method of any one of claims 1-47, wherein the IL-22 dimer is administered on day 1 and day 6 of a 10-day treatment cycle, or day 1 and day 8 of a 14-day treatment cycle.~~

2549. The ~~method-use~~ of any one of claims 1-2448, wherein:

(a) the individual is at least about 55 years old; and/or

(b) the use further comprising selecting an individual based on that the individual is at least about 55 years old.

~~50. The method of any one of claims 1-49, further comprising selecting the individual based on that the individual is at least about 55 years old.~~