

or noninfectious. SIRS is closely related to sepsis. When SIRS is due to an infection, it is considered as sepsis. Noninfectious causes of SIRS include trauma, burns, pancreatitis, ischemia, and hemorrhage. Sepsis is a serious medical condition characterized by a whole-body inflammatory state, and can lead to septic shock. Both SIRS and sepsis can progress to severe sepsis, and eventually MODS, or death. The underline mechanism of MODS is not well understood.

[0007] At present, there is no agent that can reverse established organ failure. Therapy is therefore limited to supportive care. Prevention and treatment of organ injury or failure, sepsis, septic shock, and MODS are important to emergency medical conditions, such as injury caused by traffic accident, burns, heart attacks, and severe infective diseases. The development of an effective drug is in urgent need.

[0008] The disclosures of all publications, patents, patent applications, and published patent applications referred to herein are incorporated herein by reference in their entirety.

SUMMARY

[0009] In one example of the present disclosure, there is provided a method of preventing or treating a virus-induced organ injury or failure in an individual (e.g., human, such as a human of at least about 55 years old), comprising administering to the individual an effective amount of an IL-22 dimer.

[0010] In another example of the present disclosure, there is provided a method of protecting an organ (e.g., lung, heart, liver, kidney) from virus-induced organ injury or failure in an individual (e.g., human, such as a human of at least about 55 years old), comprising administering to the individual an effective amount of an IL-22 dimer.

[0011] In another example of the present disclosure, there is provided a method of promoting regeneration of injured tissue or organ (e.g., lung, heart, liver, kidney) due to virus infection in an individual (e.g., human, such as a human of at least about 55 years old), comprising administering to the individual an effective amount of an IL-22 dimer.

[0012] In another example of the present disclosure, there is provided a method of treating or preventing endothelial dysfunction in an injured tissue or organ (e.g., lung, heart, kidney, liver)

due to virus infection in an individual (e.g., human, such as a human of at least about 55 years old), comprising administering to the individual an effective amount of an IL-22 dimer.

[0013] In another example of the present disclosure, there is provided a method of reducing inflammation (e.g., cytokine storm, sepsis, SIRS) due to virus infection in an individual (e.g., human, such as a human of at least about 55 years old), comprising administering to the individual an effective amount of an IL-22 dimer.

[0013a] In one aspect, the present disclosure refers to use of 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.

[0014] In some examples according to any of the methods described above, the virus-induced organ injury or failure comprises endothelial cell injury, dysfunction, or death. In some examples, the injured tissue or organ comprises injured or dysfunctional endothelial cells. In some examples, endothelial dysfunction comprises endothelial glycocalyx degradation. In some examples, the method comprises preventing and/or reducing endothelial glycocalyx degradation, down-regulating Toll-like Receptor 4 (TLR4) signaling, and/or regenerating endothelial glycocalyx. In some examples, the endothelial cell is a pulmonary endothelial cell.

[0015] In some examples according to any of the methods described above, the virus-induced organ injury or failure is virus-induced lung injury or failure, such as pulmonary fibrosis, pneumonia, acute lung injury (ALI), SARS, MERS, COVID-19, H1N1 swine flu, H5N1 bird flu, or acute respiratory distress syndrome (ARDS). In some examples, the virus-induced organ injury or failure is virus-induced sepsis, septic shock, or multiple organ dysfunction syndrome (MODS).

[0016] In some examples according to any of the methods described above, the virus-induced organ injury or failure is caused by a virus of any one of the *Orthomyxoviridae*, *Filoviridae*, *Flaviviridae*, *Coronaviridae*, and *Poxviridae* families. In some examples, 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. In some examples, the virus is an Influenza A virus or any subtype or reassortant thereof, such as Influenza A virus subtype H1N1 (H1N1) or Influenza A virus subtype H5N1 (H5N1). In some examples, 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). In some examples, the virus is SARS-CoV, MERS-CoV, or SARS-CoV-2. In some examples, the virus is a *Filoviridae* virus selected from Ebola virus (EBOV) and Marburg virus (MARV). In some examples, 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).

[0017] In some examples according to any of the methods described above, comprising administering to the individual an effective amount of another therapeutic agent. In some examples, 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 mixtures thereof. In some examples, the antiviral agent is selected from the group consisting of remdesivir, lopinavir/ritonavir (Kaletra®), IFN- α (e.g., IFN- α 2a or IFN- α 2b), 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. In some examples, the other therapeutic agent is selected from the group consisting of remdesivir, lopinavir/ritonavir (Kaletra®, e.g., tablet), IFN- α (e.g., IFN- α 2a or IFN- α 2b, via inhalation), favipiravir, lopinavir, ritonavir, penciclovir, galidesivir, disulfiram, darunavir, cobicistat, ASC09F, disulfiram, nafamostat, griffithsin, alisporivir, chloroquine, nitazoxanide, baloxavir marboxil, and any combinations thereof, and the virus-induced organ injury or failure is induced by SARS-CoV-2. In some examples, the other therapeutic agent is remdesivir and the virus-induced organ injury or failure is induced by SARS-CoV-2. In some examples, the other therapeutic agent is lopinavir/ritonavir (Kaletra®, e.g., tablet) and IFN- α (e.g., via inhalation), and the virus-induced organ injury or failure is induced by SARS-CoV-2. In some examples, the other therapeutic agent is selected from the group consisting of oseltamivir, zanamivir, peramivir, favipiravir, umifenovir (Arbidol®), teicoplanin derivatives, benzo-heterocyclic amine derivative, pyrimidine, baloxavir marboxil, lopinavir/ritonavir (Kaletra®, e.g., tablet), IFN- α (e.g., e.g., IFN- α 2a, IFN- α 2b, via inhalation), and any combinations thereof, and the virus-

induced organ injury or failure is induced by H1N1 or H5N1. In some examples, the other therapeutic agent is lopinavir/ritonavir (Kaletra®, e.g., tablet) and IFN- α (e.g., IFN- α 2a, IFN- α 2b, via inhalation), and the virus-induced organ injury or failure is induced by H1N1 or H5N1. In some examples, the anti-fibrotic agent is selected from the group consisting of nintedanib, pirfenidone, and *N*-Acetylcysteine (NAC). In some examples, the IL-22 dimer is administered simultaneously or sequentially with the other therapeutic agent.

[0018] In some examples according to any of the methods described above, the IL-22 dimer comprises two monomeric subunits, and wherein each monomeric subunit comprises an IL-22 monomer and a dimerization domain. In some examples, the IL-22 monomer is connected to the dimerization domain via an optional linker. In some examples, the linker comprises the sequence of any one of SEQ ID NOs: 1-20 and 32, such as SEQ ID NO: 1 or 10. In some examples, the linker is about 6 to about 30 (e.g., about 6 to about 15) amino acids in length. In some examples, the dimerization domain comprises at least two (e.g., 2, 3, 4) cysteines capable of forming intermolecular disulfide bonds. In some examples, the dimerization domain comprises at least a portion of an Fc fragment. In some examples, the Fc fragment comprises CH2 and CH3 domains. In some examples, the Fc fragment comprises the sequence of SEQ ID NO: 22 or 23. In some examples, the IL-22 monomer comprises the sequence of SEQ ID NO: 21. In some examples, the IL-22 monomer is N-terminal to the dimerization domain. In some examples, the IL-22 monomer is C-terminal to the dimerization domain. In some examples, each monomeric subunit comprises the sequence of any of SEQ ID NOs: 24-27, such as SEQ ID NO: 24.

[0019] In some examples according to any of the methods described above, the effective amount of the IL-22 dimer is about 2 $\mu\text{g/kg}$ to about 200 $\mu\text{g/kg}$, such as about 5 $\mu\text{g/kg}$ to about 80 $\mu\text{g/kg}$, about 10 $\mu\text{g/kg}$ to about 45 $\mu\text{g/kg}$ (e.g., 10 $\mu\text{g/kg}$, 30 $\mu\text{g/kg}$, or 45 $\mu\text{g/kg}$), or about 30 $\mu\text{g/kg}$ to about 45 $\mu\text{g/kg}$.

[0020] In some examples according to any of the methods described above, the IL-22 dimer is administered intravenously, intrapulmonarily, or via inhalation (e.g., through mouth or nose) or insufflation. In some examples, the IL-22 dimer is administered intravenously.

[0021] In some examples according to any of the methods described above, the IL-22 dimer is administered at least once a week. In some examples, the IL-22 dimer is

administered on day 1 and day 6 of a 10-day treatment cycle. In some examples, the IL-22 dimer is administered on day 1 and day 8 of a 14-day treatment cycle.

[0022] In some examples according to any of the methods described above, the individual (e.g., human) is at least about 55 years old (e.g., at least about any of 60, 65, 70, 75, 80, 85, 90 years old, or older).

[0023] In some examples according to any of the methods described above, the method further comprises selecting the individual based on that the individual is at least about 55 years old (e.g., at least about any of 60, 65, 70, 75, 80, 85, 90 years old, or older).

[0024] Also provided are compositions, kits, and articles of manufactures comprising any of the IL-22 dimers described herein for use in any methods described herein.

[0025] These and other examples and advantages of the present disclosure will become apparent from the subsequent detailed description and the appended claims. It is to be understood that one, some, or all of the properties of the various examples described herein may be combined to form other examples of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] FIG. 1 depicts an exemplary IL-22 dimer according to the present invention. In the figure, "-" represents a linker, and the oval-shaped object labeled with "IL-22" represents an IL-22 monomer.

[0027] FIGs. 2A-2B depict exemplary IL-22 dimers according to the present invention. In the figures, "-" represents an amino acid linker and the oval-shaped object labeled with "IL-22" represents an IL-22 monomer. As illustrated in FIG. 2A, the oval-shaped object labeled with "C" represents a carrier protein wherein the IL-22 is disposed at the N-terminal of the carrier protein. As illustrated in FIG. 2B, the half oval-shaped object labeled with "Fc" represents an Fc fragment as a dimerization domain, showing a dimer is formed by the coupling of two Fc fragments via disulfide bond(s).

[0028] FIGs. 3A-3B depict exemplary IL-22 dimers according to the present invention. In the figures, "-" represents an amino acid linker, the oval-shaped object labeled with "IL-22" represents an IL-22 monomer. As illustrated in FIG. 3A, the oval-shaped object labeled with "C" represents a carrier protein wherein the IL-22 is disposed at the C-terminal of the carrier protein.