METHODS AND COMPOSITIONS FOR TREATING INFLAMMATORY CONDITIONS ASSOCIATED WITH INFECTIOUS DISEASE

This application claims the benefit of U.S. Provisional Application No. 63/198,706, filed on November 6, 2020 and U.S. Provisional Application No. 63/013,865, filed on April 22, 2020, applications which are incorporated herein by reference in their entirety.

I. BACKGROUND

There are currently no effective biologic treatments for coronaviruses, especially for COVID-19. Commercially available products do not act concurrently and synergistically to directly affect viral infection and/or replication as well as to regulate downstream inflammation and vascular cell related pathologies in response to the viral infection. Therefore, what is needed is a method and composition for an intravenous or pulmonary route of delivery of autogenous or allogenic MSC derived growth factors and exosomes, wherein the products are acellular and useful for the treatment of various viruses, while simultaneously avoiding the potential negative long-term effects associated with introducing cellular living MSCs into a recipient.

II. SUMMARY

Disclosed are methods and compositions related to a composition comprising MSC secretome (such as, for example, including, but not limited to MSC growth factor, MSC exosome, MSC extracts and/or extracellular vesicle comprising compositions) and/or one or more biomolecules for use treating diseases.

In one aspect, there is provided a use of a composition comprising a bone marrow mesenchymal stem cell (MSC) secretome in the manufacture of a medicament for ameliorating one or more secondary conditions caused by a microbial infection in a subject in need thereof, wherein the bone marrow MSC secretome comprises stromal cell derived factor-1 (SDF-1), ferritin protein, PAI-1, and thrombomodulin.

In another aspect, there is provided a use of a bone marrow mesenchymal stem cell (MSC) secretome in the manufacture of a medicament for ameliorating acute respiratory distress syndrome (ARDS) caused by a microbial infection in a subject in need thereof, wherein the bone marrow MSC secretome comprises stromal cell derived factor-1 (SDF-1), ferritin protein, PAI-1, and thrombomodulin.

In one example, disclosed herein are compositions comprising a therapeutically effective amount of a MSC secretome (such as, for example, including, but not limited to MSC growth factor, MSC exosome, MSC extracts and/or extracellular vesicle comprising compositions) and one or more biomolecules (such as, for example, a peptide, polypeptide,

protein, siRNA, shRNA, and/or microRNA (miRNA)) that selectively bind to one or more microbial immunogens, or inhibit the ability of a microbe to inhabit a host, or inhibit, decrease, reduce, ameliorate, and/or prevent one or more secondary conditions caused by a microbial infection (such as, for example, comprise a peptide, polypeptide, protein, siRNA, shRNA, microRNA (miRNA) which act concurrently and synergistically to directly affect viral infection and/or replication and/or act concurrently and synergistically to regulate downstream inflammation and vascular cell related pathologies in response to microbial infection). For example, disclosed herein are compositions comprising a therapeutically effective amount of a MSC secretome (such as, for example, including, but not limited to MSC growth factor, MSC exosome, MSC extracts and/or extracellular vesicle comprising compositions) and one or more biomolecules

comprise a ferritin protein, PAI-1, thrombomodulin, and/or a miRNA is selected from the group of miRNA comprising hsa-let-7a-5p, hsa-let-7b-5p, hsa-let-7c-5p, hsa-let-7d-3p, hsa-let-7e-5p, hsa-let-7g-5p, hsa-let-7i, hsa-let-7i-5p, hsa-miR-100-5p, hsa-miR-103a-3p, hsa-miR-106a-5p, hsa-miR-106b-5p, hsa-mir-10b, hsa-miR-10b-5p, hsa-mir-1246, hsa-miR-1246, hsa-miR-125a-5p, hsa-miR-125b-5p, hsa-miR-130a-3p, hsa-mir-130b, hsa-miR-130b-3p, hsa-miR-132-3p, hsa-miR-136-5p, hsa-miR-138-5p, hsa-miR-139-5p, hsa-mir-140, hsa-miR-140-3p, hsa-miR-145-5p, hsa-mir-146a, hsa-miR-146a-5p, hsa-miR-148a-3p, hsa-miR-152-3p, hsa-miR-15a-5p, hsa-miR-15b-5p, hsa-mir-16-1, hsa-mir-16-2, hsa-miR-16-5p, hsa-miR-17-5p, hsa-miR-181a-5p, hsa-miR-191-5p, hsa-miR-193a-5p, hsa-miR-193b-3p, hsa-miR-197-3p, hsa-miR-199a-3p, hsa-miR-199a-5p, hsa-miR-199b-5p, hsa-miR-19a-3p, hsa-miR-19b-3p, hsa-miR-20a-5p, hsa-mir-203a, hsa-miR-203a-3p, hsa-miR-214-3p, hsa-mir-21, hsa-miR-21-3p, hsa-miR-21-5p, hsa-mir-221, hsa-miR-221-3p, hsa-mir-222, hsa-miR-222-3p, hsa-miR-22-3p, hsa-miR-23a-3p, hsa-miR-23b-3p, hsa-mir-24-1, hsa-mir-24-2, hsa-miR-24-3p, hsa-mir-25, hsa-miR-25-3p, hsa-miR-26a-5p, hsa-miR-27a-3p, hsa-mir-27b, hsa-miR-27b-3p, hsa-miR-29a-3p, hsa-miR-29c-3p, hsa-miR-30a-5p, hsa-miR-30a-5p, hsa-miR-30b-5p, hsa-miR-30c-5p, hsa-mir-30d, hsa-miR-30d-5p, hsa-mir-30e, hsa-miR-30e-5p, hsa-miR-31-3p, hsa-miR-31-5p, hsa-miR-320a, hsa-miR-342-3p, hsa-miR-345-5p, hsa-miR-34a-5p, hsa-miR-361-5p, hsa-miR-376a-3p, hsa-miR-376c-3p, hsa-miR-423-3p, hsa-miR-423-5p, hsa-miR-424-5p, hsa-miR-484, hsa-mir-486-1, hsa-mir-486-2, hsa-miR-486-5p, hsa-miR-570-3p, hsa-miR-574-3p, hsa-miR-663a, hsa-miR-874-3p, hsa-mir-92a-1, hsa-mir-92a-2, hsa-miR-92a-3p, hsa-miR-92b-3p, hsa-mir-93, hsa-miR-93-5p, hsa-miR-940, hsa-miR-99a-5p, and hsa-miR-99b-5p.

Also disclosed herein are compositions of any preceding aspect, wherein the one or more biomolecules inhibit the bradykinin pathway (for example, by inhibiting translation of Bradykinin 2), angiotensin-converting enzyme 2 (ACE 2) receptor, inhibits the transmembrane protease, serine 2 (TMPRSS2) enzyme, inhibits Kallikrein B1, and/or inhibits IL-1β, IL-6, TNF-α, GM-CSF, or M-CSF.

In one example, disclosed herein are compositions of any preceding aspect, wherein the MSC secretome further comprises prostaglandin E2 (PGE2), transforming growth factor β1 (TGF-β1), hepatocyte growth factor (HGF), stromal cell derived factor-1 (SDF-1), nitric oxide, indoleamine 2,3-dioxygenase, interleukin-4 (IL-4), IL-6, interleukin-10 (IL-10), IL-1 receptor antagonist and soluble TNF-α receptor, insulin-like growth factors, fibroblast growth factors (FGF) 1-23 (especially, FGF1 and FGF2), bone morphogenetic proteins (BMPs) 1-15, epidermal growth factor (EGF), transforming growth factor-α (TGF-α) macrophage-stimulating protein (MSP), platelet derived growth factor (PLGF), vascular endothelial growth factor (VEGF),

macrophage colony stimulating factor (M-CSF), insulin, granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF estrogen, and/or thyroid hormones.

Also disclosed herein are methods of treating, decreasing, inhibiting, reducing, ameliorating and/or preventing a microbial infection (such as, for example, a viral, bacterial, fungal, or parasitic infection) or symptoms thereof (including, but not limited to microbial induced cytokine storm, microbial initiated bradykinin storm, and/or acute respiratory distress syndrome) in a subject comprising administering to a subject the composition of any preceding aspect.

In one example, disclosed herein are methods of treating, decreasing, inhibiting, reducing, ameliorating and/or preventing a microbial infection or symptoms thereof of any preceding aspect, wherein the microbial infection comprises an infection from a virus selected from the group of viruses consisting of Herpes Simplex virus- 1, Herpes Simplex virus-2, Varicella-Zoster virus, Epstein-Barr virus, Cytomegalovirus, Human Herpes virus-6, Variola virus, Vesicular stomatitis virus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Hepatitis D virus, Hepatitis E virus, Rhinovirus, Coronavirus (including, but not limited to avian coronavirus (IBV), porcine coronavirus HKU15 (PorCoV HKU15), Porcine epidemic diarrhea virus (PEDV), HCoV-229E, HCoV-OC43, HCoV-HKU1, HCoV-NL63, SARS-CoV, SARS-CoV-2, or MERS-CoV), Influenza virus A, Influenza virus B, Measles virus, Polyomavirus, Human Papillomavirus, Respiratory syncytial virus, Adenovirus, Coxsackie virus, Chikungunya virus, Dengue virus, Mumps virus, Poliovirus, Rabies virus, Rous sarcoma virus, Reovirus, Yellow fever virus, Ebola virus, Marburg virus, Lassa fever virus, Eastern Equine Encephalitis virus, Japanese Encephalitis virus, St. Louis Encephalitis virus, Murray Valley fever virus, West Nile virus, Rift Valley fever virus, Rotavirus A, Rotavirus B, Rotavirus C, Sindbis virus, Simian Immunodeficiency virus, Human T-cell Leukemia virus type-1, Hantavirus, Rubella virus, Simian Immunodeficiency virus, Human Immunodeficiency virus type-1, and Human Immunodeficiency virus type-2.

Also disclosed herein are methods of treating, decreasing, inhibiting, reducing, ameliorating and/or preventing a microbial infection or symptoms thereof of any preceding aspect, wherein the microbial infection comprises an infection from a bacteria selected from the group of bacteria consisting of Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium bovis strain BCG, BCG substrains, Mycobacterium avium, Mycobacterium intracellular, Mycobacterium africanum, Mycobacterium kansasii, Mycobacterium marinum, Mycobacterium ulcerans, Mycobacterium avium subspecies paratuberculosis, Mycobacterium

chimaera, Nocardia asteroides, other Nocardia species, Legionella pneumophila, other Legionella species, Acetinobacter baumanii, Salmonella typhi, Salmonella enterica, other Salmonella species, Shigella boydii, Shigella dysenteriae, Shigella sonnei, Shigella flexneri, other Shigella species, Yersinia pestis, Pasteurella haemolytica, Pasteurella multocida, other Pasteurella species, Actinobacillus pleuropneumoniae, Listeria monocytogenes, Listeria ivanovii, Brucella abortus, other Brucella species, Cowdria ruminantium, Borrelia burgdorferi, Bordetella avium, Bordetella pertussis, Bordetella bronchiseptica, Bordetella trematum, Bordetella hinzii, Bordetella pteri, Bordetella parapertussis, Bordetella ansorpii other Bordetella species, Burkholderia mallei, Burkholderia psuedomallei, Burkholderia cepacian, Chlamydia pneumoniae, Chlamydia trachomatis, Chlamydia psittaci, Coxiella burnetii, Rickettsial species, Ehrlichia species, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Vibrio cholerae, Campylobacter species, Neiserria meningitidis, Neiserria gonorrhea, Pseudomonas aeruginosa, other Pseudomonas species, Haemophilus influenzae, Haemophilus ducreyi, other Hemophilus species, Clostridium tetani, other Clostridium species, Yersinia enterolitica, and other Yersinia species, and Mycoplasma species. In one aspect the bacteria is not Bacillus anthracis.

In one example, also disclosed herein are methods of treating, decreasing, inhibiting, reducing, ameliorating and/or preventing a microbial infection or symptoms thereof of any preceding aspect, wherein the microbial infection comprises an infection from a fungus selected from the group of fungi consisting of Candida albicans, Cryptococcus neoformans, Histoplasma capsulatum, Aspergillus fumigatus, Coccidiodes immitis, Paracoccidiodes brasiliensis, Blastomyces dermitidis, Pneumocystis carinii, Penicillium marneffi, and Alternaria alternata.

Also disclosed herein are methods of treating, decreasing, inhibiting, reducing, ameliorating and/or preventing a microbial infection or symptoms thereof of any preceding aspect, wherein the microbial infection comprises a parasitic infection with a parasite selected from the group of parasitic organisms consisting of Toxoplasma gondii, Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, other Plasmodium species, Entamoeba histolytica, Naegleria fowleri, Rhinosporidium seeberi, Giardia lamblia, Enterobius vermicularis, Enterobius gregorii, Ascaris lumbricoides, Ancylostoma duodenale, Necator americanus, Cryptosporidium spp., Trypanosoma brucei, Trypanosoma cruzi, Leishmania major, other Leishmania species, Diphyllobothrium latum, Hymenolepis nana, Hymenolepis diminuta, Echinococcus granulosus, Echinococcus multilocularis, Echinococcus vogeli, Echinococcus oligarthrus, Diphyllobothrium latum, Clonorchis sinensis; Clonorchis viverrini, Fasciola hepatica, Fasciola gigantica,

V. CLAIMS

What is claimed is:

1. Use of a composition comprising a bone marrow mesenchymal stem cell (MSC) secretome in the manufacture of a medicament for ameliorating one or more secondary conditions caused by a microbial infection, wherein the bone marrow MSC secretome comprises stromal cell derived factor-1 (SDF-1), ferritin protein, PAI-1, and thrombomodulin.

2. The use of claim 1, wherein the bone marrow MSC secretome comprises one or more miRNAs selected from the group consisting of: hsa-let-7a-5p, hsa-let-7b-5p, hsa-let-7c-5p, hsa-let-7d-3p, hsa-let-7e-5p, hsa-let-7g-5p, hsa-let-7i, hsa-let-7i-5p, hsa-miR-100-5p, hsa-miR-103a-3p, hsa-miR-106a-5p, hsa-miR-106b-5p, hsa-mir-10b, hsa-miR-10b-5p, hsa-mir-1246, hsa-miR-1246, hsa-miR-125a-5p, hsa-miR-125b-5p, hsa-miR-130a-3p, hsa-mir-130b, hsa-miR-130b-3p, hsa-miR-132-3p, hsa-miR-136-5p, hsa-miR-138-5p, hsa-miR-139-5p, hsa-mir-140, hsa-miR-140-3p, hsa-miR-145-5p, hsa-mir-146a, hsa-miR-146a-5p, hsa-miR-148a-3p, hsa-miR-152-3p, hsa-miR-15a-5p, hsa-miR-15b-5p, hsa-mir-16-1, hsa-mir-16-2, hsa-miR-16-5p, hsa-miR-17-5p, hsa-miR-181a-5p, hsa-miR-191-5p, hsa-miR-193a-5p, hsa-miR-193b-3p, hsa-miR-197-3p, hsa-miR-199a-3p, hsa-miR-199a-5p, hsa-miR-199b-5p, hsa-miR-19a-3p, hsa-miR-19b-3p, hsa-miR-20a-5p, hsa-mir-203a, hsa-miR-203a-3p, hsa-miR-214-3p, hsa-mir-21, hsa-miR-21-3p, hsa-miR-21-5p, hsa-mir-221, hsa-miR-221-3p, hsa-mir-222, hsa-miR-222-3p, hsa-miR-22-3p, hsa-miR-23a-3p, hsa-miR-23b-3p, hsa-mir-24-1, hsa-mir-24-2, hsa-miR-24-3p, hsa-mir-25, hsa-miR-25-3p, hsa-miR-26a-5p, hsa-miR-27a-3p, hsa-mir-27b, hsa-miR-27b-3p, hsa-miR-29a-3p, hsa-miR-29c-3p, hsa-miR-30a-5p, hsa-miR-30b-5p, hsa-miR-30c-5p, hsa-mir-30d, hsa-miR-30d-5p, hsa-mir-30e, hsa-miR-30e-5p, hsa-miR-31-3p, hsa-miR-31-5p, hsa-miR-320a, hsa-miR-342-3p, hsa-miR-345-5p, hsa-miR-34a-5p, hsa-miR-361-5p, hsa-miR-376a-3p, hsa-miR-376c-3p, hsa-miR-423-3p, hsa-miR-423-5p, hsa-miR-424-5p, hsa-miR-484, hsa-mir-486-1, hsa-mir-486-2, hsa-miR-486-5p, hsa-miR-570-3p, hsa-miR-574-3p, hsa-miR-663a, hsa-miR-874-3p, hsa-mir-92a-1, hsa-mir-92a-2, hsa-miR-92a-3p, hsa-miR-92b-3p, hsa-mir-93, hsa-miR-93-5p, hsa-miR-940, hsa-miR-99a-5p, and hsa-miR-99b-5p.

3. The use of claim 2, wherein the miRNA inhibits the bradykinin pathway and is selected from the group consisting of: hsa-let-7a-5p, hsa-let-7b-5p, hsa-let-7c-5p, hsa-let-7g-5p, hsa-let-7i-5p, hsa-let-7i, hsa-miR-106a-5p, hsa-miR-106b-5p, hsa-miR-15a-5p, hsa-miR-15b-5p, hsa-miR-16-5p, hsa-miR-17-5p, hsa-miR-20a-5p, hsa-miR-23a-3p, hsa-miR-23b-3p, hsa-mir-24-1, hsa-mir-24-2, hsa-miR-25-3p, hsa-miR-92a-3p, hsa-miR-92b-3p, and hsa-miR-93-5p.

4. The use of claim 2, wherein the miRNA inhibits the translation of Bradykinin 2 and is

selected from the group consisting of: hsa-miR-19a-3p and hsa-miR-19b-3p.

5. The use of claim 2, wherein the miRNA inhibits the angiotensin-converting enzyme 2 (ACE 2) receptor or inhibits the transmembrane protease, serine 2 (TMPRSS2) enzyme and is a miRNA selected from the group consisting of: hsa-let-7a-5p, hsa-let-7b-5p, hsa-let-7c-5p, hsa-let-7g-5p, hsa-let-7i-5p, hsa-miR-214-3p, and hsa-miR-27a-3p.

6. The use of any of claims 1-5, wherein the bone marrow MSC secretome further comprises prostaglandin E2 (PGE2), transforming growth factor β1 (TGF-β1), hepatocyte growth factor (HGF), nitric oxide, indoleamine 2,3-dioxygenase, interleukin-4 (IL-4), IL-6, interleukin-10 (IL-10), IL-1 receptor antagonist and soluble TNF-α receptor, insulin-like growth factor, fibroblast growth factor 1 (FGF-1), FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, FGF-15, FGF-16, FGF-17, FGF-18, FGF-19, FGF-20, FGF-21, FGF-22, FGF-23, bone morphogenetic protein 1 (BMP-1), BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, epidermal growth factor (EGF), transforming growth factor-α (TGF-α), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), macrophage colony stimulating factor (M-CSF), granulocyte colony stimulating factor (G-CSF), and/or granulocyte macrophage colony stimulating factor (GM-CSF).

7. The use of any one of claims 1-6, wherein the composition ameliorates microbial induced cytokine storm and/or microbial initiated bradykinin storm.

8. Use of a bone marrow mesenchymal stem cell (MSC) secretome in the manufacture of a medicament for ameliorating acute respiratory distress syndrome (ARDS) caused by a microbial infection, wherein the bone marrow MSC secretome comprises stromal cell derived factor-1 (SDF-1), ferritin protein, PAI-1, and thrombomodulin.

9. The use of any of claims 1-8, wherein the microbial infection comprises an infection from SARS-CoV-2.

10. The use of any one of claims 1-9, wherein the composition ameliorates fluid leakage in the lungs, improves oxygen uptake in the lungs, ameliorates lung damage, and/or to ameliorates airway epithelial cell injury.

11. The use of any one of claims 1-10, wherein the composition (i) increases interleukin-10 (IL-10) secretion by immune regulatory cells to inhibit hyperactive immune cell action; (ii) blocks plasmin production; (iii) suppresses micro-blood clotting frequency; (iv) reduces thrombotic emboli; (v) reduces host cell death or NETosis; or (vi) any combination of two or more thereof.

12. The use of any one of claims 1-11, wherein the composition increases (i) the level of total lymphocyte count by at least 20%; (ii) the level of one or more of CD3+ T lymphocytes, CD4+ T lymphocytes, CD8+ T lymphocytes, or combinations thereof by at least 25%; or (iii) both (i) and (ii).

13. The use of any one of claims 1-12, wherein the composition is formulated for parenteral administration.

14. The use of any one of claims 1-12, wherein the composition is formulated for intravenous administration.

15. The use of any one of claims 1-14, wherein the bone marrow MSC is a human bone marrow MSC.