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(54) **Title:** METHODS OF TREATING COVID-19 USING TETRACYCLINE COMPOUNDS

(57) **Abstract:** The present disclosure provides methods of treating or preventing a viral infection, e.g., SARS-CoV-2 infection or an influenza infection; for treating a viral disease, e.g., COVID-19 or influenza; for preventing a secondary bacterial pneumonia in a subject with a viral infection or a viral disease; and for modulating an immune response. The methods comprise administering to a subject in need thereof omadacycline or a pharmaceutically acceptable salt thereof.

WO 2021/231314 A1

METHODS OF TREATING COVID-19 USING TETRACYCLINE COMPOUNDS

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 63/022,974, filed on May 11, 2020, the entire contents of which are hereby incorporated herein by reference.

INTRODUCTION

Coronavirus disease (COVID-19) is caused by a newly discovered coronavirus (SARS-CoV-2). Most individuals infected with the COVID-19 virus experience mild to moderate respiratory illness and recover without requiring targeted treatment. However older people, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop severe illness (Del Rio *et al.*, *JAMA* 2020, 10.1001/jama.2020.3072; Wu *et al.*, *JAMA* 2020, 10.1001/jama.2020.2648). Accumulating evidence suggests that a subgroup of patients with severe COVID-19 develop a cytokine storm syndrome that is associated with multi-system organ failure and death (Huang *et al.*, *Lancet* 2020, 395:497-506). Patients with COVID-19 infection are also at risk for developing secondary bacterial pneumonia which has been associated with worse clinical outcomes (Zhou *et al.*, *Lancet* 2020, 395:1054-1062).

Secondary bacterial pneumonia is a major cause of morbidity and mortality associated with both seasonal and pandemic respiratory viral illness. The pathogenesis of secondary bacterial infections is characterized by complex interactions between co-infecting pathogens and the host, leading to the disruption of physical barriers, dysregulation of immune responses and delays in a return to homeostasis. The net effect of this cascade can be the outgrowth of the pathogens, immune-mediated pathology, and increased morbidity (McCullers, *Nat Rev Microbiol.* 2014, 12(4):252-62).

Available data from hospitalized patients with COVID-19 demonstrates that secondary infection occurs in about 10-15% of cases (Huang *et al.*, *Lancet* 2020, 395:497-506; Zhou *et al.*, *Lancet* 2020, 395:1054-1062). Identifying bacterial coinfection in patients with COVID-19 is challenging, as the symptoms may be indistinguishable from those of the underlying viral infection. The time to onset of severe disease in COVID-19 and onset of

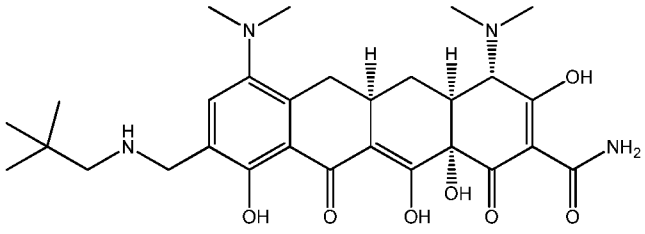
secondary bacterial pneumonia with other respiratory viral infections is similar (Wang et al., *JAMA* 2020, 323(11):1061-1069; Chertow *et al.*, *JAMA* 2013, 309(3):275-82). Therefore, it is possible that secondary bacterial pneumonia may contribute to disease progression in COVID-19 patients who develop severe symptoms. Thus, safe and effective therapies are needed for treating COVID-19, and for preventing secondary bacterial infections associated with COVID-19, such as secondary bacterial pneumonia.

SUMMARY OF THE INVENTION

The present invention is based on a surprising discovery that omadacycline or a pharmaceutically acceptable salt thereof, may be effective for treating viral infections, *e.g.*, SARS-CoV-2 infections. The present invention is also based on a surprising discovery that omadacycline, or a pharmaceutically acceptable salt thereof, may be effective for treating viral diseases, *e.g.*, COVID-19. The present invention is also based on a surprising discovery that omadacycline, or a pharmaceutically acceptable salt thereof, may be effective in preventing secondary bacterial pneumonia in subjects with a viral infection, *e.g.*, SARS-CoV-2 infection or an influenza infection, or with a viral disease, *e.g.*, COVID-19 or influenza. The present invention is also based on a surprising discovery that omadacycline may possess immunomodulatory, *e.g.*, anti-inflammatory, properties, that may contribute to its effectiveness in treating a viral infection, *e.g.*, SARS-CoV-2 infection, or a viral disease, *e.g.*, COVID-19, and preventing secondary bacterial pneumonia in a subject with a viral infection, *e.g.*, SARS-CoV-2 infection or an influenza infection, or with a viral disease, *e.g.*, COVID-19 or influenza.

Omadacycline, which may also be referred to herein as OMC or PTK 0796, which is sold under the brand name NUZYRA®, is a novel aminomethylcycline antibiotic in the tetracycline class. It is a broad spectrum antibiotic active against a wide range of gram positive and gram negative bacterial species, including antibiotic resistant bacteria, such as methicillin-resistant Staphylococcus aureus (MRSA). In the United States, omadacycline has received approval of the Food and Drug Administration (FDA) in 2018 for the treatment of community acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI). Omadacycline is (4aS,5aR,12aS)-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-9-((neopentylamino)methyl)-1,11-dioxo-1,4,4a,5,5a,6,11,12a-

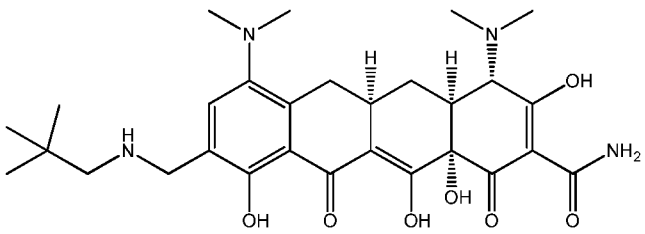
octahydrotetracene-2-carboxamide, or 9-[(2,2-dimethyl-propyl amino)-methyl]-minocycline, which is represented by formula (A):



(A).

The advantages provided by the use of omadacycine for treating subjects at risk for secondary bacterial pneumonia include: a) the activity of omadacycline against pathogens associated with secondary bacterial pneumonia, including *Staphylococcus aureus*; b) extensive tissue distribution of omadacycline into lung; c) established safety profile of omadacycline, including no prolongation of the QTc interval; d) availability of omadacycline oral formulation, once-daily dosing, and no required dose adjustments in special populations; and e) no expected metabolic interactions between omadacycline and other drugs. In addition, the immunomodulatory, *e.g.*, anti-inflammatory properties of omadacycline, may contribute to its effectiveness in treating a viral infection, *e.g.*, SARS-CoV-2 infection, or a viral disease, *e.g.*, COVID-19, and preventing secondary bacterial pneumonia in a subject with a viral infection, *e.g.*, SARS-CoV-2 infection or an influenza infection, or a viral disease, *e.g.*, COVID-19 or influenza.

Accordingly, in some embodiments, the present invention provides a method of treating or preventing a viral infection in a subject in need thereof, the method comprising administering to the subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that the viral infection in the subject is treated or prevented.

In some embodiments, the viral infection is caused by a virus belonging to a family selected from the group consisting of *Abyssoviridae, Ackermannviridae, Adenoviridae, Alloherpesviridae, Alphaflexiviridae, Alphasatellitidae, Alphatetraviridae, Alvernaviridae, Amalgaviridae, Amnoonviridae, Ampullaviridae, Anelloviridae, Arenaviridae, Arteriviridae, Artoviridae, Ascoviridae, Asfaviridae, Aspiviridae, Astroviridae, Autographiviridae, Avsunviroidae, Baccilladnaviridae, Baculoviridae, Barnaviridae, Belpaoviridae, Benyviridae, Betaflexiviridae, Bicaudaviridae, Bidnaviridae, Birnaviridae, Bornaviridae, Botourmiarividae, Bromoviridae, Caliciviridae, Carmotetraviridae, Caulimoviridae, Chaseviridae, Chrysoviridae, Chuviridae, Circoviridae, Clavaviridae, Closteroviridae, Coronaviridae, Corticoviridae, Cremegaviridae, Cruliviridae, Cystoviridae, Deltaflexiviridae, Demerecviridae, Cicistroviridae, Drexlerviridae, Endomaviridae, Euroniviridae, Filoviridae, Fimoviridae, Finnalakeviridae, Flaviviridae, Fuselloviridae, Gammaflexiviridae, Geminiviridae, Genomoviridae, Globuloviridae, Gresnaviridae, Guttaviridae, Halspiviridae, Hantaviridae, Hepadnaviridae, Hepeviridae, Herelleviridae, Herpesviridae, Hypoviridae, Hytrosaviridae, Iflaviridae, Inoviridae, Iridoviridae, Kitaviridae, Lavidaviridae, Leishbuviridae, Leviviridae, Lipothrixviridae, Lispiviridae, Luteoviridae, Malacoherperviridae, Marnaviridae, Marseilleviridae, Matonaviridae, Mayoviridae, Medionviridae, Megabirnaviridae, Mesoniviridae, Metaviridae, Microviridae, Mimiviridae, Mitoviridae, Mononiviridae, Mymonaviridae, Myoviridae, Mypoviridae, Nairoviridae, Nanghoshaviridae, Nanhypoviridae, Nanoviridae, Narnaviridae, Nimaviridae, Nodaviridae, Nudiviridae, Nyamiviridae, Olifoviridae, Orthomyxoviridae, Ovaliviridae, Papillomaviridae, Paramyxoviridae, Partitiviridae, Parvoviridae, Peribunyaviridae, Permutotetraviridae, Phasmaviridae, Phenuiviridae, Phycodnaviridae, Picobimaviridae, Picornaviridae, Plasmaviridae, Plectroviridae, Pleolipoviridae, Pneumoviridae, Podoviridae, Polycipiviridae, Polydnaviridae, Polymycoviridae, Polymaviridae, Portogloboviridae, Pospiviroidae, Potyviridae, Poxviridae, Pseudoviridae, Qinviridae, Quadrivirdae, Redondoviridae, Reoviridae, Retroviridae, Rhabdoviridae, Roniviridae, Rudiviridae, Sarthroviridae, Secoviridae, Sinhaliviridae, Siphviridae, Smacoviridae, Solemoviridae, Solinviviridae, Sphaerolipoviridae, Spiraviridae, Sunviridae, Tectiviridae, Thaspiviridae, Tobaniviridae, Togaviridae, Tolecusatellitidae, Tombusviridae, Tospoviridae, Totiviridae, Tristromaviridae, Turniviridae, Tymoviridae, Virgaviridae, Wupedeviridae, Xinmoviridae and Yueviridae.*

In some aspects, the virus belongs to a family *Coronaviridae*. In some aspects, the virus belongs to a genus selected from the group consisting of *Alphaletovirus,*

Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus. In some aspects, the virus belongs to a genus *Betacoronavirus.* In some embodiments, the virus belongs to a species selected from the group consisting of *Betacoronavirus 1, China Rattus coronavirus HKU24, Human coronavirus HKU1, Murine coronavirus, Myodes coronavirus 2JL14, Bat Hp-betacoronavirus Zhejiang2013, Hedgehog coronavirus 1, Middle East respiratory syndrome-related coronavirus, Pipistrellus bat coronavirus HKU5, Tylonycteris bat coronavirus HKU4, Eidolon bat coronavirus C704, Rousettus bat coronavirus GCCDC1, Rousettus bat coronavirus HKU9 and Severe acute respiratory syndrome-related coronavirus.*

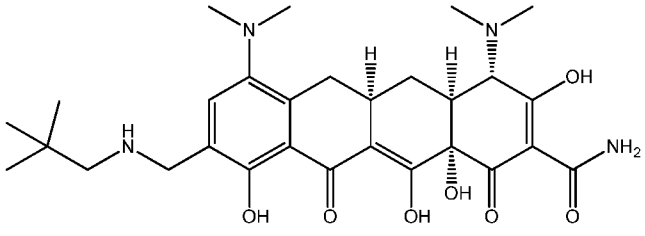
In some embodiments, the virus belongs to a species *Severe acute respiratory syndrome-related coronavirus.* In some embodiments, the virus is selected from the group consisting of SARSr-CoV BtKY72, SARS-CoV-2, SARSr-CoV RaTG13, SARS-CoV PC4-227 and SARS-CoV.

In one embodiment, the virus is SARS-CoV-2. In a further embodiment, the subject has Coronavirus disease 2019 {COVID-19).

In some aspects, the virus is selected from the group consisting of MERS-CoV, HCoV HKU1, HCoV OC43, HCoV NL63 and HCoV 229E. In some embodiments, the virus belongs to family *Orthomyxoviridae.* In some embodiments, the virus belongs to a genus selected from the group consisting of *Alphainfluenzavirus*, *Betainfluenzavirus*, *Deltainfluenzavirus* and *Gammainfluenzavirus.* In a further embodiment, the virus belongs to a species selected from the group consisting of *Influenza A virus*, *Influenza B virus*, *Influenza D virus* and *Influenza C virus.*

In some embodiments, administering the tetracycline compound or a pharmaceutically acceptable salt thereof leads to a reduction in viral load in the subject.

In some embodiments, the present invention also provides a method of treating or preventing SARS-CoV-2 infection in a subject in need thereof, the method comprising administering to the subject an effective amount of a tetracycline compound represented by formula (A):

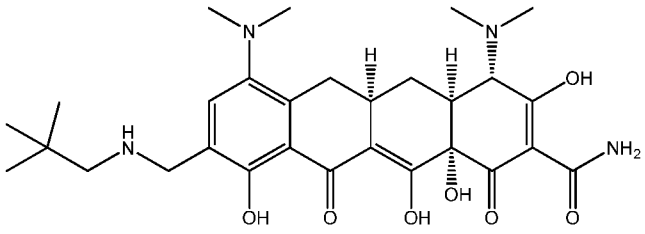


(A),

or a pharmaceutically acceptable salt thereof, such that the SARS-CoV-2 infection in the subject is treated or prevented. In one embodiment, the subject has COVID-19.

In some embodiments, administering of the tetracycline compound leads to a reduction in the load of SARS-CoV-2 virus in the subject.

In some embodiments, the present invention also provides a method of treating or preventing a viral disease in a subject in need thereof, the method comprising administering to the subject an effective amount of a tetracycline compound represented by formula (A):



(A),

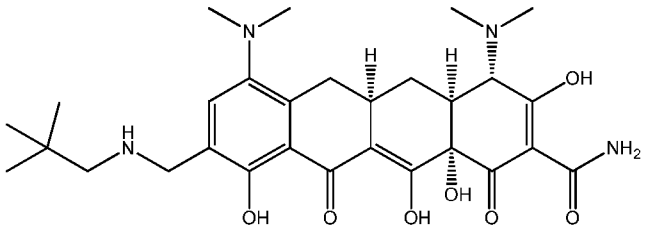
or a pharmaceutically acceptable salt thereof, such that the viral disease in the subject is treated or prevented.

In some aspects, the viral disease is selected from the group consisting of gastroenteritis, keratoconjunctivitis, pharyngitis, croup, pneumonia, cystitis, hand, food and mouth disease, pleurodynia, meningitis, pericarditis, myocarditis, infectious mononucleosis, hepatitis, hepatic cirrhosis, cytomegalic inclusion disease, AIDS, Dengue fever, influenza, measles, postinfections encephalomyelitis, mumps, common cold, rabies, viral encephalitis, disease caused by West Nile virus, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19.

In one aspect, the viral disease is COVID-19.

In some embodiments, administering of the tetracycline compound leads to a reduction in viral load in the subject.

In some embodiments, the present invention also provides a method of treating or preventing COVID-19 in a subject in need thereof, the method comprising administering to the subject an effective amount of a tetracycline compound represented by formula (A):

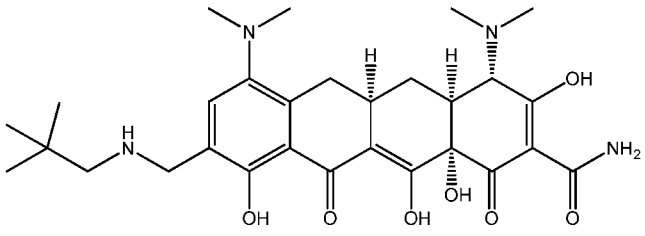


(A),

or a pharmaceutically acceptable salt thereof, such that the COVID-19 in the subject is treated or prevented.

In some aspects, administering of the tetracycline compound leads to a reduction in the load of SARS-CoV-2 virus in the subject.

In some embodiments, the present invention also provides a method of modulating an immune response in a subject in need thereof, the method comprising administering to the subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that the immune response in the subject is modulated.

In some aspects, the subject has a viral infection or is at a high risk of the viral infection.

In some aspects, the viral infection is caused by a virus belonging to a family selected from the group consisting of *Abyssoviridae, Ackermannviridae, Adenoviridae, Alloherpesviridae, Alphaflexiviridae, Alphasatellitidae, Alphatetraviridae, Alvernaviridae, Amalgaviridae, Amnoonviridae, Ampullaviridae, Anelloviridae, Arenaviridae, Arteriviridae, Artoviridae, Ascoviridae, Asfaviridae, Aspiviridae, Astroviridae, Autographiviridae,*

Avsunviroidae, Baccilladnaviridae, Baculoviridae, Barnaviridae, Belpaoviridae, Benyviridae, Betaflexiviridae, Bicaudaviridae, Bidnaviridae, Birnaviridae, Bornaviridae, Botourmiarividae, Bromoviridae, Caliciviridae, Carmotetraviridae, Caulimoviridae, Chaseviridae, Chrysoviridae, Chuviridae, Circoviridae, Clavaviridae, Closteroviridae, Coronaviridae, Corticoviridae, Cremegaviridae, Cruliviridae, Cystoviridae, Deltaflexiviridae, Demerecviridae, Cicistroviridae, Drexlerviridae, Endomaviridae, Euroniviridae, Filoviridae, Fimoviridae, Finnalakeviridae, Flaviviridae, Fuselloviridae, Gammaflexiviridae, Geminiviridae, Genomoviridae, Globuloviridae, Gresnaviridae, Guttaviridae, Halspiviridae, Hantaviridae, Hepadnaviridae, Hepeviridae, Herelleviridae, Herpesviridae, Hypoviridae, Hytrosaviridae, Iflaviridae, Inoviridae, Iridoviridae, Kitaviridae, Lavidaviridae, Leishbuviridae, Leviviridae, Lipothrixviridae, Lispiviridae, Luteoviridae, Malacoherperviridae, Marnaviridae, Marseilleviridae, Matonaviridae, Mayoviridae, Medionviridae, Megabirnaviridae, Mesoniviridae, Metaviridae, Microviridae, Mimiviridae, Mitoviridae, Mononiviridae, Mymonaviridae, Myoviridae, Mypoviridae, Nairoviridae, Nanghoshaviridae, Nanhypoviridae, Nanoviridae, Narnaviridae, Nimaviridae, Nodaviridae, Nudiviridae, Nyamiviridae, Olifoviridae, Orthomyxoviridae, Ovaliviridae, Papillomaviridae, Paramyxoviridae, Partitiviridae, Parvoviridae, Peribunyaviridae, Permutotetraviridae, Phasmaviridae, Phenuiviridae, Phycodnaviridae, Picobimaviridae, Picornaviridae, Plasmaviridae, Plectroviridae, Pleolipoviridae, Pneumoviridae, Podoviridae, Polycipiviridae, Polydnaviridae, Polymycoviridae, Polymaviridae, Portogloboviridae, Pospiviroidae, Potyviridae, Poxviridae, Pseudoviridae, Qinviridae, Quadrivirdae, Redondoviridae, Reoviridae, Retroviridae, Rhabdoviridae, Roniviridae, Rudiviridae, Sarthroviridae, Secoviridae, Sinhaliviridae, Siphviridae, Smacoviridae, Solemoviridae, Solinviviridae, Sphaerolipoviridae, Spiraviridae, Sunviridae, Tectiviridae, Thaspiviridae, Tobaniviridae, Togaviridae, Tolecusatellitidae, Tombusviridae, Tospoviridae, Totiviridae, Tristromaviridae, Turniviridae, Tymoviridae, Virgaviridae, Wupedeviridae, Xinmoviridae and Yueviridae.

In some aspects, the virus belongs to a family *Coronaviridae*. In some aspects, the virus belongs to a genus selected from the group consisting of *Alphaletovirus, Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus*. In some aspects, the virus belongs to a genus *Betacoronavirus*. In some aspects, the virus belongs to a species selected from the group consisting of *Betacoronavirus 1, China Rattus coronavirus HKU24, Human coronavirus HKU1, Murine coronavirus, Myodes coronavirus 2JL14, Bat Hp-betacoronavirus Zhejiang2013, Hedgehog coronavirus 1, Middle East respiratory*

syndrome-related coronavirus, Pipistrellus bat coronavirus HKU5, Tylonycteris bat coronavirus HKU4, Eidolon bat coronavirus C704, Rousettus bat coronavirus GCCDC1, Rousettus bat coronavirus HKU9 and Severe acute respiratory syndrome-related coronavirus.

In some embodiments, the virus belongs to a species *Severe acute respiratory syndrome-related coronavirus*. In some embodiments, the virus is SARSr-CoV BtKY72, SARS-CoV-2, SARSr-CoV RaTG13, SARS-CoV PC4-227 and SARS-CoV.

In one embodiment, the virus is SARS-CoV-2. In a further embodiment, the subject has COVID-19.

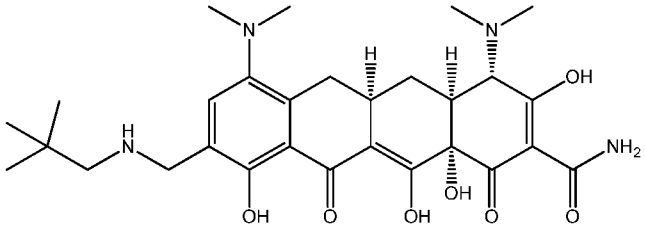
In some embodiments, the virus that belongs to a family *Orthomyxoviridae*. In some embodiments, the virus belongs to a genus selected from the group consisting of *Alphainfluenzavirus*, *Betainfluenzavirus*, *Deltainfluenzavirus* and *Gammainfluenzavirus*. In some embodiments, the virus belongs to a species selected from the group consisting of *Influenza A virus*, *Influenza B virus*, *Influenza D virus* and *Influenza C virus*.

In some embodiments, the subject has a viral disease. In further aspects, the viral disease is selected from the group consisting of gastroenteritis, keratoconjunctivitis, pharyngitis, croup, pneumonia, cystitis, hand, food and mouth disease, pleurodynia, meningitis, pericarditis, myocarditis, infectious mononucleosis, hepatitis, hepatic cirrhosis, cytomegalic inclusion disease, AIDS, Dengue fever, influenza, measles, postinfections encephalomyelitis, mumps, common cold, rabies, viral encephalitis, disease caused by West Nile virus and COVID-19.

In one specific embodiment, the viral disease is COVID-19.

In another specific embodiment, the viral disease is influenza.

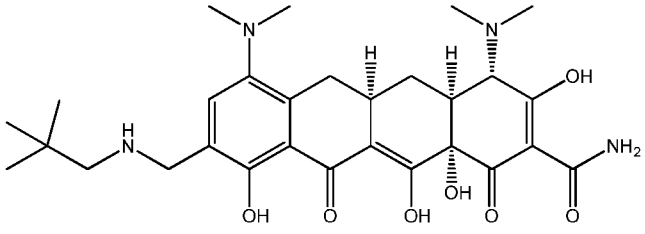
In some embodiments, the present invention also provides a method of modulating an immune response in a subject with a SARS-CoV-2 infection, the method comprising administering to the subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that the immune response in the subject is modulated.

In some embodiments, the present invention also provides a method of modulating an immune response in a subject afflicted with COVID-19, the method comprising administering to the subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that the immune response in the subject is modulated.

In some aspects, administering of the tetracycline compound modulates at least one inflammatory biomarker in the subject. In further aspects, the inflammatory biomarker is selected from the group consisting of C-reactive protein (CRP), leukocyte count, neutrophil count, monocyte count, eosinophil count, basophil count, erythrocyte sedimentation count, serum ferritin, white blood cell count (WBC count), serum amyloid A (SAA), procalcitonin (PCT), tumor necrosis factor α (TNF-α), interferon-γ (INF-γ), interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-12 (IL-12), interleukin-15 (IL-15), interleukin-18 (IL-18), interleukin-1β (IL-1β), colony-stimulating factor 2 (CSF 2), colony-stimulating factor 3 (CSF 3), nitric oxide synthase (iNOS), monokine induced by gamma (MIG), CXCL1 (KC Protein), interferon gamma-induced protein 10 (IP-10), a methyl-accepting chemotaxis protein (MCP), an Intercellular Adhesion

Molecule (ICAM), a metalloproteinase, a macrophage inflammatory protein, a complement protein, and a prostaglandin.

In some embodiments, administering of the tetracycline compound alleviates at least one symptom associated with COVID-19 in the subject. In further aspects, the at least one symptom associated with COVID-19 is selected from the group consisting of fever, body ache, muscle and joint pain, dry cough, fatigue, chills, headache, sore throat, shortness of breath, sputum production, hemoptysis, sneezing, runny nose, chest tightness, palpitation, a neurological symptom and a gastrointestinal (GI) symptom.

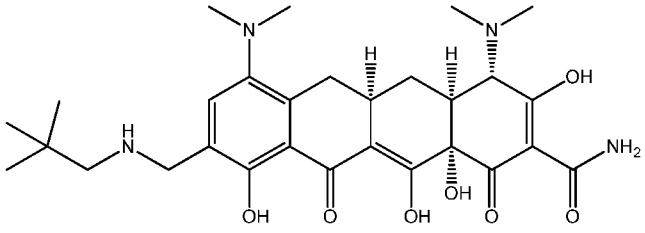
In some embodiments, the neurological symptom is selected from the group consisting of decreased sense of smell, inability to taste, muscle weakness, tingling or numbness in the hands and feet, dizziness, confusion, delirium, seizure and stroke.

In some embodiments, the GI symptom is selected from the group consisting of loss of appetite, nausea, vomiting, diarrhea and abdominal pain or discomfort.

In some embodiments, administering of the tetracycline compound prevents at least one complication associated with COVID-19 in the subject. In further embodiments, the at least one complication associated with COVID-19 is selected from the group consisting of acute respiratory failure, pneumonia, acute respiratory distress syndrome (ARDS), sepsis associated syndrome, acute liver injury, acute cardiac injury, acute kidney injury, disseminated intravascular coagulation (DIC), blood clots and rhabdomyolysis. In one aspect, the pneumonia is secondary bacterial pneumonia.

In some embodiments, the sepsis associated state is systemic inflammatory response syndrome (SIRS). In some aspects, the SIRS comprises cytokine storm syndrome (CSS). In some aspects, the sepsis associated state is septic shock.

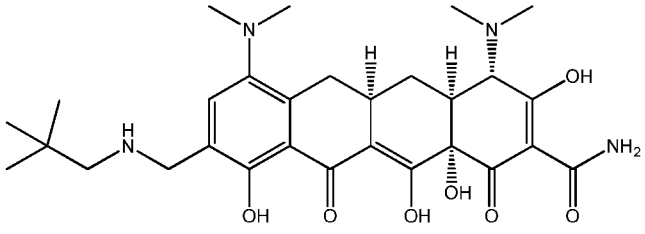
In some embodiments, the present invention also provides a method of preventing secondary bacterial pneumonia in a subject with a viral infection, the method comprising administering to the subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that the secondary bacterial pneumonia in the subject is prevented.

In some embodiments, the present invention also provides a method of reducing the severity of secondary bacterial pneumonia in a subject with a viral infection, the method comprising administering to the subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that the severity of the secondary bacterial pneumonia in the subject is reduced.

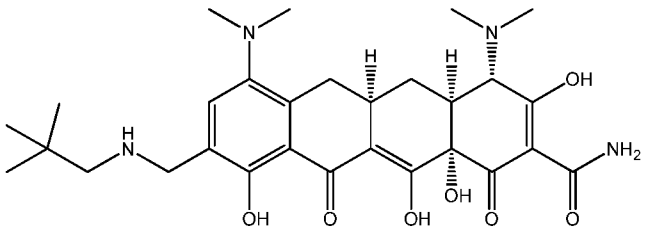
In some aspects, the viral infection is caused by a virus that belongs to a family *Coronaviridae*. In some aspects, the virus belongs to a genus selected from the group consisting of *Alphaletovirus, Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus*. In some aspects, the virus belongs to a genus *Betacoronavirus*. In some aspects, the virus belongs to a species selected from the group consisting of *Betacoronavirus 1, China Rattus coronavirus HKU24, Human coronavirus HKU1, Murine coronavirus, Myodes coronavirus 2JL14, Bat Hp-betacoronavirus Zhejiang2013, Hedgehog coronavirus 1, Middle East respiratory syndrome-related coronavirus, Pipistrellus bat coronavirus HKU5, Tylonycteris bat coronavirus HKU4, Eidolon bat coronavirus C704, Rousettus bat coronavirus GCCDC1, Rousettus bat coronavirus HKU9 and Severe acute respiratory syndrome-related coronavirus*.

In some embodiments, the virus belongs to a species *Severe acute respiratory syndrome-related coronavirus*. In some embodiments, the virus is SARSr-CoV BtKY72, SARS-CoV-2, SARSr-CoV RaTG13, SARS-CoV PC4-227 and SARS-CoV.

In one embodiment, the virus is SARS-CoV-2.

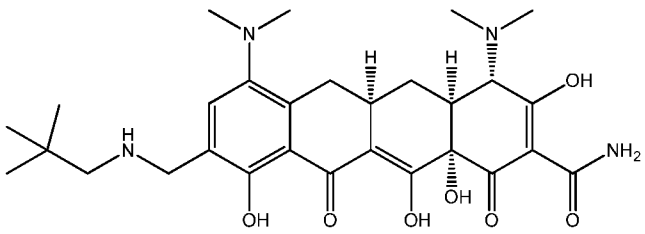
In some embodiments, the viral infection is caused by a virus that belongs to a family *Orthomyxoviridae*. In some aspects, the virus belongs to a genus selected from the group consisting of *Alphainfluenzavirus*, *Betainfluenzavirus*, *Deltainfluenzavirus* and *Gammainfluenzavirus*. In some aspects, the virus belongs to a species selected from the group consisting of *Influenza A virus*, *Influenza B virus*, *Influenza D virus* and *Influenza C virus*.

In some embodiments, the present invention also provides a method of preventing secondary bacterial pneumonia in a subject afflicted with a viral disease, the method comprising administering to the subject an effective amount of a tetracycline compound represented by formula (A):


(A),

or a pharmaceutically acceptable salt thereof, such that the secondary bacterial pneumonia in the subject is prevented.

In some embodiments, the present invention also provides a method of reducing the severity of secondary bacterial pneumonia in a subject afflicted with a viral disease, the method comprising administering to the subject an effective amount of a tetracycline compound represented by formula (A):

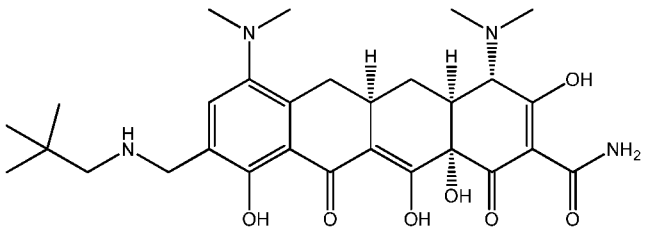

(A),

or a pharmaceutically acceptable salt thereof, such that the severity of the secondary bacterial pneumonia in the subject is reduced.

In some embodiments, the viral disease is COVID-19.

In some embodiments, the viral disease in influenza.

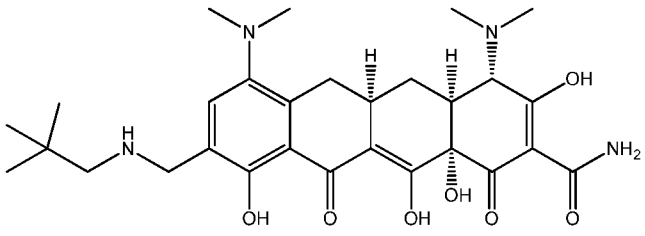
In some embodiments, the present invention also provides a method of preventing secondary bacterial pneumonia in a subject with a SARS-CoV-2 infection, the method comprising administering to the subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that the secondary bacterial pneumonia in the subject is prevented.

In some embodiments, the present invention also provides a method of reducing the severity of secondary bacterial pneumonia in a subject with a SARS-CoV-2 infection, the method comprising administering to the subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that the severity of the secondary bacterial pneumonia in the subject is reduced.

In some aspects, the administering of the tetracycline compound for preventing secondary bacterial pneumonia or for reducing the severity of secondary bacterial pneumonia prevents at least one complication associated with COVID-19. In further aspects, the at least

one complication associated with COVID-19 is selected from the group consisting of acute respiratory failure, pneumonia, acute respiratory distress syndrome (ARDS), sepsis associated syndrome, acute liver injury, acute cardiac injury, acute kidney injury, disseminated intravascular coagulation (DIC), blood clots and rhabdomyolysis.

In some aspects, the sepsis associated state is systemic inflammatory response syndrome (SIRS). In further aspects, the SIRS comprises cytokine storm syndrome (CSS).

In some aspects, the sepsis associated state is septic shock.

In some aspects, the subject has no known bacterial infection.

In some embodiments, the tetracycline compound is administered in accordance with methods of the present invention in combination with at least one additional therapeutic agent.

In some embodiments, the at least one additional therapeutic agent is selected from the group consisting of an antiviral agent, an antibacterial agent, an anti-parasitic agent, an immunomodulatory agent and a therapeutic antibody.

In some aspects, the antiviral agent is selected from the group consisting of remdesivir, favipiravir, umifenovir, azvudine, baloxavir marboxil, danoprevir, lopinavir, ritonavir, sofosbuvir, valacyclovir, darunavir, cobicistat, inosine pranobex, EIDD-2801, BLD-2660, triazavirin, and ribavirin.

In some aspects, the antibacterial agent is selected from the group consisting of a penicillin, a tetracycline, a cephalosporin, a quinolone, a lincomycin, a macrolide, a sulfonamide, a glycopeptide, an aminoglycoside and a carbapenem.

In some aspects, the antibacterial agent is a macrolide selected from the group consisting of azithromycin, clarithromycin, erythromycin, spiramycin, teicoplanin, oritavancin, dalbavancin and monensin. In some aspects, the antibacterial agent is selected from the group consisting of sulfamethoxazole/trimethoprim, kolimycin, minocycline, doxycycline and azithromycin.

In some aspects, the antiparasitic agent is selected from the group consisting of chloroquine, hydroxychloroquine, nitazoxanide, mefloquine, levamisole, suramin, and ivermectin.

In some aspects, the immunomodulatory agent is selected from the group consisting of interferon beta, ciclesonide, colchicine, a corticosteroid, leflunomide, baricitinib, sirolimus, tacrolimus, tetrandrine, tranilast, an NSAID, aescin, anakinra, fingolimod, XPro1595, and a neutralizing antibody against a cytokine associated with a cytokine storm.

In some aspects, the therapeutic antibody is selected from the group consisting of tocilizumab, sarilumab, bevacizumab, eculizamab, avdoralimab, canakinumab, ravalizumab, clazakizumab, nivolumab, BMS-986253, emapalumab, ixekizumab, leronimab, lenziulumab, ixekizumab, mepolizumab, siltuximab, IFX-1, TJ003234 and an anti-PD-1 antibody.

In some embodiments, the at least one additional therapeutic agent is selected from the group consisting of peginterferon lambda-1a, formoterol, Cd24f, CM4620, LY3127804, OM-85, MRx-4DP0004, recombinant tissue-Plasminogen Activator (rt-PA), viral macrophage inflammatory protein (vMIP), granulocyte-colony stimulating factor (G-CSF), human alpha-1 proteinase inhibitor, human antithrombin-III, human angiotensin-converting enzyme 2, vafidemstat, nafamostat, lenalidomide, Jakotinib, tofacitinib, itraconazole, ruxolitinib, acalabrutinib, estradiol, progesterone, dexmedetomidine, solnatide, etoposide, enoxaparin, vazegepant, linagliptin, sitagliptin, dalargin, hyperbaric oxygen, nitric oxide, ozone, bismuth potassium citrate, chlorine phosphate (Arechin), ramipril, spironolactone, sevoflurane, bromhexine, IB-MECA (methyl 1-[N6-(3-iodobenzyl)-adenin-9-yl]-b-D-ribofuronamide), pyridostigmine, chlorpromazine, ciclesonide, methotrexate, fluvoxamine, losartan, APN01, melatonin, curcumin, metmorfin, angiotensin, imatinib, nintedanib, noscapine, sargramostim, selinexor, isotretinoin, prazosin, defibrotide, brilacidin, griffithsin, an anticoagulant, an anti-hypertensive, famotidine, dipyridamole, sildenafil, avipladil, tradipitant, bezafibrate, fenofibrate, intravenous vitamin C, dapagliflozin, a statin, alteplase, almitrine, deferoxamine, Sn-protoporphyrin IX (SnPPIX), sulfonatoporphyrin(TPPS), polyinosinic:polycytidylic acid, lipoic acid, amiodarone, verapamil, tranexamic acid, dornase alfa, thalidomide, berberine, REGN3048, TZLS-501, AT-001, PUL-042, crocetin, an ACE inhibitor (*e.g.*, captopril), Crostop solution, Croguard syrup, zinc, lithium, heparin, tinzaparin, fondaparinux, clopidogrel, tirofiban, eicosapentaenoic acid, medium-chain triglycerides (MCTs), vitamin A, vitamin D, a derivative of vitamin D, Zofa (Hyssop) syrup, pirfenidone, valsartan, camostat, enoxaparin, intravenous immunoglobulin, extracorporeal blood purification, mesenchymal stem cell therapy, hydrogen-oxygen inhalation, extracorporeal membrane oxygenation (ECMO), hemodialysis, and convalescent plasma.

In some embodiments, the subject being administered the tetracycline compound, or a pharmaceutically acceptable salt thereof, in accordance with methods of the present invention is a human.

In some embodiments, the subject is over 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 years old or older.

In some embodiments, the subject has a pre-existing or underlying condition selected from the group consisting of: hypertension, diabetes mellitus, a cardiovascular disease, cancer, chronic kidney disease, liver disease, excess weight and a respiratory disease. In some aspects, the respiratory disease comprises chronic lung disease, asthma or lung damage. In some aspects, the lung damage is associated with smoking or drug use.

In some embodiments, the subject is immunocompromised. In some aspects, the subject is immunocompromised due to one of more of the following: undergoing cancer treatment, undergoing organ transplantation, having an immune deficiency, smoking, or prolonged use of immune weakening medication.

In some embodiments, the subject is a male.

In some embodiments, the tetracycline compound, or a pharmaceutically acceptable salt thereof, is administered in accordance with methods of the present invention parenterally, orally, topically or via an aerosol.

In some embodiments, the tetracycline compound, or a pharmaceutically acceptable salt thereof, is administered parenterally. In some embodiments, the tetracycline compound, or a pharmaceutically acceptable salt thereof, is administered intravenously. In some embodiments, the tetracycline compound, or a pharmaceutically acceptable salt thereof, is administered intravenously at a dose of about 100 to about 300 mg.

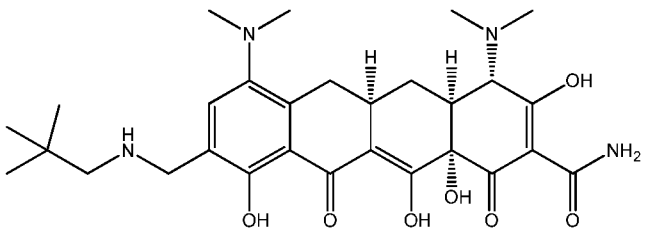
In some embodiments, the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered intravenously at a dose of about 100 mg, about 150 mg, about 200 mg, about 250 mg or about 300 mg. In some embodiments, the tetracycline compound, or a pharmaceutically acceptable salt thereof, is administered orally. In some embodiments, the tetracycline compound, or a pharmaceutically acceptable salt thereof, is administered orally at a dose of about 150 to about 600 mg. In some

embodiments, the tetracycline compound, or a pharmaceutically acceptable salt thereof, is administered orally at a dose of about 150, about 300 mg, about 450 mg or about 600 mg.

DETAILED DESCRIPTION OF THE INVENTION

Methods of Treating or Preventing Viral Infections

The present invention provides methods of treating or preventing a viral infection in a subject in need thereof. The methods of treating or preventing a viral infection comprise administering to a subject in need thereof an effective amount of omadacycline, or a pharmaceutically acceptable salt thereof. The term "omadacycline", which may also be used herein interchangeably with the terms "OMC", "PTK 0796", or its brand name NUZYRA®, refers to (4aS,5aR,12aS)-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-9-((neopentylamino)methyl)-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide, or 9-[(2,2-dimethyl-propyl amino)-methyl]-minocycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof. Omadacycline may be represented by formula (A):



(A).

In some examples, omadacycline may be administered to the subject in the form a salt, *e.g.*, a pharmaceutically acceptable salt, such as a tosylate salt. Tosylate salts of omadacycline may be amorphous or crystalline, *e.g.*, Form 1 polymorph, Form 2 polymorph or Form 3 polymorph of the crystalline tosylate salt of omadacycline as described in U.S. Patent No. 8,383,610, the entire contents of which are incorporated herein by reference. In some examples, omadacycline may be administered to the subject in the form of a freebase, *e.g.*, crystalline freebase.

The term "viral infection", as used herein, refers to an infection caused by a virus. Methods of the present invention encompass treating infections caused by a virus belonging to any known family of viruses. For example, methods of the present invention encompass

treating infections that may be caused by a virus belonging to a family selected from the group consisting of *Abyssoviridae, Ackermannviridae, Adenoviridae, Alloherpesviridae, Alphaflexiviridae, Alphasatellitidae, Alphatetraviridae, Alvernaviridae, Amalgaviridae, Amnoonviridae, Ampullaviridae, Anelloviridae, Arenaviridae, Arteriviridae, Artoviridae, Ascoviridae, Asfaviridae, Aspiviridae, Astroviridae, Autographiviridae, Avsunviroidae, Baccilladnaviridae, Baculoviridae, Barnaviridae, Belpaoviridae, Benyviridae, Betaflexiviridae, Bicaudaviridae, Bidnaviridae, Birnaviridae, Bornaviridae, Botourmiarividae, Bromoviridae, Caliciviridae, Carmotetraviridae, Caulimoviridae, Chaseviridae, Chrysoviridae, Chuviridae, Circoviridae, Clavaviridae, Closteroviridae, Coronaviridae, Corticoviridae, Cremegaviridae, Cruliviridae, Cystoviridae, Deltaflexiviridae, Demerecviridae, Cicistroviridae, Drexlerviridae, Endomaviridae, Euroniviridae, Filoviridae, Fimoviridae, Finnalakeviridae, Flaviviridae, Fuselloviridae, Gammaflexiviridae, Geminiviridae, Genomoviridae, Globuloviridae, Gresnaviridae, Guttaviridae, Halspiviridae, Hantaviridae, Hepadnaviridae, Hepeviridae, Herelleviridae, Herpesviridae, Hypoviridae, Hytrosaviridae, Iflaviridae, Inoviridae, Iridoviridae, Kitaviridae, Lavidaviridae, Leishbuviridae, Leviviridae, Lipothrixviridae, Lispiviridae, Luteoviridae, Malacoherperviridae, Marnaviridae, Marseilleviridae, Matonaviridae, Mayoviridae, Medionviridae, Megabirnaviridae, Mesoniviridae, Metaviridae, Microviridae, Mimiviridae, Mitoviridae, Mononiviridae, Mymonaviridae, Myoviridae, Mypoviridae, Nairoviridae, Nanghoshaviridae, Nanhypoviridae, Nanoviridae, Narnaviridae, Nimaviridae, Nodaviridae, Nudiviridae, Nyamiviridae, Olifoviridae, Orthomyxoviridae, Ovaliviridae, Papillomaviridae, Paramyxoviridae, Partitiviridae, Parvoviridae, Peribunyaviridae, Permutotetraviridae, Phasmaviridae, Phenuiviridae, Phycodnaviridae, Picobimaviridae, Picornaviridae, Plasmaviridae, Plectroviridae, Pleolipoviridae, Pneumoviridae, Podoviridae, Polycipiviridae, Polydnaviridae, Polymycoviridae, Polymaviridae, Portogloboviridae, Pospiviroidae, Potyviridae, Poxviridae, Pseudoviridae, Qinviridae, Quadrivirdae, Redondoviridae, Reoviridae, Retroviridae, Rhabdoviridae, Roniviridae, Rudiviridae, Sarthroviridae, Secoviridae, Sinhaliviridae, Siphviridae, Smacoviridae, Solemoviridae, Solinviviridae, Sphaerolipoviridae, Spiraviridae, Sunviridae, Tectiviridae, Thaspiviridae, Tobaniviridae, Togaviridae, Tolecusatellitidae, Tombusviridae, Tospoviridae, Totiviridae, Tristromaviridae, Turniviridae, Tymoviridae, Virgaviridae, Wupedeviridae, Xinmoviridae* and *Yueviridae.*

In some examples, the virus may belong to a family *Coronaviridae*. For example, the virus may belong to a genus selected from the group consisting of *Alphaletovirus,*

Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus. In one specific example, the virus may belong to a genus *Betacoronavirus*, *e.g.*, to a species selected from the group consisting of *Betacoronavirus 1, China Rattus coronavirus HKU24, Human coronavirus HKU1, Murine coronavirus, Myodes coronavirus 2JL14, Bat Hp-betacoronavirus Zhejiang2013, Hedgehog coronavirus 1, Middle East respiratory syndrome-related coronavirus, Pipistrellus bat coronavirus HKU5, Tylonycteris bat coronavirus HKU4, Eidolon bat coronavirus C704, Rousettus bat coronavirus GCCDC1, Rousettus bat coronavirus HKU9 and Severe acute respiratory syndrome-related coronavirus*.

In some embodiments, the virus may belong to a species *Severe acute respiratory syndrome-related coronavirus*. In further embodiment, the virus may be selected from the group consisting of SARSr-CoV BtKY72, SARS-CoV-2, SARSr-CoV RaTG13, SARS-CoV PC4-227 and SARS-CoV-1 (also known as SARS-CoV).

In one specific example, the virus may be SARS-CoV-2. In some embodiments, a subject with a SARS-CoV-2 infection may have Coronavirus disease 2019 (COVID-19).

In another example, the virus may be SARS-CoV. In some embodiments, a subject with a SARS-CoV infection may have Severe Acute Respiratory Syndrome (SARS).

In some embodiments, the virus may belong to a species *Middle East respiratory syndrome-related coronavirus*, *e.g.*, MERS-CoV. In some embodiments, a subject with a MERS-CoV infection may have Middle East Respiratory Syndrome (MERS).

In some embodiments, the virus may belong to family *Orthomyxoviridae*. For example, the virus may belong to a genus selected from the group consisting of *Alphainfluenzavirus*, *Betainfluenzavirus*, *Deltainfluenzavirus* and *Gammainfluenzavirus*. In some examples, the virus may belong to a species selected from the group consisting of *Influenza A virus*, *Influenza B virus*, *Influenza D virus* and *Influenza C virus*. In some embodiments, a subject with an *Influenza A*, *Influenza B*, *Influenza D* and *Influenza C* infection may have influenza.

In some embodiments, the present invention provides a method of treating or preventing SARS-CoV-2 infection in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt thereof, such that the SARS-CoV-2 infection in the subject is treated or prevented.

In some aspects, administering of omadacycline, or a pharmaceutically acceptable salt thereof, may lead to a reduction in viral load in the subject. For example, administering omadacycline, or a pharmaceutically acceptable salt thereof, to a subject infected with SARS-CoV-2 may lead to a reduction in the load of SARS-CoV-2 virus in the subject. In another example, administering omadacycline, or a pharmaceutically acceptable salt thereof, to a subject infected with SARS-CoV may lead to a reduction in the load of SARS-CoV virus in the subject. In yet another example, administering omadacycline, or a pharmaceutically acceptable salt thereof, to a subject infected with MERS-CoV may lead to a reduction in the load of MERS-CoV virus in the subject. In yet another example, administering omadacycline, or a pharmaceutically acceptable salt thereof, to a subject infected with *Influenza A virus*, *Influenza B virus*, *Influenza D virus* or *Influenza C virus* may lead, respectively, to a reduction in the load of *Influenza A virus*, *Influenza B virus*, *Influenza D virus* or *Influenza C virus* in the subject. The viral load, *e.g.*, load of SARS-CoV-2 virus, SARS-CoV-1 (also known as SARS-CoV) virus, MERS-CoV virus, *Influenza A* virus, *Influenza B* virus, *Influenza D* virus or *Influenza C* virus, may be measured by any method known in the art for measuring viral load.

In some embodiments, the methods of treating or preventing a viral infection, *e.g.*, infection with SARS-CoV-2, also comprise administering omadacycline, or a pharmaceutically acceptable salt thereof, to a subject at risk of SARS-CoV-2 infection. For example, methods of treating or preventing a viral infection comprise, *e.g.*, selecting a subject at risk of the infection with SARS-CoV-2; and administering omadacycline, or a pharmaceutically acceptable salt thereof, to the subject.

Methods of Treating or Preventing Viral Diseases

The present invention provides methods of treating or preventing viral diseases in a subject in need thereof. The methods of treating or preventing viral diseases comprise administering to a subject in need thereof an effective amount of omadacycline, or a pharmaceutically acceptable salt thereof.

In some examples, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to the subject for treating or preventing a viral disease in the form a salt. The salt may be a pharmaceutically acceptable salt, such as a tosylate salt. For example, tosylate

salts of omadacycline may be amorphous or crystalline, *e.g.*, Form 1 polymorph, Form 2 polymorph or Form 3 polymorph of the crystalline tosylate salt of omadacycline as described in U.S. Patent No. 8,383,610, the entire contents of which are incorporated herein by reference. In some examples, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to the subject in the form of a freebase, *e.g.*, crystalline freebase.

The term "viral disease", as used herein, refers to a disease that may be associated with, *e.g.*, caused by, a viral infection. A viral infection may be an infection with any one or more of the viruses belonging to families, genii or species as listed above. For example, a viral disease may be associated with, *e.g.*, caused by an infection with a virus belonging to a family selected from the group consisting of *Abyssoviridae, Ackermannviridae, Adenoviridae, Alloherpesviridae, Alphaflexiviridae, Alphasatellitidae, Alphatetraviridae, Alvernaviridae, Amalgaviridae, Amnoonviridae, Ampullaviridae, Anelloviridae, Arenaviridae, Arteriviridae, Artoviridae, Ascoviridae, Asfaviridae, Aspiviridae, Astroviridae, Autographiviridae, Avsunviroidae, Baccilladnaviridae, Baculoviridae, Barnaviridae, Belpaoviridae, Benyviridae, Betaflexiviridae, Bicaudaviridae, Bidnaviridae, Birnaviridae, Bornaviridae, Botourmiarividae, Bromoviridae, Caliciviridae, Carmotetraviridae, Caulimoviridae, Chaseviridae, Chrysoviridae, Chuviridae, Circoviridae, Clavaviridae, Closteroviridae, Coronaviridae, Corticoviridae, Cremegaviridae, Cruliviridae, Cystoviridae, Deltaflexiviridae, Demerecviridae, Cicistroviridae, Drexlerviridae, Endomaviridae, Euroniviridae, Filoviridae, Fimoviridae, Finnalakeviridae, Flaviviridae, Fuselloviridae, Gammaflexiviridae, Geminiviridae, Genomoviridae, Globuloviridae, Gresnaviridae, Guttaviridae, Halspiviridae, Hantaviridae, Hepadnaviridae, Hepeviridae, Herelleviridae, Herpesviridae, Hypoviridae, Hytrosaviridae, Iflaviridae, Inoviridae, Iridoviridae, Kitaviridae, Lavidaviridae, Leishbuviridae, Leviviridae, Lipothrixviridae, Lispiviridae, Luteoviridae, Malacoherperviridae, Marnaviridae, Marseilleviridae, Matonaviridae, Mayoviridae, Medionviridae, Megabirnaviridae, Mesoniviridae, Metaviridae, Microviridae, Mimiviridae, Mitoviridae, Mononiviridae, Mymonaviridae, Myoviridae, Mypoviridae, Nairoviridae, Nanghoshaviridae, Nanhypoviridae, Nanoviridae, Narnaviridae, Nimaviridae, Nodaviridae, Nudiviridae, Nyamiviridae, Olifoviridae, Orthomyxoviridae, Ovaliviridae, Papillomaviridae, Paramyxoviridae, Partitiviridae, Parvoviridae, Peribunyaviridae, Permutotetraviridae, Phasmaviridae, Phenuiviridae, Phycodnaviridae, Picobimaviridae, Picornaviridae, Plasmaviridae, Plectroviridae, Pleolipoviridae, Pneumoviridae, Podoviridae, Polycipiviridae, Polydnaviridae, Polymycoviridae, Polymaviridae, Portogloboviridae, Pospiviroidae,*

Potyviridae, Poxviridae, Pseudoviridae, Qinviridae, Quadrivirdae, Redondoviridae, Reoviridae, Retroviridae, Rhabdoviridae, Roniviridae, Rudiviridae, Sarthroviridae, Secoviridae, Sinhaliviridae, Siphviridae, Smacoviridae, Solemoviridae, Solinviviridae, Sphaerolipoviridae, Spiraviridae, Sunviridae, Tectiviridae, Thaspiviridae, Tobaniviridae, Togaviridae, Tolecusatellitidae, Tombusviridae, Tospoviridae, Totiviridae, Tristromaviridae, Turniviridae, Tymoviridae, Virgaviridae, Wupedeviridae, Xinmoviridae and *Yueviridae.*

In some examples, the viral disease may be caused by an infection with a virus belonging to a family *Coronaviridae*. For example, the viral disease may be caused by an infection with a virus belonging to a genus selected from the group consisting of *Alphaletovirus, Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus*. In one specific example, the viral disease may be caused by an infection with a virus belonging to a genus *Betacoronavirus*, *e.g.*, to a species selected from the group consisting of *Betacoronavirus 1, China Rattus coronavirus HKU24, Human coronavirus HKU1, Murine coronavirus, Myodes coronavirus 2JL14, Bat Hp-betacoronavirus Zhejiang2013, Hedgehog coronavirus 1, Middle East respiratory syndrome-related coronavirus, Pipistrellus bat coronavirus HKU5, Tylonycteris bat coronavirus HKU4, Eidolon bat coronavirus C704, Rousettus bat coronavirus GCCDC1, Rousettus bat coronavirus HKU9 and Severe acute respiratory syndrome-related coronavirus.*

In some embodiments, the viral disease may be caused by an infection with a virus belonging to a species *Severe acute respiratory syndrome-related coronavirus*. In further embodiment, the viral disease may be caused by an infection with a virus selected from the group consisting of SARSr-CoV BtKY72, SARS-CoV-2, SARSr-CoV RaTG13, SARS-CoV PC4-227 and SARS-CoV.

In one specific example, the viral disease may be caused by an infection with SARS-CoV-2, and may be COVID-19.

In another example, the viral disease may be caused by an infection with SARS-CoV, and may be SARS.

In some embodiments, the viral disease may be caused by an infection with a virus belonging to a species *Middle East respiratory syndrome-related coronavirus*, *e.g.*, MERS-CoV, and may be MERS.

In some embodiments, the viral disease may be caused by an infection with a virus belonging to family *Orthomyxoviridae*. For example, the viral disease may be caused by an infection with a virus belonging to a genus selected from the group consisting of *Alphainfluenzavirus*, *Betainfluenzavirus*, *Deltainfluenzavirus* and *Gammainfluenzavirus*. In some examples, the viral disease may be caused by an infection with a virus belonging to a species selected from the group consisting of *Influenza A virus*, *Influenza B virus*, *Influenza D virus* and *Influenza C virus*, and may be influenza.

In some aspects, administering of omadacycline, or a pharmaceutically acceptable salt thereof, to a subject for treating or preventing a viral disease may lead to a reduction in viral load in the subject. For example, administering omadacycline, or a pharmaceutically acceptable salt thereof, to a subject with COVID-19 may lead to a reduction in the load of SARS-CoV-2 virus in the subject. In another example, administering omadacycline, or a pharmaceutically acceptable salt thereof, to a subject afflicted with SARS may lead to a reduction in the load of SARS-CoV virus in the subject. In yet another example, administering omadacycline, or a pharmaceutically acceptable salt thereof, to a subject afflicted with MERS may lead to a reduction in the load of MERS-CoV virus in the subject. In yet another example, administering omadacycline, or a pharmaceutically acceptable salt thereof, to a subject afflicted with influenza may lead, respectively, to a reduction in the load of *Influenza A virus*, *Influenza B virus*, *Influenza D virus* or *Influenza C virus* in the subject. The viral load, *e.g.*, load of SARS-CoV-2 virus, SARS-CoV virus, MERS-CoV virus, *Influenza A* virus, *Influenza B* virus, *Influenza D* virus or *Influenza C* virus, may be measured by any method known in the art for measuring viral load.

In some embodiments, the present invention provides methods for treating or preventing a viral disease selected from the group consisting of gastroenteritis, keratoconjunctivitis, pharyngitis, croup, pneumonia, cystitis, hand, food and mouth disease, pleurodynia, meningitis, pericarditis, myocarditis, infectious mononucleosis, hepatitis, hepatic cirrhosis, cytomegalic inclusion disease, AIDS, Dengue fever, influenza, measles, postinfections encephalomyelitis, mumps, common cold, rabies, viral encephalitis, disease caused by West Nile virus, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19. In one specific embodiment, the viral disease may be COVID-19.

In some embodiments, the present invention provides a method of treating or preventing COVID-19 in a subject in need thereof that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt thereof, such that the COVID-19 in the subject is treated or prevented.

In some embodiments, administering of omadacycline, or a pharmaceutically acceptable salt thereof, for treating or preventing an infection with SARS-CoV-2 or for treating or preventing COVID-19 in a subject alleviates at least one symptom associated with COVID-19. Exemplary symptoms associated with COVID-19 may include one or more of the following: fever, body ache, muscle and joint pain, cough (*e.g.*, dry cough), fatigue, chills, headache, sore throat, shortness of breath, sputum production, hemoptysis, sneezing, runny nose, chest tightness, palpitation, a neurological symptom and a gastrointestinal (GI) symptom. A neurological symptom may include one or more of the following: decreased sense of smell, inability to taste, muscle weakness, tingling or numbness in the hands and feet, dizziness, confusion, delirium, seizure and stroke. A GI symptom may include one of more of the following: loss of appetite, nausea, vomiting, diarrhea and abdominal pain or discomfort.

In some embodiments, administering of omadacycline, or a pharmaceutically acceptable salt thereof, for treating or preventing an infection with SARS-CoV-2, or for treating or preventing COVID-19 in a subject, prevents at least one complication associated with COVID-19 in the subject. Exemplary complications associated with COVID-19 may include at least one of the following: acute respiratory failure, pneumonia, acute respiratory distress syndrome (ARDS), sepsis associated syndrome, acute liver injury, acute cardiac injury, acute kidney injury, disseminated intravascular coagulation (DIC), blood clots and rhabdomyolysis.

In one example, the administering of omadacycline, or a pharmaceutically acceptable salt thereof, for treating or preventing an infection with SARS-CoV-2 or for treating or preventing COVID-19 in a subject prevents secondary bacterial pneumonia.

In another example, the administering of omadacycline, or a pharmaceutically acceptable salt thereof, for treating or preventing an infection with SARS-CoV-2, or for treating or preventing COVID-19, in a subject prevents a sepsis associated state. The term "sepsis associated state", as used herein, refers to any one condition in the sepsis continuum,

as defined by the American College of Chest Physicians and the Society of Critical Care Medicine (Bone *et al.* (1992) *Chest*, **101**(6):1644-55, the entire contents of which are hereby incorporated herein by reference). In some embodiments, the term "sepsis associated state" can refer to any one of Systemic Inflammatory Response Syndrome (SIRS), Sepsis, Severe Sepsis and Septic Shock.

Systemic Inflammatory Response Syndrome (SIRS) is defined by the presence of two or more of the following: a) hypothermia or fever; b) increased heart rate (> 90 beats per minute); c) tachypnea or hypocapnia due to hyperventilation; and d) leukopenia, leukocytosis, or bandemia.

Sepsis is defined as SIRS in response to a confirmed infectious process, *e.g.*, an infection with SARS-CoV-2.

Severe Sepsis is defined as sepsis with organ dysfunction, hypoperfusion, or hypotension.

Septic Shock is defined as sepsis with refractory arterial hypotension or hypoperfusion abnormalities in spite of adequate fluid resuscitation. Signs of systemic hypoperfusion may be either end-organ dysfunction or increased serum lactate (> 4 mmol/L). Other signs include oliguria and altered mental status. Patients are defined as having septic shock if they have sepsis plus hypotension after aggressive fluid resuscitation (typically upwards of 6 liters or 40 ml/kg of crystalloid solution).

In some examples, the administering of omadacycline, or a pharmaceutically acceptable salt thereof, for treating or preventing an infection with SARS-CoV-2 or for treating or preventing COVID-19 in a subject prevents SIRS. In further examples, the SIRS may comprise cytokine storm syndrome (CSS).

In some examples, the administering of omadacycline, or a pharmaceutically acceptable salt thereof, for treating or preventing an infection with SARS-CoV-2 or for treating or preventing COVID-19 in a subject prevents septic shock.

In some examples, the administering, *e.g.*, orally administering, of omadacycline, or a pharmaceutically acceptable salt thereof, for treating or preventing an infection with SARS-

CoV-2, or for treating or preventing COVID-19 in a subject, prevents utilization of health care professional (HCP) resources by the subject, *e.g.*, prevents hospitalization of the subject.

In some examples, the administering, *e.g.*, orally administering, of omadacycline, or a pharmaceutically acceptable salt thereof, for treating or preventing an infection with SARS-CoV-2 or for treating or preventing COVID-19 in a subject prevents death of the subject.

Methods of Preventing Secondary Bacterial Pneumonia

The present invention provides methods of preventing secondary bacterial pneumonia or methods of reducing the likelihood of onset, or severity of secondary bacterial pneumonia in a subject in need thereof. The methods of preventing secondary bacterial pneumonia or reducing the likelihood of onset, or severity of secondary bacterial pneumonia comprise administering to a subject in need thereof an effective amount of omadacycline, or a pharmaceutically acceptable salt thereof.

In some examples, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to the subject for preventing secondary bacterial pneumonia or reducing the likelihood of onset, or severity of secondary bacterial pneumonia in the form a salt. The salt may be a pharmaceutically acceptable salt, such as a tosylate salt. For example, tosylate salts of omadacycline may be amorphous or crystalline, *e.g.*, Form 1 polymorph, Form 2 polymorph or Form 3 polymorph of the crystalline tosylate salt of omadacycline as described in U.S. Patent No. 8,383,610, the entire contents of which are incorporated herein by reference. In some examples, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to the subject in the form of a freebase, *e.g.*, crystalline freebase.

The term "secondary bacterial pneumonia", as used herein, refers to pneumonia that is associated with, *e.g.*, is caused by, a bacterial infection and that occurs after infection with another pathogen, *e.g.*, after a viral infection. For example, secondary bacterial pneumonia may occur after an infection with influenza virus, *e.g.*, as described in Morris *et al.*, *Frontiers in Microbiology* 2017, 8:1041, the entire contents of which are hereby incorporated herein by reference. In another example, a secondary bacterial pneumonia may occur after SARS-CoV-2 infection. Secondary bacterial pneumonia is a major cause of morbidity and mortality

associated with both seasonal viral illnesses, *e.g.*, influenza, and pandemic respiratory illnesses, *e.g.*, COVID-19.

Specifically, available data from hospitalized patients with COVID-19 demonstrates that secondary infection occurs in about 10-15% of cases (Huang *et al.*, *Lancet* 2020, 395:497-506; Zhou *et al.*, *Lancet* 2020, 395:1054-1062). Identifying bacterial coinfection in patients with COVID-19 may be challenging, as the symptoms may be indistinguishable from those of the underlying viral infection. The time to onset of severe disease in COVID-19 and onset of secondary bacterial pneumonia with other respiratory viral infections is similar (Wang et al., *JAMA* 2020, 323(11):1061-1069; Chertow *et al.*, *JAMA* 2013, 309(3):275-82). Therefore, secondary bacterial pneumonia may contribute to disease progression in COVID-19 patients who develop severe symptoms. Secondary bacterial pneumonia may be identified in a subject by detecting bacteria in the sputum of a subject with a viral infection, *e.g.*, SARS-CoV-2 infection.

The present inventors discovered that secondary bacterial pneumonia in a subject with a viral infection may be prevented, or the likelihood of onset, or the severity of secondary bacterial pneumonia in the subject with a viral infection may be reduced by administering to the subject omadacycline, or a pharmaceutically acceptable salt thereof. In some examples, the viral infection in a subject who is administered omadacycline, or a pharmaceutically acceptable salt thereof, for preventing secondary bacterial pneumonia or for reducing the severity of secondary bacterial pneumonia, may be caused by a virus belonging to a family *Coronaviridae*. For example, the virus may belong to a genus selected from the group consisting of *Alphaletovirus, Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus*. In one specific example, the virus may belong to a genus *Betacoronavirus*, *e.g.*, to a species selected from the group consisting of *Betacoronavirus 1, China Rattus coronavirus HKU24, Human coronavirus HKU1, Murine coronavirus, Myodes coronavirus 2JL14, Bat Hp-betacoronavirus Zhejiang2013, Hedgehog coronavirus 1, Middle East respiratory syndrome-related coronavirus, Pipistrellus bat coronavirus HKU5, Tylonycteris bat coronavirus HKU4, Eidolon bat coronavirus C704, Rousettus bat coronavirus GCCDC1, Rousettus bat coronavirus HKU9 and Severe acute respiratory syndrome-related coronavirus*.

In some embodiments, the virus may belong to a species *Severe acute respiratory syndrome-related coronavirus*. In further embodiment, the virus may be selected from the

group consisting of SARSr-CoV BtKY72, SARS-CoV-2, SARSr-CoV RaTG13, SARS-CoV PC4-227 and SARS-CoV.

In one specific example, the viral infection in a subject who is administered omadacycline, or a pharmaceutically acceptable salt thereof, for preventing secondary bacterial pneumonia or for reducing the likelihood of onset, or the severity of secondary bacterial pneumonia may be caused by SARS-CoV-2. In some embodiments, a subject with a SARS-CoV-2 infection may have COVID-19.

In another example, the viral infection in a subject who is administered omadacycline, or a pharmaceutically acceptable salt thereof, for preventing secondary bacterial pneumonia or for reducing the likelihood of onset, or the severity of secondary bacterial pneumonia may be caused by SARS-CoV. In some embodiments, a subject with a SARS-CoV infection may have Severe Acute Respiratory Syndrome (SARS).

In some embodiments, the viral infection in a subject who is administered omadacycline, or a pharmaceutically acceptable salt thereof, for preventing secondary bacterial pneumonia or for reducing the likelihood of onset, or the severity of secondary bacterial pneumonia may be caused by *Middle East respiratory syndrome-related coronavirus*, *e.g.*, MERS-CoV. In some embodiments, a subject with a MERS-CoV infection may have Middle East Respiratory Syndrome (MERS).

In some embodiments, the viral infection in a subject who is administered omadacycline, or a pharmaceutically acceptable salt thereof, for preventing secondary bacterial pneumonia or for reducing the likelihood of onset, or the severity of secondary bacterial pneumonia may be caused by a virus belonging to family *Orthomyxoviridae*. For example, the virus may belong to a genus selected from the group consisting of *Alphainfluenzavirus*, *Betainfluenzavirus*, *Deltainfluenzavirus* and *Gammainfluenzavirus*. In some examples, the virus may belong to a species selected from the group consisting of *Influenza A virus*, *Influenza B virus*, *Influenza D virus* and *Influenza C virus*. In some embodiments, a subject with an *Influenza A*, *Influenza B*, *Influenza D* and *Influenza C* infection may have influenza.

In some embodiments, the present invention provides a method of preventing, or reducing the likelihood of onset, or the severity of secondary bacterial pneumonia in a subject with SARS-CoV-2 infection, that comprises administering to the subject an effective amount

of omadacycline, or a pharmaceutically acceptable salt thereof, such that the secondary bacterial pneumonia in the subject is prevented, or the severity of secondary bacterial pneumonia in the subject is reduced.

The present invention also provides methods for preventing, or reducing the likelihood of onset, or severity of secondary bacterial pneumonia in a subject with a viral disease. In some examples, the viral disease may be caused by an infection with a virus belonging to a family *Coronaviridae*. For example, the viral disease may be caused by an infection with a virus belonging to a genus selected from the group consisting of *Alphaletovirus, Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus*. In one specific example, the viral disease may be caused by an infection with a virus belonging to a genus *Betacoronavirus*, *e.g.*, to a species selected from the group consisting of *Betacoronavirus 1, China Rattus coronavirus HKU24, Human coronavirus HKU1, Murine coronavirus, Myodes coronavirus 2JL14, Bat Hp-betacoronavirus Zhejiang2013, Hedgehog coronavirus 1, Middle East respiratory syndrome-related coronavirus, Pipistrellus bat coronavirus HKU5, Tylonycteris bat coronavirus HKU4, Eidolon bat coronavirus C704, Rousettus bat coronavirus GCCDC1, Rousettus bat coronavirus HKU9 and Severe acute respiratory syndrome-related coronavirus.*

In some embodiments, the viral disease may be caused by an infection with a virus belonging to a species *Severe acute respiratory syndrome-related coronavirus*. In further embodiment, the viral disease may be caused by an infection with a virus selected from the group consisting of SARSr-CoV BtKY72, SARS-CoV-2, SARSr-CoV RaTG13, SARS-CoV PC4-227 and SARS-CoV.

In one specific example, the viral disease in a subject who is administered omadacycline, or a pharmaceutically acceptable salt thereof, for preventing secondary bacterial pneumonia or for reducing the likelihood of onset, or the severity of secondary bacterial pneumonia may be caused by an infection with SARS-CoV-2, *e.g.*, may be COVID-19.

In another example, the viral disease in a subject who is administered omadacycline, or a pharmaceutically acceptable salt thereof, for preventing secondary bacterial pneumonia or for reducing the likelihood of onset, or the severity of secondary bacterial pneumonia may be caused by an infection with SARS-CoV-2, *e.g.*, may be SARS.

In some embodiments, the viral disease in a subject who is administered omadacycline, or a pharmaceutically acceptable salt thereof, for preventing secondary bacterial pneumonia or for reducing the likelihood of onset, or the severity of secondary bacterial pneumonia may be caused by an infection with a virus belonging to a species *Middle East respiratory syndrome-related coronavirus*, *e.g.*, MERS-CoV, and may be MERS.

In some embodiments, the viral disease in a subject who is administered omadacycline, or a pharmaceutically acceptable salt thereof, for preventing secondary bacterial pneumonia or for reducing the likelihood of onset, or the severity of secondary bacterial pneumonia may be caused by an infection with a virus belonging to family *Orthomyxoviridae*. For example, the viral disease may be caused by an infection with a virus belonging to a genus selected from the group consisting of *Alphainfluenzavirus*, *Betainfluenzavirus*, *Deltainfluenzavirus* and *Gammainfluenzavirus*. In some examples, the viral disease may be caused by an infection with a virus belonging to a species selected from the group consisting of *Influenza A virus*, *Influenza B virus*, *Influenza D virus* and *Influenza C virus*, and may be influenza.

In some embodiments, administering of omadacycline, or a pharmaceutically acceptable salt thereof, for preventing secondary bacterial pneumonia, or for reducing the likelihood of onset, or the severity of secondary bacterial pneumonia, in a subject with a SARS-CoV-2 infection or a subject afflicted with COVID-19, prevents, or reduces the severity of, at least one complication associated with COVID-19 in the subject. Exemplary complications associated with COVID-19 may include at least one of the following: acute respiratory failure, pneumonia, acute respiratory distress syndrome (ARDS), sepsis associated syndrome, acute liver injury, acute cardiac injury, acute kidney injury, disseminated intravascular coagulation (DIC), blood clots and rhabdomyolysis. In one example, the complication associated with COVID-19 may be a sepsis associated state, *e.g.*, SIRS or septic shock. In a further embodiment, the SIRS may comprise cytokine storm syndrome (CSS).

In some examples, the administering, *e.g.*, orally administering, omadacycline, or a pharmaceutically acceptable salt thereof, for preventing secondary bacterial pneumonia, or for reducing the likelihood of onset, or the severity of secondary bacterial pneumonia, in a subject with a SARS-CoV-2 infection, or a subject afflicted with COVID-19, prevents utilization of HCP resources by the subject, *e.g.*, prevents hospitalization of the subject.

In some examples, the administering, *e.g.*, orally administering, omadacycline, or a pharmaceutically acceptable salt thereof, for preventing secondary bacterial pneumonia, or for reducing the likelihood of onset, or the severity of secondary bacterial pneumonia, in a subject with a SARS-CoV-2 infection, or a subject afflicted with COVID-19, prevents death of the subject.

In some embodiments, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject with a viral infection, *e.g.*, SARS-CoV-2 infection, or a subject afflicted with a viral disease, *e.g.*, COVID-19, prophylactically, *i.e.*, prior to the subject developing secondary bacterial pneumonia in order to prevent, or reduce the likelihood of onset of secondary bacterial pneumonia, or severity of secondary bacterial pneumonia. For example, omadacycline, or a pharmaceutically acceptable salt thereof, may be prophylactically administered to a subject with a viral infection, *e.g.*, SARS-CoV-2 infection, or a subject afflicted with a viral disease, *e.g.*, COVID-19, prior to the subject being identified as having secondary bacterial pneumonia, *e.g.*, prior to bacteria being detected in the sputum of the subject. In another example, omadacycline, or a pharmaceutically acceptable salt thereof, may be prophylactically administered to a subject with a a viral infection, *e.g.*, SARS-CoV-2 infection, who is asymptomatic; *i.e.*, after the subject has been identified as having a viral infection, *e.g.*, SARS-CoV-2 infection, but prior to the subject developing any symptoms associated with the viral infection, *e.g.*, SARS-CoV-2 infection, or symptoms associated with a viral disease, *e.g.*, COVID-19. In further examples, the subject with a viral infection, *e.g.*, SARS-CoV-2 infection, or the subject with a viral disease, *e.g.*, COVID-19, has no known bacterial infection.

Methods of Modulating an Immune Response

In some embodiments, the present invention also provides methods of modulating an immune response in a subject in need thereof. The methods comprise administering to the subject omadacycline, or a pharmaceutically acceptable salt thereof, such that the immune response in the subject is modulated. The present invention is based on a surprising discovery that omadacycline is capable of modulating an immune response in a subject.

The term "modulating an immune response", as used herein, refers to causing a modification of or an adjustment, *e.g.*, a decrease, in the immune response in a subject. "Modulating an immune response" encompasses, in some embodiments, modulating inflammation, *e.g.*, decreasing or attenuating inflammation, in the subject.

In some aspects, "modulating an immune response" also encompasses modulating one or more inflammatory biomarkers in a subject. For example, "modulating an immune response" may causing increased or decreased amount of one or more inflammatory biomarkers in a subject, *e.g.*, a subject with a viral infection or a subject afflicted with a viral disease. The term "modulating an immune response" also encompasses causing increased or decreased activity of one or more inflammatory biomarkers in a subject, *e.g.*, a subject with a viral infection or a subject afflicted with a viral disease.

Exemplary inflammatory biomarkers that may be modulated by administering omadacycline, or a pharmaceutically acceptable salt thereof, in the context of the present invention include, *e.g.*, C-reactive protein (CRP), leukocyte count, neutrophil count, monocyte count, eosinophil count, basophil count, erythrocyte sedimentation count, serum ferritin, white blood cell count (WBC count), serum amyloid A (SAA), procalcitonin (PCT), tumor necrosis factor α (TNF-α), interferon-γ (INF-γ), interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-12 (IL-12), interleukin-15 (IL-15), interleukin-18 (IL-18), interleukin-1β (IL-1β), colony-stimulating factor 2 (CSF 2), colony-stimulating factor 3 (CSF 3), nitric oxide synthase (iNOS), monokine induced by gamma (MIG), CXCL1 (KC Protein), interferon gamma-induced protein 10 (IP-10), a methyl-accepting chemotaxis protein (MCP), an Intercellular Adhesion Molecule (ICAM), a metalloproteinase, a macrophage inflammatory protein, a complement protein (*e.g.*, complement factor 3 or complement factor 4) and a prostaglandin. In some embodiment, an inflammatory biomarker may be any biomarker as described, *e.g.*, in Qin *et al.*, *Clin Infect Dis*. 2020, ciaa248, the entire contents of which are hereby incorporated herein by reference. Methods that may be used to measure the amount or activity of one or more inflammatory biomarkers may be determined by one of ordinary skill in the art.

In some embodiments, the subject being administered omadacycline, or a pharmaceutically acceptable salt thereof, for modulating an immune response in accordance with the methods of the present invention may have a viral infection. The viral infection may be any viral infection as described above and may be caused by a virus belonging to a family

selected from the group consisting of *Abyssoviridae, Ackermannviridae, Adenoviridae, Alloherpesviridae, Alphaflexiviridae, Alphasatellitidae, Alphatetraviridae, Alvernaviridae, Amalgaviridae, Amnoonviridae, Ampullaviridae, Anelloviridae, Arenaviridae, Arteriviridae, Artoviridae, Ascoviridae, Asfaviridae, Aspiviridae, Astroviridae, Autographiviridae, Avsunviroidae, Baccilladnaviridae, Baculoviridae, Barnaviridae, Belpaoviridae, Benyviridae, Betaflexiviridae, Bicaudaviridae, Bidnaviridae, Birnaviridae, Bornaviridae, Botourmiarividae, Bromoviridae, Caliciviridae, Carmotetraviridae, Caulimoviridae, Chaseviridae, Chrysoviridae, Chuviridae, Circoviridae, Clavaviridae, Closteroviridae, Coronaviridae, Corticoviridae, Cremegaviridae, Cruliviridae, Cystoviridae, Deltaflexiviridae, Demerecviridae, Cicistroviridae, Drexlerviridae, Endomaviridae, Euroniviridae, Filoviridae, Fimoviridae, Finnalakeviridae, Flaviviridae, Fuselloviridae, Gammaflexiviridae, Geminiviridae, Genomoviridae, Globuloviridae, Gresnaviridae, Guttaviridae, Halspiviridae, Hantaviridae, Hepadnaviridae, Hepeviridae, Herelleviridae, Herpesviridae, Hypoviridae, Hytrosaviridae, Iflaviridae, Inoviridae, Iridoviridae, Kitaviridae, Lavidaviridae, Leishbuviridae, Leviviridae, Lipothrixviridae, Lispiviridae, Luteoviridae, Malacoherperviridae, Marnaviridae, Marseilleviridae, Matonaviridae, Mayoviridae, Medionviridae, Megabirnaviridae, Mesoniviridae, Metaviridae, Microviridae, Mimiviridae, Mitoviridae, Mononiviridae, Mymonaviridae, Myoviridae, Mypoviridae, Nairoviridae, Nanghoshaviridae, Nanhypoviridae, Nanoviridae, Narnaviridae, Nimaviridae, Nodaviridae, Nudiviridae, Nyamiviridae, Olifoviridae, Orthomyxoviridae, Ovaliviridae, Papillomaviridae, Paramyxoviridae, Partitiviridae, Parvoviridae, Peribunyaviridae, Permutotetraviridae, Phasmaviridae, Phenuiviridae, Phycodnaviridae, Picobimaviridae, Picornaviridae, Plasmaviridae, Plectroviridae, Pleolipoviridae, Pneumoviridae, Podoviridae, Polycipiviridae, Polydnaviridae, Polymycoviridae, Polymaviridae, Portogloboviridae, Pospiviroidae, Potyviridae, Poxviridae, Pseudoviridae, Qinviridae, Quadrivirdae, Redondoviridae, Reoviridae, Retroviridae, Rhabdoviridae, Roniviridae, Rudiviridae, Sarthroviridae, Secoviridae, Sinhaliviridae, Siphviridae, Smacoviridae, Solemoviridae, Solinviviridae, Sphaerolipoviridae, Spiraviridae, Sunviridae, Tectiviridae, Thaspiviridae, Tobaniviridae, Togaviridae, Tolecusatellitidae, Tombusviridae, Tospoviridae, Totiviridae, Tristromaviridae, Turniviridae, Tymoviridae, Virgaviridae, Wupedeviridae, Xinmoviridae* and *Yueviridae*.

In some examples, the viral infection may be caused by a virus belonging to a family *Coronaviridae*. For example, the virus may belong to a genus selected from the group

consisting of *Alphaletovirus, Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus*. In one specific example, the virus may belong to a genus *Betacoronavirus*, *e.g.*, to a species selected from the group consisting of *Betacoronavirus 1, China Rattus coronavirus HKU24, Human coronavirus HKU1, Murine coronavirus, Myodes coronavirus 2JL14, Bat Hp-betacoronavirus Zhejiang2013, Hedgehog coronavirus 1, Middle East respiratory syndrome-related coronavirus, Pipistrellus bat coronavirus HKU5, Tylonycteris bat coronavirus HKU4, Eidolon bat coronavirus C704, Rousettus bat coronavirus GCCDC1, Rousettus bat coronavirus HKU9 and Severe acute respiratory syndrome-related coronavirus*.

In some embodiments, the viral infection may be caused by a virus belonging to a species *Severe acute respiratory syndrome-related coronavirus*. In further embodiment, the virus may be selected from the group consisting of SARSr-CoV BtKY72, SARS-CoV-2, SARSr-CoV RaTG13, SARS-CoV PC4-227 and SARS-CoV.

In one specific example, the viral infection in a subject being administered omadacycline, or a pharmaceutically acceptable salt thereof, for modulating an immune response may be caused by SARS-CoV-2. In some embodiments, the subject may have COVID-19.

In another example, the viral infection in a subject being administered omadacycline, or a pharmaceutically acceptable salt thereof, for modulating an immune response may be caused by SARS-CoV. In some embodiments, the subject may have SARS.

In some embodiments, the viral infection in a subject being administered omadacycline, or a pharmaceutically acceptable salt thereof, for modulating an immune response may be caused by a virus belonging to a species *Middle East respiratory syndrome-related coronavirus*, *e.g.*, MERS-CoV. In some embodiments, the subject may have MERS.

In some embodiments, the viral infection in a subject being administered omadacycline, or a pharmaceutically acceptable salt thereof, for modulating an immune response may be caused by a virus belonging to family *Orthomyxoviridae*. For example, the virus may belong to a genus selected from the group consisting of *Alphainfluenzavirus*, *Betainfluenzavirus*, *Deltainfluenzavirus* and *Gammainfluenzavirus*. In some examples, the virus may belong to a species selected from the group consisting of *Influenza A virus*,

Influenza B virus, *Influenza D virus* and *Influenza C virus*. In some embodiments, the subject may have influenza.

In some embodiments, the present invention provides a method of modulating an immune response in a subject with a SARS-CoV-2 infection that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt thereof, such that the immune response in the subject is modulated.

In some embodiments, the subject being administered omadacycline, or a pharmaceutically acceptable salt thereof, for modulating an immune response may be afflicted with a viral disease. The viral disease may be associated with, *e.g.*, caused by, a viral infection, such as an infection with any one or more of the viruses belonging to families, genii or species as listed above. For example, a viral disease may be associated with, *e.g.*, caused by, an infection with a virus belonging to a family selected from the group consisting of *Abyssoviridae, Ackermannviridae, Adenoviridae, Alloherpesviridae, Alphaflexiviridae, Alphasatellitidae, Alphatetraviridae, Alvernaviridae, Amalgaviridae, Amnoonviridae, Ampullaviridae, Anelloviridae, Arenaviridae, Arteriviridae, Artoviridae, Ascoviridae, Asfaviridae, Aspiviridae, Astroviridae, Autographiviridae, Avsunviroidae, Baccilladnaviridae, Baculoviridae, Barnaviridae, Belpaoviridae, Benyviridae, Betaflexiviridae, Bicaudaviridae, Bidnaviridae, Birnaviridae, Bornaviridae, Botourmiarividae, Bromoviridae, Caliciviridae, Carmotetraviridae, Caulimoviridae, Chaseviridae, Chrysoviridae, Chuviridae, Circoviridae, Clavaviridae, Closteroviridae, Coronaviridae, Corticoviridae, Cremegaviridae, Cruliviridae, Cystoviridae, Deltaflexiviridae, Demerecviridae, Cicistroviridae, Drexlerviridae, Endomaviridae, Euroniviridae, Filoviridae, Fimoviridae, Finnalakeviridae, Flaviviridae, Fuselloviridae, Gammaflexiviridae, Geminiviridae, Genomoviridae, Globuloviridae, Gresnaviridae, Guttaviridae, Halspiviridae, Hantaviridae, Hepadnaviridae, Hepeviridae, Herelleviridae, Herpesviridae, Hypoviridae, Hytrosaviridae, Iflaviridae, Inoviridae, Iridoviridae, Kitaviridae, Lavidaviridae, Leishbuviridae, Leviviridae, Lipothrixviridae, Lispiviridae, Luteoviridae, Malacoherperviridae, Marnaviridae, Marseilleviridae, Matonaviridae, Mayoviridae, Medionviridae, Megabirnaviridae, Mesoniviridae, Metaviridae, Microviridae, Mimiviridae, Mitoviridae, Mononiviridae, Mymonaviridae, Myoviridae, Mypoviridae, Nairoviridae, Nanghoshaviridae, Nanhypoviridae, Nanoviridae, Narnaviridae, Nimaviridae, Nodaviridae, Nudiviridae, Nyamiviridae, Olifoviridae, Orthomyxoviridae, Ovaliviridae, Papillomaviridae, Paramyxoviridae, Partitiviridae, Parvoviridae,*

Peribunyaviridae, Permutotetraviridae, Phasmaviridae, Phenuiviridae, Phycodnaviridae, Picobimaviridae, Picornaviridae, Plasmaviridae, Plectroviridae, Pleolipoviridae, Pneumoviridae, Podoviridae, Polycipiviridae, Polydnaviridae, Polymycoviridae, Polymaviridae, Portogloboviridae, Pospiviroidae, Potyviridae, Poxviridae, Pseudoviridae, Qinviridae, Quadrivirdae, Redondoviridae, Reoviridae, Retroviridae, Rhabdoviridae, Roniviridae, Rudiviridae, Sarthroviridae, Secoviridae, Sinhaliviridae, Siphviridae, Smacoviridae, Solemoviridae, Solinviviridae, Sphaerolipoviridae, Spiraviridae, Sunviridae, Tectiviridae, Thaspiviridae, Tobaniviridae, Togaviridae, Tolecusatellitidae, Tombusviridae, Tospoviridae, Totiviridae, Tristromaviridae, Turniviridae, Tymoviridae, Virgaviridae, Wupedeviridae, Xinmoviridae and *Yueviridae.*

In some examples, the viral disease may be caused by an infection with a virus belonging to a family *Coronaviridae*. For example, the viral disease may be caused by an infection with a virus belonging to a genus selected from the group consisting of *Alphaletovirus, Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus*. In one specific example, the viral disease may be caused by an infection with a virus belonging to a genus *Betacoronavirus*, *e.g.*, to a species selected from the group consisting of *Betacoronavirus 1, China Rattus coronavirus HKU24, Human coronavirus HKU1, Murine coronavirus, Myodes coronavirus 2JL14, Bat Hp-betacoronavirus Zhejiang2013, Hedgehog coronavirus 1, Middle East respiratory syndrome-related coronavirus, Pipistrellus bat coronavirus HKU5, Tylonycteris bat coronavirus HKU4, Eidolon bat coronavirus C704, Rousettus bat coronavirus GCCDC1, Rousettus bat coronavirus HKU9 and Severe acute respiratory syndrome-related coronavirus.*

In some embodiments, the viral disease may be caused by an infection with a virus belonging to a species *Severe acute respiratory syndrome-related coronavirus*. In further embodiment, the viral disease may be caused by an infection with a virus selected from the group consisting of SARSr-CoV BtKY72, SARS-CoV-2, SARSr-CoV RaTG13, SARS-CoV PC4-227 and SARS-CoV.

In one specific example, the subject being administered omadacycline, or a pharmaceutically acceptable salt thereof, for modulating an immune response, may be afflicted with a viral disease caused by an infection with SARS-CoV-2, *e.g.*, COVID-19.

In another example, the subject being administered omadacycline, or a pharmaceutically acceptable salt thereof, for modulating an immune response, may be afflicted with the viral disease caused by an infection with SARS-CoV, *e.g.*, SARS.

In some embodiments, the viral disease may be caused by an infection with a virus belonging to a species *Middle East respiratory syndrome-related coronavirus*, *e.g.*, MERS-CoV, and may be MERS.

In some embodiments, the subject being administered omadacycline, or a pharmaceutically acceptable salt thereof, for modulating an immune response, may be afflicted with a viral disease caused by an infection with a virus belonging to family *Orthomyxoviridae*. For example, the viral disease may be caused by an infection with a virus belonging to a genus selected from the group consisting of *Alphainfluenzavirus*, *Betainfluenzavirus*, *Deltainfluenzavirus* and *Gammainfluenzavirus*. In some examples, the viral disease may be caused by an infection with a virus belonging to a species selected from the group consisting of *Influenza A virus*, *Influenza B virus*, *Influenza D virus* and *Influenza C virus*, and may be influenza.

In some embodiments, the subject being administered omadacycline, or a pharmaceutically acceptable salt thereof, for modulating an immune response may be afflicted with a viral disease selected from the group consisting of gastroenteritis, keratoconjunctivitis, pharyngitis, croup, pneumonia, cystitis, hand, food and mouth disease, pleurodynia, meningitis, pericarditis, myocarditis, infectious mononucleosis, hepatitis, hepatic cirrhosis, cytomegalic inclusion disease, AIDS, Dengue fever, influenza, measles, postinfections encephalomyelitis, mumps, common cold, rabies, viral encephalitis, disease caused by West Nile virus, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19. In one specific embodiment, the viral disease may be COVID-19.

In some embodiments, the present invention provides a method of modulating an immune response in a subject afflicted with COVID-19 that comprises administering to the subject an effective amount of omadacycline, or a pharmaceutically acceptable salt thereof, such that the immune response in the subject is modulated.

In some embodiments, administering of omadacycline, or a pharmaceutically acceptable salt thereof, for modulating an immune response in a subject with SARS-CoV-2

infection, or a subject afflicted with COVID-19, alleviates at least one symptom associated with COVID-19. Exemplary symptoms associated with COVID-19 may include one or more of the following: fever, body ache, muscle and joint pain, cough (*e.g.*, dry cough), fatigue, chills, headache, sore throat, shortness of breath, sputum production, hemoptysis, sneezing, runny nose, chest tightness, palpitation, a neurological symptom and a gastrointestinal (GI) symptom. A neurological symptom may include one or more of the following: decreased sense of smell, inability to taste, muscle weakness, tingling or numbness in the hands and feet, dizziness, confusion, delirium, seizure and stroke. A GI symptom may include one of more of the following: loss of appetite, nausea, vomiting, diarrhea and abdominal pain or discomfort.

In some embodiments, administering of omadacycline, or a pharmaceutically acceptable salt thereof, for modulating an immune response in a subject with SARS-CoV-2 infection, or a subject afflicted with COVID-19, prevents at least one complication associated with COVID-19 in the subject. Exemplary complications associated with COVID-19 may include at least one of the following: acute respiratory failure, pneumonia, acute respiratory distress syndrome (ARDS), sepsis associated syndrome, acute liver injury, acute cardiac injury, acute kidney injury, disseminated intravascular coagulation (DIC), blood clots and rhabdomyolysis. In one example, the complication associated with COVID-19 may be a sepsis associated state, *e.g.*, SIRS or septic shock. In a further embodiment, the SIRS may comprise cytokine storm syndrome (CSS).

In some examples, the administering, *e.g.*, orally administering, omadacycline, or a pharmaceutically acceptable salt thereof, for modulating an immune response in a subject with a SARS-CoV-2 infection, or a subject afflicted with COVID-19, prevents utilization of HCP resources by the subject, *e.g.*, prevents hospitalization of the subject.

In some examples, the administering, *e.g.*, orally administering, omadacycline, or a pharmaceutically acceptable salt thereof, for modulating an immune response in a subject with a SARS-CoV-2 infection, or a subject afflicted with COVID-19, prevents death of the subject.

Administration of Omadacycline, or a Pharmaceutically Acceptable Salt Thereof

Omadacycline or a pharmaceutically acceptable salt thereof, may be administered to a subject in accordance with methods of the present invention either alone or as a part of a pharmaceutical composition. An exemplary pharmaceutical composition may comprise an effective amount of omadacycline, *e.g.*, a salt of omadacycline or omadacycline freebase, and, optionally, a pharmaceutically acceptable carrier. The tetracycline compound, such as the salt of omadacycline, *e.g.*, tosylate salt, or omadacycline freebase, may in an amorphous form or in a crystalline form.

The language "pharmaceutically acceptable carrier" includes substances capable of being co-administered with omadacycline, or a pharmaceutically acceptable salt thereof, and which may allow both to perform their intended function, *e.g.*, treat or prevent a viral infection, a viral disease, prevent a secondary bacterial pneumonia or modulate an immune response. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, and the like. The pharmaceutical compositions may be sterilized and, if desired, mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously react with omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof.

The pharmaceutical compositions that may be used in the methods of the present invention may be adapted for administration via either the oral, parenteral, or topical routes. For oral administration, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered in the form of a tablet or a capsule. The tablet or a capsule may comprise one or more excipients, such as a diluent (*e.g.*, lactose and/or microcrystalline cellulose), a stabilizer (*e.g.*, sodium bisulfite), a glidant (*e.g.*, colloidal silicon dioxide), a lubricant (*e.g.*, sodium stearyl fumarate or magnesium stearate) or a disintegrant (*e.g.*, crosspovidone).

For parenteral administration omadacycline, or a pharmaceutically acceptable salt thereof may be administered in the form of an injectable formulation. Such injectable formulations may be in the form of a dry, *e.g.*, lyophilized, powder, that is reconstituted with a carrier, *e.g.*, an aqueous carrier, such as water, prior to administration. In some embodiments, the injectable formulation may also comprise at least one or more of an

additional ingredient, such as a lyoprotectant (*e.g.*, sucrose), and a pH adjustment compound (*e.g.*, sodium hydroxide and/or hydrochloric acid).

Certain pharmaceutical compositions comprising omadacycline, or a pharmaceutically acceptable salt, ester or a prodrug thereof, that may be suitable for use in the methods of the present invention, are described, *e.g.*, in U.S. Patent No. 9,315,475, the entire contents of which are hereby incorporated herein by reference.

In the methods of the present invention, omadacycline or a pharmaceutically acceptable salt thereof, may also be administered to a subject by an aerosol. An aerosol pharmaceutical composition comprising omadacycline, or a pharmaceutically acceptable salt thereof, may be in the form of a solution, a suspension, a powder formulation or a liposomal formulation. An aerosol pharmaceutical composition comprising omadacycline, or a pharmaceutically acceptable salt thereof, may be contained in an aerosol dispenser that may, in some examples, also comprise a metered dose spray device. In some examples, the aerosol dispenser may be a nebulizer, *e.g.*, a small-volume nebulizer (SVN), a pressurized metered-dose inhaler (pMDI) or a dry-powder inhaler (DPI).

For topical administration, omadacycline, or a pharmaceutically acceptable salt thereof, may also be administered to a subject as a part of a pharmaceutical composition adapted for topical administration. Such compositions may be in a form of a gel, an ointment, a lotion or a cream, and may comprise the tetracycline compound suitably admixed in a pharmacologically inert topical carrier. The pharmacologically inert topical carriers may include water, glycerol, alcohol, propylene glycol, fatty alcohols, triglycerides, fatty acid esters, or mineral oils. Other possible topical carriers may be liquid petrolatum, isopropylpalmitate, polyethylene glycol, ethanol, polyoxyethylene monolauriate, sodium lauryl sulfate and the like. In addition, materials such as anti-oxidants, humectants, viscosity stabilizers and the like also may be added if desired.

Omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject in accordance with the methods of the present invention in an effective amount. The term "effective amount" of omadacycline is that amount which is necessary or sufficient to treat or prevent a viral infection, *e.g.*, SARS-CoV-2 infection, in a subject; or that amount which is necessary or sufficient to treat or prevent a viral disease, *e.g.*, COVID-19 in a subject; or that amount which is necessary or sufficient to modulate an immune response in a

subject; or that amount which is necessary or sufficient to prevent a secondary bacterial pneumonia in a subject with a viral infection, *e.g.*, SARS-CoV-2 injection, or in a subject afflicted with a viral disease, *e.g.*, COVID-19. One of ordinary skill in the art can determine an effective amount of omdacycline, or a pharmaceutically acceptable salt thereof, for administration to a subject.

In some embodiments, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject in accordance with the methods of the present invention at a dose, *e.g.*, daily dose, of from about 100 to about 200 mg, from about 100 to about 300 mg, from about 100 to 400 mg, from about 100 to about 500 mg, from about 100 to about 600 mg, from about 200 to about 500 mg, or from about 300 to about 600 mg of omadacycline, or a pharmaceutically acceptable salt thereof. In a further example, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered orally. In another further example, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered intravenously.

In some aspects, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject at a dose of about 50 to about 150 mg, about 50 to about 400 mg, about 50 to about 300 mg, about 50 to about 200 mg, about 100 to about 300 mg or about 200 to about 300 mg, or about 100 mg. For example, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject at a dose, *e.g.*, a daily dose, of about 100 mg, about 150 mg, about 200 mg, about 250 mg or about 300 mg. In one embodiment, the dose is an intravenous dose.

In some aspects, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject at a dose of from about 50 to about 800 mg, about 100 to about 700 mg, about 250 to about 600 mg, about 300 to about 500 mg, about 100 to about 400 mg, about 100 to about 600 mg, or about 300 mg. For example, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered at a dose of about 300 mg, about 450 mg or about 600 mg. In one embodiment, the dose is an oral dose.

In an embodiment, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered intravenously at a dose of about 100 mg, about 200 mg, or about 300 mg. In another embodiment, omadacycline, or salt thereof, may be administered orally at the dose of about 300 mg, about 600 mg, or about 900 mg.

In some examples, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered as an aerosol dose, *e.g.*, delivered using an aerosol dispenser. In some examples, the aerosol dispenser may comprise at a dose of omadacycline, or a pharmaceutically acceptable salt thereof of about 1 to about 2000 mg, *e.g.*, about 1 to about 500 mg, about 25 to about 300 mg, about 50 to about 400 mg, about 100 to about 500 mg, about 200 to about 800 mg, about 500 mg to about 1000 mg, about 10 mg to about 200 mg or about 300 mg to about 700 mg. In some examples, the aerosol dispenser may comprise a dose of omadacycline, or a pharmaceutically acceptable salt thereof of about 1 mg, about 5 mg, about 10 mg, about 30 mg, about 50 mg, about 80 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg or about 1000 mg.

In some examples, omadacycline or a pharmaceutically acceptable salt thereof, may be administered topically, *e.g.*, by applying to an affected area pharmaceutical composition adapted for topical administration comprising omadacycline or a pharmaceutically acceptable salt thereof. For example, the pharmaceutical composition adapted for topical administration may be in the form of a solution and comprise omadacycline or a pharmaceutically acceptable salt thereof, at a concentration of about 0.01% to about 20% w/v based on the volume of the composition, *e.g.*, about 0.01% to about 10% w/v, about 0.1% to about 20% w/v, about 0.5% to about 5% w/v, about 1% to about 10% w/v or about 5% to about 20% w/v. For example, the pharmaceutical composition adapted for topical administration may comprise omadacycline or a pharmaceutically acceptable salt thereof, at a concentration of about 0.01% w/v, about 0.05% w/v, about 0.1% w/v, about 0.5% w/v, about 1% w/v, about 5% w/v, about 10% w/v, about 15% w/v or about 20% w/v.

In another example, the pharmaceutical composition adapted for topical administration may comprise omadacycline or a pharmaceutically acceptable salt thereof, at a concentration of about 0.01% to about 20% w/w based on the volume of the composition, *e.g.*, about 0.01% to about 10% w/w, about 0.1% to about 20% w/w, about 0.5% to about 5% w/w, about 1% to about 10% w/w or about 5% to about 20% w/w. For example, the pharmaceutical composition adapted for topical administration may comprise omadacycline or a pharmaceutically acceptable salt thereof, at a concentration of about 0.01% w/w, about

0.05% w/w, about 0.1% w/w, about 0.5% w/w, about 1% w/w, about 5% w/w, about 10% w/w, about 15% w/w or about 20% w/w.

In some examples, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered at the doses as described above at least once daily, *e.g.*, once daily, twice daily, three times daily or four times daily. In further examples, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject twice daily. In one specific example, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered orally to a subject twice daily. In another specific example, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered orally to a subject once daily.

It should be understood that administration of dose ranges comprising the above listed doses is also included in the present invention. For example, any of the above doses may be a lower part or an upper part of a dose range that is included in the methods of the present invention. Even further, it should be understood that all lists or collections of numerical values used throughout the present application also are intended to include ranges of the numerical values wherein any of the listed numerical values can be the lower part or upper part of a range. These ranges are intended to be included in the present invention.

In one embodiment, an oral dose of omadacycline, or a pharmaceutically acceptable salt thereof, may be 3 times larger than an intravenous dose of omadacycline, or a pharmaceutically acceptable salt thereof.

It will be understood that for all listed embodiments, the dose of omadacycline, or a pharmaceutically acceptable salt thereof, is also an effective amount of the omadacycline, or a pharmaceutically acceptable salt thereof.

In one embodiment, the effective amount of omadacycline, or a pharmaceutically acceptable salt thereof, when administered orally, may be from about 100 to about 1000 mg, *e.g.*, from about 200 to about 750 mg, about 100 to about 500 mg, about 200 to about 600 or about 400 to about 600. In a further example, the effective amount of omadacycline, or a pharmaceutically acceptable salt thereof, when administered orally, may be about 300 mg, about 450 mg or about 600 mg.

In another embodiment, the effective amount of omadacycline, or a pharmaceutically acceptable salt thereof, when administered intravenously, may be from about 50 to about 500

mg, *e.g.*, about 50 to about 400 mg, about 100 to about 300 mg or about 50 to about 200 mg. For example, the effective amount of omadacycline, or a pharmaceutically acceptable salt thereof, when administered intravenously, may be about 100 mg, about 150 mg, about 200 mg, about 250 mg or about 300 mg.

In some examples, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered in the context of the present invention via either the oral, parenteral, systemic, topical routes, or via aerosol delivery. In general, omadacycline, or a pharmaceutically acceptable salt thereof, is most desirably administered in an effective dosage, depending upon the weight and condition of the subject being treated and the particular route of administration chosen. Variations may occur depending upon the species of the subject being treated and its individual response to the medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out.

In some embodiments, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered for at least 3 days, at least 7 days, at least 14 days, at least 21 days, at least 30 days or at least 60 days. For example, the administration of omadacycline, or a pharmaceutically acceptable salt thereof, may last from 3 days to 7 days, from 3 days to 14 days, from 3 days to 21 days, from 3 days to 30 days, from 3 days to 60 days, from 7 days to 14 days, from 7 days to 21 days, from 7 days to 30 days, from 7 days to 60 days, from 14 days to 21 days, from 14 days to 30 days, from 14 days to 60 days, from 21 days to 30 days, from 21 days to 60 days, or from 30 days to 60 days.

For example, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered for 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, 31 days, 32 days, 33 days, 34 days, 35 days, 36 days, 37 days, 38 days, 39 days, 40 days, 41 days, 42 days, 43 days, 44 days, 45 days, 46 days, 47 days, 48 days, 49 days, 50 days, 51 days, 52 days, 53 days, 54 days, 55 days, 56 days, 57 days, 58 days, 59 days or 60 days.

In some embodiments, administration of omadacycline, or a pharmaceutically acceptable salt thereof, to a subject in the context of the methods of the present invention may comprise administering one or more loading doses of omadacycline, or a pharmaceutically

acceptable salt thereof, followed by one or more maintenance doses of omadacycline, or a pharmaceutically acceptable salt thereof. In some embodiments, the one or more loading dose of omadacycline, or a pharmaceutically acceptable salt thereof, may be greater than the one or more maintenance dose of omadacycline, or a pharmaceutically acceptable salt thereof. For example, the loading dose may be about 450 mg daily dose, *e.g.*, a daily oral dose, while the maintenance dose may be about 300 mg daily dose, *e.g.*, a daily oral dose. In another example, the loading dose may be about 200 mg daily dose, *e.g.*, a daily intravenous dose, while the maintenance dose may be about 100 mg daily dose, *e.g.*, a daily intravenous dose, or a 300 mg daily dose, *e.g.*, a daily oral dose.

The loading dose of omadacycline, or a pharmaceutically acceptable salt thereof, and the maintenance dose of omadacycline, or a pharmaceutically acceptable salt thereof may be administered via the same route or different routes. For example, the loading dose(s) may be administered intravenously and the maintenance dose may be administered orally. In other embodiments, both the loading dose(s) and the maintenance doses may be administered orally. In yet other embodiments, both the loading dose(s) and the maintenance dose may be administered intravenously.

In some examples, the loading dose of omadacycline, or a pharmaceutically acceptable salt thereof, may be an oral dose or an intravenous dose administered twice daily, and the maintenance dose may be an oral dose or an intravenous dose administered once daily. For example, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered as an intravenous loading dose of 100 mg twice daily, followed by an intravenous maintenance dose of 100 mg once daily. In another example omadacycline, or a pharmaceutically acceptable salt thereof, may be administered as an intravenous loading dose of 100 mg twice daily, followed by an oral maintenance dose of 300 mg once daily. In yet another example, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered as an oral loading dose of 300 mg twice daily, followed by an oral maintenance dose of 300 mg once daily.

In another example, administration of omadacycline, or a pharmaceutically acceptable salt thereof, may not comprise administration of one or more loading doses of omadacycline, or a pharmaceutically acceptable salt thereof. Thus, in some examples, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject at the same dose throughout the treatment period. For example, omadacycline, or a pharmaceutically

acceptable salt thereof, may be administered to the subject at an intravenous dose of about 100 mg, about 200 mg or about 300 mg. The intravenous dose may be administered to the subject once or twice daily throughout the treatment. In another example, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject at an oral dose of about 300 mg, about 450 mg or about 600 mg. The oral dose may be administered to the subject once daily throughout the treatment period.

The above described doses and dosing schdules of omadacycline, or a pharmaceutically acceptable salt thereof, may be prophylactic doses or prophylactic dosing schedules, *i.e.*, doses or dosing schedules of omadacycline, or a pharmaceutically acceptable salt thereof, that are administered to a subject prophylactically, *e.g.*, to a subject with no known bacterial infecton. For example, the above described doses of omadacycline, or a pharmaceutically acceptable salt thereof, may be prophylactically administered to a subject with a viral infection, *e.g.*, SARS-CoV-2 infection, or a subject with a viral disease, *e.g.*, COVID-19, for preventing secondary bacterial pneumonia, or for reducing the likelihood of onset, or the severity of secondary bacterial pneumonia in the subject.

In some examples, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject in accordance with the methods of the present invention alone or in combination with at least one additional therapeutic agent. The language "in combination with" a therapeutic agent is intended to include simultaneous administration of omadacycline, or a pharmaceutically acceptable salt thereof, and the therapeutic agent; administration of omadacycline, or a pharmaceutically acceptable salt thereof, first, followed by the therapeutic agent; and administration of the therapeutic agent first, followed by omadacycline, or a pharmaceutically acceptable salt thereof.

In some examples, the at least one additional therapeutic agent that may be administered to a subject, *e.g.*, a subject with a SARS-CoV-2 infection or a subject afflicted with COVID-19, may be selected from the group consisting of an antiviral agent, an antibacterial agent, an anti-parasitic agent and an immunomodulatory agent. For example, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject, *e.g.*, a subject with a SARS-CoV-2 infection, in combination with an antiviral agent, such as remdesivir, favipiravir, umifenovir (Arbidol), azvudine, baloxavir marboxil, danoprevir, lopinavir, ritonavir, sofosbuvir, valacyclovir, darunavir, cobicistat, inosine pranobex, EIDD-2801, BLD-2660, triazavirin, or ribavirin.

In some embodiments, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject, *e.g.*, a subject with a SARS-CoV-2 infection or a subject afflicted with COVID-19, in combination with an antibacterial agent, *e.g.*, sulfamethoxazole/trimethoprim, kolimycin, minocycline, doxycycline, or a macrolide, such as azithromycin, clarithromycin, erythromycin, spiramycin, teicoplanin, oritavancin, dalbavancin or monensin. In one embodiment, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject, *e.g.*, a subject with a SARS-CoV-2 infection or a subject afflicted with COVID-19, in combination with azithromycin.

In some embodiments, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject, *e.g.*, a subject with a SARS-CoV-2 infection or a subject afflicted with COVID-19, in combination with an antiparasitic agent, such as chloroquine, hydroxychloroquine, nitazoxanide, mefloquine, levamisole, suramin, or ivermectin.

In some embodiments, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject, *e.g.*, a subject with a SARS-CoV-2 infection or a subject afflicted with COVID-19, in combination with an immunomodulatory agent, such as an interferon, *e.g.*, interferon β, ciclesonide, colchicine, a corticosteroid, leflunomide, baricitinib, sirolimus, tacrolimus, tetrandrine, tranilast, an NSAID (*e.g.*, aspirin, acetaminophen, naproxen, celecoxib, or ibuprofen), aescin, anakinra, fingolimod, XPro1595, or a neutralizing antibody against a cytokine associated with a cytokine storm, *e.g.*, tocilizumab.

In some embodiments, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject, *e.g.*, a subject with SARS-CoV-2 infection or a subject afflicted with COVID-19, in combination a therapeutic antibody. Non-limiting examples of therapeutic antibodies comprise, *e.g.*, tocilizumab, sarilumab, bevacizumab, eculizamab, avdoralimab, canakinumab, ravalizumab, clazakizumab, nivolumab, BMS-986253, emapalumab, ixekizumab, leronimab, lenziulumab, ixekizumab, mepolizumab, siltuximab, IFX-1, TJ003234 and an anti-PD-1 antibody (*e.g.*, cemiplimab, nivolumab, pembrolizumab, avelumab, durvalumab or atezolizumab).

In some embodiments, omadacycline, or a pharmaceutically acceptable salt thereof, may be administered to a subject, *e.g.*, a subject with a SARS-CoV-2 infection, in combination with at least one additional therapeutic agent is selected from the group consisting of peginterferon lambda-1a, formoterol, Cd24f, CM4620, LY3127804, OM-85,

MRx-4DP0004, recombinant tissue-Plasminogen Activator (rt-PA), viral macrophage inflammatory protein (vMIP), granulocyte-colony stimulating factor (G-CSF), human alpha-1 proteinase inhibitor, human antithrombin-III, human angiotensin-converting enzyme 2, vafidemstat, nafamostat, lenalidomide, Jakotinib, tofacitinib, itraconazole, ruxolitinib, acalabrutinib, estradiol, progesterone, dexmedetomidine, solnatide, etoposide, enoxaparin, vazegepant, linagliptin, sitagliptin, dalargin, hyperbaric oxygen, nitric oxide, ozone, bismuth potassium citrate, chlorine phosphate (Arechin), ramipril, spironolactone, sevoflurane, bromhexine, IB-MECA (methyl 1-[N6-(3-iodobenzyl)-adenin-9-yl]-b-D-ribofuronamide), pyridostigmine, chlorpromazine, ciclesonide, methotrexate, fluvoxamine, losartan, APN01, melatonin, curcumin, metmorfin, angiotensin, imatinib, nintedanib, noscapine, sargramostim, selinexor, isotretinoin, prazosin, defibrotide, brilacidin, griffithsin, an anticoagulant, an antihypertensive (*e.g.*, telmisartan), famotidine, dipyridamole, sildenafil, avipladil, tradipitant, bezafibrate, fenofibrate, vitamin C, dapagliflozin, a statin (*e.g.*, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin), alteplase, almitrine, deferoxamine, Sn-protoporphyrin IX (SnPPIX), sulfonatoporphyrin(TPPS), polyinosinic:polycytidylic acid, lipoic acid (*e.g.*, alpha-lipoic acid), amiodarone, verapamil, tranexamic acid, dornase alfa, thalidomide, berberine, REGN3048, TZLS-501, AT-001, PUL-042, crocetin, an ACE inhibitor (*e.g.*, captopril), Crostop solution, Croguard syrup, zinc, lithium, heparin, tinzaparin, fondaparinux, clopidogrel, tirofiban, eicosapentaenoic acid, medium-chain triglycerides (MCTs), vitamin A, vitamin D, a derivative of vitamin D (*e.g.*, calcifediol), Zofa (Hyssop) syrup, pirfenidone, valsartan, camostat, enoxaparin, intravenous immunoglobulin (*e.g.*, IVIG or J06BA02), extracorporeal blood purification (*e.g.*, for treatment of cytokine storm and inflammation, such as CytoSorb®, or for removal of endotoxins, such as Toraymyxin), mesenchymal stem cell therapy (*e.g.*, NestCell®), hydrogen-oxygen inhalation, extracorporeal membrane oxygenation (ECMO), hemodialysis, and convalescent plasma.

The term "treating" or "treatment", as used herein, includes one or more of the following: (a) inhibiting, controlling, arresting, reducing, or delaying the advancement or the development of a viral infection, *e.g.*, SARS-CoV-2 infection, or a viral disease, *e.g.*, COVID-19, or a relapse thereof in case of maintenance treatment, of at least one clinical or subclinical symptom thereof; and/or (b) relieving, *i.e.*, ameliorating or diminishing at least one clinical or subclinical symptom of a viral infection, *e.g.*, SARS-CoV-2 infection, or a

viral disease, *e.g.*, COVID-19. The benefit to a subject to be treated is either statistically significant or at least perceptible to the subject or to the physician.

The term "prophylaxis", "prevent", "preventing" or "prevention", as used herein, includes preventing or reducing the risk of a viral infection, *e.g.*, SARS-CoV-2 infection, or a viral disease, *e.g.*, COVID-19, or secondary bacterial pneumonia. In some examples, this term includes preventing or delaying the appearance of clinical symptoms of a viral infection, *e.g.*, SARS-CoV-2 infection, or a viral disease, *e.g.*, COVID-19, or secondary bacterial pneumonia, in a subject who may already be infected with a virus, *e.g.*, SARS-CoV-2, but who has not yet developed a viral disease, *e.g.*, COVID-19, or who is not displaying symptoms of a viral infection or a viral disease. In some examples, this term also includes reducing the likelihood that a subject who has already developed a viral disease, *e.g.*, COVID-19, will develop a secondary bacterial pneumonia. In some examples, this term also includes reducing the likelihood that a subject who has been exposed to a virus, *e.g.*, SARS-CoV-2, will develop a viral infection, a viral disease, or a symptom thereof.

A treatment or preventive effect is evident when there is a statistically significant improvement in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change in a measurable parameter of a symptom of a viral infection, a viral disease or a secondary bacterial pneumonia, *e.g.*, a decrease in duration of viral shedding, may be indicative of effective treatment. For example, the favorable change in a measurable parameter of a symptom of a viral infection, a viral disease or a secondary bacterial pneumonia may be a change of at least 10%, and preferably at least 20%, 30%, 40%, 50% or more. In another example, any positive change resulting in *e.g.*, lessening of severity of a symptom of a viral infection, a viral disease or a secondary bacterial pneumonia measured using the appropriate scale, represents adequate treatment using omadacycline or a pharmaceutically acceptable salt thereof, as described herein.

The term "subject" includes animals which are subject to a viral infection, a viral disease or a secondary bacterial pneumonia. Examples of subjects include animals such as farm animals (*e.g.*, cows, pigs, horses, goats, rabbits, sheep, chickens, etc.), lab animals (mice, rats, monkeys, chimpanzees, etc.), pets (*e.g.*, dogs, cats, ferrets, hamsters, *etc.*), birds (*e.g.*, chickens, turkeys, ducks, geese, crows, ravens, sparrows, *etc.*), primates (*e.g.*, monkeys, gorillas, chimpanzees, bonobos, and humans), and other animals (*e.g.*, squirrels, raccoons,

mice, rats, *etc.*). In one embodiment, the subject is a mouse or rat. In one embodiment, the subject is a cow, a pig, or a chicken.

In one embodiment, the subject is a human. In some examples, the subject may be at risk of developing a viral infection, *e.g.*, SARS-CoV-2 infection. In other examples, the subject may already have a viral infection, *e.g.*, SARS-CoV-2, and may be at a risk of developing at least one complication associated with a viral disease, *e.g.*, COVID-19.

In some embodiments, a subject who may be at risk of developing a viral infection or a subject who already has a viral infection and who is at risk of developing at least one complication associated with a viral disease may be an elderly subject. An "elderly subject" may be a subject who is over 50 years old, over 55 years old, over 60 years old, over 65 years old, over 70 years old, over 75 years old, over 80 years old, over 85 years old, over 90 years old, or over 95 years old or older.

In some embodiments, a subject who may be at risk of developing a viral infection or a subject who already has a viral infection and who is at risk of developing at least one complication associated with a viral disease may be a subject who has a pre-existing or an underlying disease or a condition. Exemplary pre-existing or underlying disease or condition may be hypertension, diabetes mellitus, a cardiovascular disease, cancer, chronic kidney disease (e.g., kidney disease requiring dialysis), liver disease, excess weight (*e.g.*, obesity, such as severe obesity characterized by a body mass index of 40 of higher), a respiratory disease, such as a chronic lung disease, asthma, or lung damage (*e.g.*, lung damage associated with smoking or drug use). In some examples, the subject may be immunocompromised. For example, a subject may be immunocompromised due to undergoing cancer treatment; undergoing organ, *e.g.*, bone marrow, transplantation; having an immune deficiency, *e.g.*, poorly controlled HIV infection or AIDS; smoking; and prolonged use of immune weakening medications, such as corticosteroids.

In some examples, the subject may be a male.

In some examples, the subject has been determined to have a viral infection, *e.g.*, SARS-CoV-2 infection, prior to the administration of omadacycline or a pharmaceutically acceptable salt thereof. Accordingly, methods of the present invention may also comprise the step of determining that the subject has a viral infection, *e.g.*, SARS-CoV-2 infection, prior to administering omadacycline or a pharmaceutically acceptable salt thereof, to the subject.

Determining that the subject has a viral infection may be accomplished by any method known in the art for diagnosing viral infections.

In some embodiments, administration of omadacycline or a pharmaceutically acceptable salt thereof, to a subject in accordance with the methods of the present invention, does not result in substantial adverse effects. In some examples, the administration may be an oral administration. In some examples, the adverse effects may be gastrointestinal adverse effects, such as nausea or vomiting, and may be mild. In some embodiments, administration of omadacycline or a pharmaceutically acceptable salt thereof does not require administration of an antiemetic agent, such as ondansetron.

The term "about", as used herein, refers to a range of values which can be 15%, 10%, 8%, 5%, 3%, 2%, 1 %, or 0.5% more or less than the specified value. For example, "about 10%" can be from 8.5% to 11.5%. In one embodiment, the term "about" refers to a range of values which are 5% more or less than the specified value. In another embodiment, the term "about" refers to a range of values which are 2% more or less than the specified value. In another embodiment, the term "about" refers to a range of values which are 1 % more or less than the specified value.

It is to be understood that wherever values and ranges are provided herein, *e.g.*, in ages of subject populations, dosages, and time durations, *etc.*, all values and ranges encompassed by these values and ranges, are meant to be encompassed within the scope of the present invention. Moreover, all values in these values and ranges may also be the upper or lower limits of a range.

EXAMPLES

Example 1. *Antiviral activity of omadacycline and azithromycin in an in vitro* model of SARS-CoV-2 infection

The goal of this experiment was to evaluate antiviral activity of omadacycline as well as that of the comparator azithromycin in an *in vitro* model of SARS-CoV-2 infection. The study utilized a standard virus neutralization (VN) assay and Vero E6 cells that are susceptible to SARS-CoV-2 infection. Vero E6 cells were cultured in growth media consisting of Dulbeco's Modified Eagle Medium/F12 supplemented with 5% FBS (Fetal Bovine Serum), and PSN (penicillin, streptomycin, and neomycin).

The Vero E6 cells were grown in 96-well plates to 60%-70% confluence. Omadacycline and azithromycin were each reconsistuted with dimethyl sulfoxide (DMSO) to a concentration of 10 mg/mL, which was then futher diluted in DMEM/F12 to 50 µg/mL. Two-fold serial dilutions were performed to down to 0.78 µg/mL. Subsequently, 50 µL of each serial dilution was pre-incubated with Vero E6 cells for 60 minutes prior to addition of 50 µL of the virus. This step was performed to allow the drug to interact with cells prior to virus introduction.

Test wells received approximately 100 Tissue Culture Infectious Dose $(TCID)_{50}$/well of SARS-CoV-2 in 50 µL. The amount of virus added was estimated using previous backtiter results from the same lot of virus. To achieve the target viral challenge, the virus was added to a 96 well plate and diluted 1:10 down the plate. The target dilution (100 $TCID_{50}$/well) was then added to Vero cells and they were observed for cytopathic effect (CPE) associated with viral growth and replication. This dilution is the lowest concentration of virus still able to reliably infect all cells but not overwhelm any potential test article/therapeutic used. Fourty-five minutes after the virus was added, 100 µL of DMEM/F12 + FBS was added to feed the cells. For the drug refresh plates, 100 µL of 75 µg/mL drug in DMEM/F12 + FBS was added to maintain the highest final concentration at 50 µg/mL.

All test articles were also assessed in the absence of virus to determine if they had any cytotoxic effect. The controls had no further additions or media changes during the testing. The assay was executed in five replicates for each condition.

Growth of the Vero E6 cells was observed, and the cells were monitored for cytopathic effects (CPE) associated with successful virus replication. All wells were examined on Day 2 and Day 4 post infection. Examination was done using a microscope (usually 10x objective to view the entire well at once) and observing the morphology of the

cells. Healthy Vero cells had a somewhat transparent appearance with pinched or rounded ends in a monolayer of cells with little to no space between cells. Dead cells displaying CPE were often not adhered to the plate, round and much smaller than living cells. There was also a lot of empty space on the bottom of the plate from where cells have detached. Any well displaying CPE was marked as positive whether the whole well was affected or only a small patch because this was indicative of the presence of a viable virus.

No cytotoxicity was observed from any drug dilution used, or from the DMSO controls. Day 2 reads showed CPE in all wells for both drugs, and Day 4 reads confirmed this finding. All uninfected controls remained healthy and did not display any CPE throughout the 4-day observation period. The back titer was consistent with previous virus growth results. The results of the experiment are summarized in Tables 1-3 below.

Table 1. Results of *In Vitro* Neutralization of SARS-CoV-2 with Azithromycin (AZTH) and Omadacycine (OMC) with Drug Refresh

Final Concentration	CPE Day 2 Read		Cytotoxicity Day 2 Read		CPE Day 4 Read		Cytotoxicity Day 4 Read	
	OMC	AZTH	OMC	AZTH	OMC	AZTH	OMC	AZTH
50 µg/mL	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox
43.75 µg/mL	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox
40.6 µg/mL	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox
39 µg/mL	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox
38.3 µg/mL	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox
37.9 µg/mL	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox

Final Concentration	CPE Day 2 Read		Cytotoxicity Day 2 Read		CPE Day 4 Read		Cytotoxicity Day 4 Read	
	OMC	AZTH	OMC	AZTH	OMC	AZTH	OMC	AZTH
0 µg/mL	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox

Table 2. Results of *In Vitro* Neutralization of SARS-CoV-2 with Azithromycin (AZTH) and Omadacycine (OMC)

Final Concentration	CPE Day 2 Read		Cytotoxicity Day 2 Read		CPE Day 4 Read		Cytotoxicity Day 4 Read	
	OMC	AZTH	OMC	AZTH	OMC	AZTH	OMC	AZTH
12.5 µg/mL	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox
6.25 µg/mL	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox
3.13 µg/mL	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox
1.56 µg/mL	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox
0.78 µg/mL	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox
0.39 µg/mL	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox
0 µg/mL	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had no cytotox

Table 3. Results of DMSO Cytotoxicity

Dilution	CPE Day 2 Read	Cytotoxicity Day 2 Read	CPE Day 4 Read	Cytotoxicity Day 4 Read
	DMSO	DMSO Cytotox	DMSO	DMSO Cytotox
0.25%	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had no cytotox
0.125%	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had no cytotox
0.125%	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had no cytotox
0.03125%	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had no cytotox
0.015625%	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had no cytotox
0.007813%	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had no cytotox
0.003906%	5/5 wells had CPE	5/5 wells had no cytotox	5/5 wells had CPE	5/5 wells had no cytotox

The results presented in the Tables 1-3 indicate that, at the conditions tested, specifically, at the omadacycline and azithromycin concentrations of 0-50 µg/mL, no inhibition of SARS-CoV-2 infection of Vero cells was observed.

Example 2. Additional evaluation of antiviral activity of omadacycline in *in vitro* models of SARS-CoV-2 infection

The goal of this experiment is to additionally evaluate antiviral activity of omadacycline in additional *in vitro* models of SARS-CoV-2 infection. To this end, *in vitro* models of SARS-CoV-2 infection are used, such as, *e.g.*, *in vitro* models as described, in Dyall *et al.*, Antimicrobial Agents and Chemotherapy 2014, 58(8):4885-4893; Yao *et al.*, *Clinical Infectious Diseases*, ciaa237 (2020); and Wilde *et al.*, *Virus Research* 2017, 228:7-13. An *in vitro* model of SARS-CoV-2 infection is used to evaluate the effect of treating SARS-CoV-2 infected cells with omadacycline, a comparator drug or vehicle control by assessing, *e.g.*, cell survival, the concentration of SARS-CoV-2 virus, CPE inhibition, or viral replication.

Example 3. Antiviral and immunomodulatory activity of omadacycline in an *in vivo* model of SARS-CoV-2 infection

The goal of this experiment is to evaluate antiviral and anti-inflammatory activity of omadacycline in an in vivo animal model of SARS-CoV-2 infection. To this end, an animal model of SARS-CoV-2 infection is used, such as, *e.g.*, a nonhuman primate model of coronavirus infection as described in Rockx *et al.*, *Science* 10.1126/science.abb7314 (2020) and Clay *et al.*, *Immunity & Ageing* 2014, 11:4; a hamster animal model of SARS-CoV-2 infection as described, *e.g.*, in Chan *et al.*, *Clinical Infectious Diseases*, ciaa325 (2020); or a ferret animal model of SARS-CoV-2 infection as described, *e.g.*, in *Kim et al.*, *Cell Host & Microbe* 27, 1-6 (2020), the entire contents of each of which are hereby incorporated herein by reference.

Antiviral activity of omadacycline in an animal model of SARS-CoV-2 infection is evaluated before and after administration of omadacycline, comparator drug or vehicle control by assessing, *e.g.*, viral shedding in nasal or throat swabs; measuring viral replication in respiratory tract tissue, *e.g.*, nasal cavity, trachea, bronchi and lung lobes; and/or evaluating histopathology of lung tissues. An animal model of SARS-CoV-2 infection is also used to assess the ability of omadacycline to prevent a SARS-CoV-2 infection, impact on tissue tropism of the SARS-CoV-2 virus, or impact on or inhibition of transmission between close contact animals.

Immunomodulatory, *e.g.*, anti-inflammatory activity of omadacycline is assessed by measuring levels of inflammatory markers, *e.g.*, cytokines, such as INF-γ, IL-1β, IL-6, IL-12, IL-18 and IL-15, before and after administration of omadacycline, comparator drug or vehicle control.

Example 4. Activity of omadacycline in preventing secondary bacterial pneumonia after viral infection

The goal of this experiment is to evaluate activity of omadacycline in preventing secondary bacterial pneumonia after viral infection. To this end, animal models of viral infection are used, such as, *e.g.*, the animal models as described in Example 3; the mouse model of *Streptococcus pneumoniae* secondary to influenza as described in Yang *et al.*,

Inflammation 2019, 42(5):1741-1753, or Roberts *et al.*, *Vaccines* 2019, 7, 146, the entire contents of each of which are hereby incorporated herein by reference. The animal models are used to evaluate animal mortality, bacterial load and levels of inflammatory markers, *e.g.*, cytokines, before and after administration of omadacycline, comparator drug or vehicle control to the animals.

Example 5. Immunomodulatory activity of omadacycline in *in vitro* models

The goal of this experiment is evaluate immunomodulatory, *e.g.*, anti-inflammatory activity of omadacycline in *in vitro* models. To this end, *in vitro* models are used as described, *e.g.*, in Muroya *et al.*, *BioScience Trends* 2012, 6(2):70-80; Kuwajima *et al.*, *Journal of Intensive Care* 2019, 7:12; and Hoyt *et al.*, *J. Immunol* 2006, 176:567-572, the entire contents of each of which are hereby incorporated herein by reference. In these models, cells are stimulated by a mixture of inflammatory cytokines, such as TNF-α, IL-1β and IFN-γ to induce cellular injury. Cells could also be stimulated with killed bacteria, killed virus and/or components of bacteria or viruses, such as toxins or lipopolysaccharide (LPS), to stimulate an inflammatory response in cells. Immunomodulatory, *e.g.*, anti-inflammatory, activity of omadacycline is evaluated by measuring viability of cells treated with omadacycline, comparator drug or vehicle control prior to, or concurrently with stimulation by inflammatory cytokines. Immunomodulatory activity of omadacycline is also evaluated by measuring expression of inflammation markers, such as nitric oxide, as well as levels of inflammatory proteins, such as iNOS, ICAM, and p38 MAPK.

Further, immunomodulatory activity of omadacycline is also evaluated by assessing the effect of omadacycline, comparator drug or vehicle control on human neutrophil chemotaxis as described, *e.g.*, Bryant *et al.*, *Journal of Medical Microbiology* 2006, 55:495-504 and Stevens *et al.*, *The Journal of Infectious Diseases* 2000, 182:1117-28, the entire contents of each of which are hereby incorporated herein by reference.

Example 6. Immunomodulatory activity of omadacycline in *in vivo* models

The goal of this experiment is to evaluate immonumodulatory, *e.g.*, anti-inflammatory activity of omadacycline in *in vivo* animal models. To this end, the experiment utilizes, *e.g.*, a mouse model of pneumonia as described in Salvatore *et al.*, Antimicrobial Agents and Chemotherapy 2009, 53(4):1546-1551 or a mouse model of lung injury caused by lipopolysaccharide (LPS) or infection with *Streptococcus pneumoniae* as described in Fujita *et al., Pulmonary Pharmacology & Therapeutics* 2007, 20:669-675, the entire contents of each of which are hereby incorporated herein by reference. Immunomodulatory, *e.g.*, anti-inflammatory activity of omadacycline is assessed in animals treated with omadacycline, comparator drug or vehicle control by measuring inflammatory cell infiltrate and levels of chemokines or cytokines in bronchoalveolar lavage fluid, including levels of TNF-α, IFN-γ, IL-1β, IL-1, IL-4, IL-5, IL-6, IL-10, IL-12, granulocyte-macrophage colony-stimulating factor, MIP-1α, MIG, KC, MCP, IP-10. Immunomodulatory, *e.g.*, anti-infammatory activity of omadacycline is also assessed by measuring MMP activation.

Example 7. Phase 2 randomized, clinical trial to assess activity of omadacycine in COVID-19 patients

A Phase 2 randomized, controlled clinical trial is conducted to assess the effectiveness of omadacycline in preventing secondary bacterial pneumonia. The trial includes outpatients who are presumed COVID-19 positive and at high risk for developing secondary pneumonia. Approximately 150 patients are randomized to receive 300 mg oral omadacycline or placebo daily for 7-14 days. A follow-up safety contact is performed approximately 2 weeks following the final dose. Patients participate for approximately 28 days. In addition, all patients receive standard of care treatment at the discretion of the investigator. Endpoints assessed in the trial include hospitalization and HCP resource utilization, progression to pneumonia, symptom improvement, and potential measurement of anti-inflammatory biomarkers.

The Phase 2 clinical trial study is designed to be consistent with standard of care treatment for COVID-19 patients and to minimize protocol specific procedures to reduce additional burden on the healthcare providers and patients. The study includes telehealth and virtual visits as well as home health care options as needed to perform procedures. In

addition, as standard of care (SOC) is rapidly evolving, the design of the study allows as much flexibility as possible while still maintaining rigor.

Example 8. Anti-inflammatory Activity of Omadacycline *In Vitro* and *In Vivo*

In bacterial pneumonia, a robust inflammatory response is required to kill bacteria and resolve infection, however, excessive and prolonged alveolar inflammation leads to alveolar epithelial cell injury and death. Thus, careful and precise modulation of the host response is important to overcome infection while avoiding acute lung injury (ALI).

It is hypothesized that omadacycline could mitigate hyper-inflammatory ALI in several ways, specifically: 1) by suppressing neutrophilic inflammatory cell infiltration into the lung alveolar space *via* reducing neutrophil chemotaxis and/or chemoattractant production ; 2) by suppressing extracellular bacterial toxins that hyper-stimulate pro-inflammatory cytokine production by alveolar macrophages; 3) by down-modulating the physiological responses of neutrophils and alveolar macrophages to infectious agents and their toxins; and 4) by stimulating endogenous host cell survival mechanisms to provide cytoprotection against cytokine-mediated cell death.

Effect of omadacycline on cytokine expression induced by LPS in monocytes in vitro

The first goal of this experiment is to determine if omadacycline inhibits cytokine expression induced by LPS in monocytes *in vitro*. Other protein synthesis inhibitor antibiotics (*e.g.*, clindamycin, azithromycin) have been shown to down modulate LPS-induced cytokine production by human monocytes, albeit with differing potencies. It was hypothesized that omadacycline, because of its mechanism of action, may have a similar, or better effect, in down modulating LPS-induced cytokine production, which could enhance its efficacy in treating infections in which a local or systemic cytokine storm mediates worse outcomes.

The experiment to test the effect of omadacycline on LPS-induced cytokine production by monocytes *in vitro* is to follow the previously published methods (Salvatore *et al.*, *Antimicrob Agents Chemother* 2009;53(4):1546-1551, the entire contents of which are hereby incorporated herein by reference). Briefly, human peripheral blood mononuclear cells

(PBMC) is isolated from 30 mL of whole blood by density gradient centrifugation, and resuspended at $5x10^5$ cells/mL in RPMI-1640 supplemented with 2 mM L-glutamine (Lonza) but without penicillin/streptomycin (cRPMI). The cell suspension (2 mL; $1x10^6$ cells/well) is added to 35 mm (6 well) tissue culture plates (Corning) and incubated at 37 °C in a 5% CO_2, humidity-controlled incubator for 2-3 h. Plates are then washed to remove nonadherent cells (mostly lymphocytes), and adherent cells (monocytes) are cultured in cRPMI supplemented with 1% pooled human serum (MPBiomedical). Omadacycline (0.25 - 64 µg/mL in 4-fold increasing concentrations), minocycline hydrochloride (50 µg/mL; Sigma) or azithromycin dihydrate (20 µg/mL; Sigma) are added to duplicate wells and incubated for 3 hours. The concentrations of minocycline and azithromycin are chosen based on studies of antibiotic-mediated suppression of LPS-induced cytokine production in human monocyte cell lines (THP-1) and on our studies of azithromycin-mediated suppression of LPS-induced TNFα production in human mononuclear cells (Tai *et al.*, *Transl Res* 2013;161(2):99-109; Stevens *et al.*, *Program & Abstracts of the Infectious Disease Society of America*, San Francisco, CA [Session 53], 181. 1997, the entire contents of each of which are hereby incorporated herein by reference).

After antibiotic treatment, the cells are stimulated with LPS (*Escherichia coli* O113, Associates of Cape Cod, Woods Hole, MA; 100 ng/10^6 monocytes). Supernatants are collected at 6 and 24 hours, centrifuged to remove cellular debris, and immediately stored at -70 °C until assayed for cytokines of interest. These times are selected to capture cytokines and immune modulators produced relatively early (*e.g.*, TNFα, IL-1β) and later (e.g., IL-6, 1L-10, IFN-γ) in the immune response. Cells cultured in media without antibiotic pre-treatment followed by LPS stimulation are to serve as the negative antibiotic treatment control; non-antibiotic treated cells without LPS stimulation are to provide the background cytokine level. Individual pro-inflammatory cytokines (*i.e.*, TNFα, IL-1β), the anti-inflammatory mediator, IL-10, and the immune modulatory cytokine, interferon-gamma (IFNγ) in the overlying culture fluid are measured by commercial ELISA (R&D Systems).

The experiment is performed in duplicates and repeated a minimum of three separate times using unique donors. Concentrations of omadacycline used is to be confirmed as non-cytotoxic in initial dose-response studies and adjusted as necessary. Statistical comparisons between means of independent samples are done using Student t-test, with a level of

significance chosen at p <.05. The correlation coefficient is calculated to measure the degree of association between variables.

Efficacy of omadacycline in a mouse model of post-influenza MRSA pneumonia

The second goal of this experiment was to determine the effeicacy of omadacycline in a mouse model of post-influenza MRSA pneumonia. Secondary bacterial pneumonia caused by methicillin resistant *Staphylococcus aureus* (MRSA) is the leading cause of death in patients following influenza A infection. Post-influenza MRSA pneumonia is characterized by widespread intra-alveolar edema/hemorrhage and massive necrosis of alveoli, and, when present, these features predict poor outcomes. Despite the availability of anti-staphylococcal antibiotics, mortality remains high and survivors require prolonged intensive care hospitalization.

Recent studies in murine models have emphasized the role of inflammation in lung histopathology and mortality during influenza and MRSA pneumonia. For example, it was shown that influenza and MRSA coinfection was characterized by greater mortality and increased inflammation and more severe lung injury compared to MRSA infection alone (Lee *et al.*, *J Infect Dis* 2010; 201(4):508-515). This increased mortality was associated with evidence of greater pathological damage to the lung parenchyma, a higher grade bacteremia, increased metastatic seeding to the liver and kidney, and an altered cellular response to infection in the infected mice. It was proposed that influenza infection activates the lung epithelium to produce chemoattractants for neutrophils which, upon exposure to Panton Valentine Leukocidin (PVL)-expressing *S. aureus* (*e.g.*, USA300 MRSA), release abundant proteases that severely damage the airway epithelium (Niemann *et al.*, *J Infect Dis* 2012;206(7):1138-1148). These studies indicate that antibiotics with both anti-microbial and anti-inflammatory properties can profoundly impact disease severity and outcome in post-influenza bacterial pneumonia.

The experiment is to utilize a previously described murine model of post-influenza MRSA pneumonia (Parimon *et al.*, *Proceedings & Abstracts of the American Thoracic Society International Conference*. 2014), which is based on the studies of Lee *et al.*, *J Infect Dis* 2010; 201(4):508-515. The study is conducted in two phases. In Phase I, mice are intranasally co-infected with influenza A and MRSA and treated with varying doses of omadacycline, linezolid as a comparator; or saline as the negative treatment control. If

survival is improved with omadacycline compared to either saline- or linezolid-treated animals, a Phase II study is undertaken to examine if the therapeutic benefit is related to omadacycline-mediated improvement in pulmonary or systemic bacterial burden, lung histopathology and/or changes in pro- and anti-inflammatory cytokine elaboration in the lung or blood.

Detailed Methods:

Animal Studies

Co-infection Model: wild-type six-week old female BALB/c mice are anesthetized with ketamine and xylazine cocktail delivered intraperitoneally (IP) prior to infection with $1x10^3$ PFU of mouse-adapted Influenza A/Puerto Rico/8/34 (H1N1) (ATCC; VR-1469) in 50 µL sterile saline via intranasal inoculation. Three days later, $2 x10^8$ CFU washed stationary phase CA-MRSA (USA300; LAC strain), is administered intranasally in 50 µL using similar technique.

Phase I: Survival Studies

Animals are co-infected as described above and treated with omadacycline at 4, 16 or 64 mg/kg via subcutaneous injection beginning 2 hours after bacterial infection. These doses of omadacycline are chosen based on pharmacokinetic/pharmacodynamic studies in neutropenic murine models of *Streptococcus pneumoniae* or *Staphylococcus aureus* pneumonia (Lepak *et al.*, *Antimicrob Agents Chemother* 2019;63(3)) and in a model of soft tissue infection due to *S. aureus* (Lepak *et al.*, *Antimicrob Agents Chemother* 2019;63(7)). Omadacycline doses are also informed by pharmacokinetic data from Paratek Pharmaceuticals, Inc. in this mouse species. Linezolid (120 mg/kg; via subcutaneous injection) serves as comparator antibiotic; as this dose of linezolid has been shown to be efficacious in an immunocompetent Balb/c MRSA pneumonia model (Tessier *et al.*, *Antimicrob Agents Chemother* 2012;56(5):2342-2346). Sterile saline serves as a negative treatment control.

Treatments are to continue q 12 h for 6 days; survival is followed for 14 days. Animals are scored daily for mortality and for signs of systemic infection, including weight loss. Any animal that develops signs/symptoms of pain or distress (*e.g.*, self-isolation, hunched posture, decreased activity and ruffled fur) is given buprenorphine (Rickitt

Benckiser Pharmaceuticals Inc; 0.1 mg/kg in 500 µL every 12 h or as needed) subcutaneously in the scruff of the neck. Animals suspected of being moribund (*e.g.*, do not move when handled, display labored breathing) are removed from the study and sacrificed by an overdose of ketamine plus xylazine cocktail (ketamine (500 mg/kg) plus xylazine (50 mg/kg)) i.p. in 250 µL sterile saline) and are counted toward mortality. Survival of animals co-infected with IAV plus MRSA, in the absence of treatment, is expected to be ≤40%, and animals exhibit significant weight loss and systemic symptoms of illness.

The number of animals used for survival analysis is as follows: Groups 1, 2, 3 (N=60): omadacycline at 4, 16 or 64 mg/kg; given SQ q 12 hours; Group 3 (N=20): linezolid at 120 mg/kg; given SQ q 12 hours; Group 4 (N=20): saline negative treatment control; given SQ q 12 hours.

Antibiotic Blood Level Determinations: Non-infected mice (3 mice/group) are administered 3 doses of either omadacycline (at 4, 16, or 64 mg/kg; SQ q 12 hours) or Linezolid (120 mg/kg subcutaneously q 12 h). Drug levels (mg/L) are measured in plasma and BALF at 1 hour after the last antibiotic dose. Groups 1, 2, 3 (N=9): Omadacycline at 4, 16 or 64 mg/kg; Group 2 (N=3): Linezolid at 120 mg/kg

Statistical Analyses: Animal experiments are performed once. Survival data are analyzed using a Kaplan-Meier survival probability estimate and the difference in each group will be determined by Wald Chi-Square. Significant differences among groups in weight loss and wellness scores are determined by two-tailed, unequal variance Student's t-test. Statistical significance is defined as $p < 0.05$.

Phase II: Pathology and Immunologic Response Studies

Phase II of the experiment is carried out if it is determined in Phase I that omadacycline improves survival of the murine model of post-influenza MRSA pneumonia. The goal of Phase II of the experiment is to determine whether the clinical benefit observed in Phase I is associated with reduced lung injury and/or cytokine production.

Detailed Methods: Mice (3/group/time point) are to receive a single dose of omadacycline deemed optimal based on survival studies in Phase I, beginning 2 hours after

bacterial challenge. Linezolid (120 mg/kg; via subcutaneous injection) serves as comparator antibiotic; this dose of linezolid has been shown to be efficacious in an immunocompetent Balb/c MRSA pneumonia model (Tessier *et al.*, *Antimicrob Agents Chemother* 2012;56(5):2342-2346) and produced a lung epithelial lining fluid (ELF) exposure comparable to that observed in humans following an intravenous regimen of 600 mg linezolid q 12 h. Sterile normal saline, given *via* the same route and on the same schedule, serves as the negative treatment control. Treatments continue q 12 hrs for 4 days.

Infection severity is assessed by lung histopathology, bacterial burden in the lung and cytokine elaboration in blood and broncho-alveolar lavage fluid (BALF) at 6, 12, 24 and 48 hours post-bacterial challenge. For this, mice are anesthetized and blood samples are collected for circulating cytokine measurements. Afterwards, mice are sacrificed by an overdose of a ketamine/xylazine cocktail (ketamine, 500 mg/kg plus xylazine, 50 mg/kg delivered intraperitoneally in 250 µL sterile saline). Tracheas are immediately lavaged twice with 1 mL of ice-cold PBS via catheter. Collected BALF is centrifuged at 2,000 rpm for 5 min at 4 °C, and the supernatants are collected and stored at −80 °C until assayed for cytokines of interest (see below) and determination of total protein content. Red cells in the resultant pellet are lysed and remaining cells are diluted to $1x10^6$/mL in ice-cold PBS. Differential cell counts are performed on cytological preparations (cytospin 500*g*, 3 min) that have been fixed and stained with Hema-3 stain (ThermoFisher) according to the manufacturer's instructions. Cells (≥400/preparation) are counted under a light microscope and the number of neutrophils expressed as the absolute number from the total cell counts.

After collection of BALF, lungs are instilled with 0.9 ml of 3.7% buffered formaldehyde in PBS via a tracheal cannula and removed from the thorax. To evaluate lung bacterial burden, the right upper lung from each animal is excised and weighed, then used for quantitative bacteriology. The remaining lung tissue is immersed in 3.7% buffered formaldehyde for 24 hours followed by paraffin embedding and routine histological processing. Lung tissue sections (4-6 um thick) are placed on standard microscope slides and stained with hematoxylin and eosin (H&E). Lung injury is graded by a blinded Clinical & Anatomical Pathologist on 5 microscopic fields from 0 (normal) to 4 (severe) in four categories: neutrophil infiltration, congestion, edema and alveolar wall thickness. A Lung Injury Score (LIS) for each animal is defined as the sum of the 4 category severity scores.

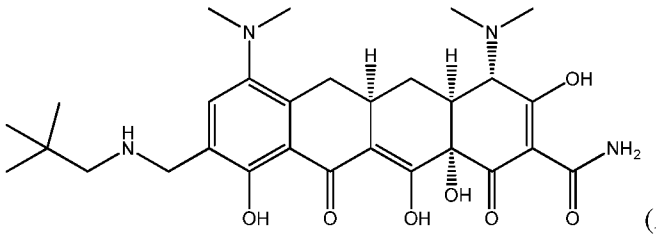
Immune Response Studies: Cytokines TNF-α, IL-6 and IL-10 in blood and BALF are measured by commercial ELISA kits (R&D systems, MN) according to the manufacturer's instructions.

Number of Balb/C mice needed = 36, with 3 animals/treatment group x 3 treatment groups x 4 time points = 36 mice, including the following groups: Group 1 (N=12): omadacycline at single optimal dose from Phase I; given SQ q 12 hours; Group 2 (N=12): Linezolid (Sigma) at 120 mg/kg; SQ q 12 hours; and Group 3 (N=12): Saline negative treatment control; given by SQ injection q 12 hours.

CLAIMS

What is claimed is:

1. A method of treating or preventing a viral infection in a subject in need thereof, said method comprising administering to said subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that said viral infection in said subject is treated or prevented.

2. The method of claim 1, wherein said viral infection is caused by a virus belonging to a family selected from the group consisting of *Abyssoviridae, Ackermannviridae, Adenoviridae, Alloherpesviridae, Alphaflexiviridae, Alphasatellitidae, Alphatetraviridae, Alvernaviridae, Amalgaviridae, Amnoonviridae, Ampullaviridae, Anelloviridae, Arenaviridae, Arteriviridae, Artoviridae, Ascoviridae, Asfaviridae, Aspiviridae, Astroviridae, Autographiviridae, Avsunviroidae, Baccilladnaviridae, Baculoviridae, Barnaviridae, Belpaoviridae, Benyviridae, Betaflexiviridae, Bicaudaviridae, Bidnaviridae, Birnaviridae, Bornaviridae, Botourmiarividae, Bromoviridae, Calicviridae, Carmotetraviridae, Caulimoviridae, Chaseviridae, Chrysoviridae, Chuviridae, Circoviridae, Clavaviridae, Closteroviridae, Coronaviridae, Corticoviridae, Cremegaviridae, Cruliviridae, Cystoviridae, Deltaflexiviridae, Demerecviridae, Cicistroviridae, Drexlerviridae, Endomaviridae, Euroniviridae, Filoviridae, Fimoviridae, Finnalakeviridae, Flaviviridae, Fuselloviridae, Gammaflexiviridae, Geminiviridae, Genomoviridae, Globuloviridae, Gresnaviridae, Guttaviridae, Halspiviridae, Hantaviridae, Hepadnaviridae, Hepeviridae, Herelleviridae, Herpesviridae, Hypoviridae, Hytrosaviridae, Iflaviridae, Inoviridae, Iridoviridae, Kitaviridae, Lavidaviridae, Leishbuviridae, Leviviridae, Lipothrixviridae, Lispiviridae, Luteoviridae, Malacoherperviridae, Marnaviridae, Marseilleviridae, Matonaviridae, Mayoviridae, Medionviridae, Megabirnaviridae, Mesoniviridae, Metaviridae, Microviridae, Mimiviridae, Mitoviridae, Mononiviridae, Mymonaviridae, Myoviridae, Mypoviridae, Nairoviridae,*

Nanghoshaviridae, Nanhypoviridae, Nanoviridae, Narnaviridae, Nimaviridae, Nodaviridae, Nudiviridae, Nyamiviridae, Olifoviridae, Orthomyxoviridae, Ovaliviridae, Papillomaviridae, Paramyxoviridae, Partitiviridae, Parvoviridae, Peribunyaviridae, Permutotetraviridae, Phasmaviridae, Phenuiviridae, Phycodnaviridae, Picobimaviridae, Picornaviridae, Plasmaviridae, Plectroviridae, Pleolipoviridae, Pneumoviridae, Podoviridae, Polycipiviridae, Polydnaviridae, Polymycoviridae, Polymaviridae, Portogloboviridae, Pospiviroidae, Potyviridae, Poxviridae, Pseudoviridae, Qinviridae, Quadrivirdae, Redondoviridae, Reoviridae, Retroviridae, Rhabdoviridae, Roniviridae, Rudiviridae, Sarthroviridae, Secoviridae, Sinhaliviridae, Siphviridae, Smacoviridae, Solemoviridae, Solinviviridae, Sphaerolipoviridae, Spiraviridae, Sunviridae, Tectiviridae, Thaspiviridae, Tobaniviridae, Togaviridae, Tolecusatellitidae, Tombusviridae, Tospoviridae, Totiviridae, Tristromaviridae, Turniviridae, Tymoviridae, Virgaviridae, Wupedeviridae, Xinmoviridae and Yueviridae.

3. The method of claim 2, wherein the virus belongs to a family *Coronaviridae*.

4. The method of claim 3, wherein the virus belongs to a genus selected from the group consisting of *Alphaletovirus, Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus*.

5. The method of claim 4, wherein the virus belongs to a genus *Betacoronavirus*.

6. The method of claim 5, wherein the virus belongs to a species selected from the group consisting of *Betacoronavirus 1, China Rattus coronavirus HKU24, Human coronavirus HKU1, Murine coronavirus, Myodes coronavirus 2JL14, Bat Hp-betacoronavirus Zhejiang2013, Hedgehog coronavirus 1, Middle East respiratory syndrome-related coronavirus, Pipistrellus bat coronavirus HKU5, Tylonycteris bat coronavirus HKU4, Eidolon bat coronavirus C704, Rousettus bat coronavirus GCCDC1, Rousettus bat coronavirus HKU9 and Severe acute respiratory syndrome-related coronavirus*.

7. The method of claim 6, wherein the virus belongs to a species *Severe acute respiratory syndrome-related coronavirus*.

8. The method of claim 7, wherein the virus is selected from the group consisting of SARSr-CoV BtKY72, SARS-CoV-2, SARSr-CoV RaTG13, SARS-CoV PC4-227 and SARS-CoV.

9. The method of claim 8, wherein the virus is SARS-CoV-2.

10. The method of claim 9, wherein the subject has Coronavirus disease 2019 {COVID-19).

11. The method of claim 3 or 4, wherein the virus is selected from the group consisting of MERS-CoV, HCoV HKU1, HCoV OC43, HCoV NL63 and HCoV 229E.

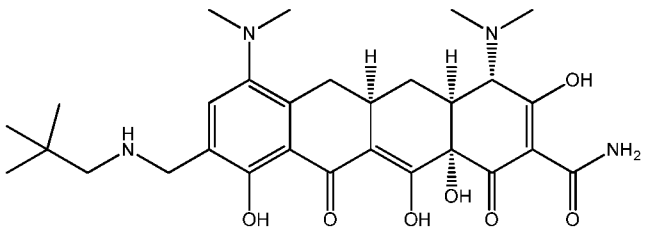
12. The method of claim 2, wherein the virus belongs to family *Orthomyxoviridae*.

13. The method of claim 12, wherein said virus belongs to a genus selected from the group consisting of *Alphainfluenzavirus*, *Betainfluenzavirus*, *Deltainfluenzavirus* and *Gammainfluenzavirus*.

14. The method of claim 13, wherein said virus belongs to a species selected from the group consisting of *Influenza A virus*, *Influenza B virus*, *Influenza D virus* and *Influenza C virus*.

15. The method of any one of claims 1-14, wherein administering the tetracycline compound or a pharmaceutically acceptable salt thereof leads to a reduction in viral load in the subject.

16. A method of treating or preventing SARS-CoV-2 infection in a subject in need thereof, said method comprising administering to said subject an effective amount of a tetracycline compound represented by formula (A):



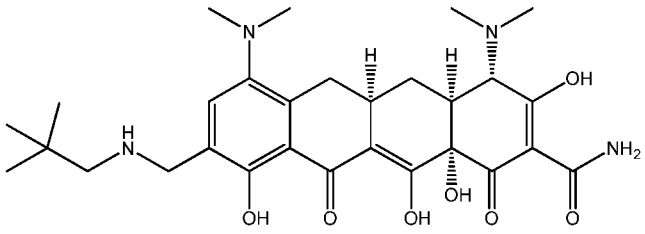
(A),

or a pharmaceutically acceptable salt thereof, such that said SARS-CoV-2 infection in said subject is treated or prevented.

17. The method of claim 15, wherein the subject has COVID-19.

18. The method of claim 16 or 17, wherein administering of the tetracycline compound leads to a reduction in the load of SARS-CoV-2 virus in said subject.

19. A method of treating or preventing a viral disease in a subject in need thereof, said method comprising administering to said subject an effective amount of a tetracycline compound represented by formula (A):



(A),

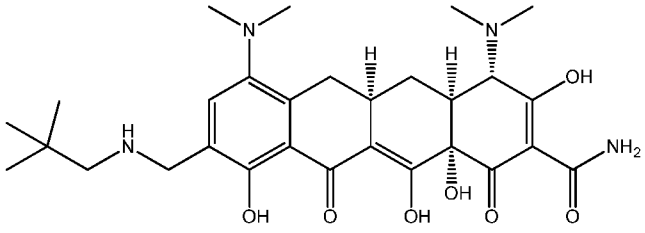
or a pharmaceutically acceptable salt thereof, such that said viral disease in said subject is treated or prevented.

20. The method of claim 19, wherein said viral disease is selected from the group consisting of gastroenteritis, keratoconjunctivitis, pharyngitis, croup, pneumonia, cystitis, hand, food and mouth disease, pleurodynia, meningitis, pericarditis, myocarditis, infectious mononucleosis, hepatitis, hepatic cirrhosis, cytomegalic inclusion disease, AIDS, Dengue fever, influenza, measles, postinfections encephalomyelitis, mumps, common cold, rabies, viral encephalitis, disease caused by West Nile virus, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19.

21. The method of claim 20, wherein said viral disease is COVID-19.

22. The method of any one of claims 17-21, wherein administering of the tetracycline compound leads to a reduction in viral load in the subject.

23. A method of treating or preventing COVID-19 in a subject in need thereof, said method comprising administering to said subject an effective amount of a tetracycline compound represented by formula (A):

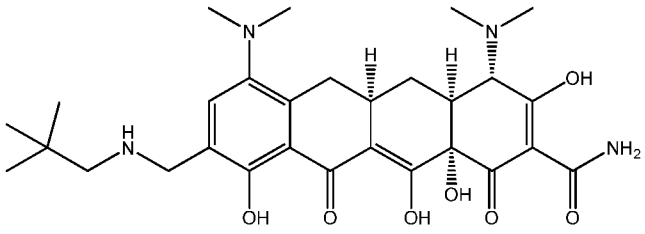


(A),

or a pharmaceutically acceptable salt thereof, such that said COVID-19 in said subject is treated or prevented.

24. The method of claim 23, wherein administering of the tetracycline compound leads to a reduction in the load of SARS-CoV-2 virus in the subject.

25. A method of modulating an immune response in a subject in need thereof, said method comprising administering to said subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that said immune response in said subject is modulated.

26. The method of claim 25, wherein the subject has a viral infection or is at a high risk of said viral infection.

27. The method of claim 26, wherein said viral infection is caused by a virus belonging to a family selected from the group consisting of *Abyssoviridae, Ackermannviridae, Adenoviridae, Alloherpesviridae, Alphaflexiviridae, Alphasatellitidae, Alphatetraviridae, Alvernaviridae, Amalgaviridae, Amnoonviridae, Ampullaviridae, Anelloviridae, Arenaviridae, Arteriviridae, Artoviridae, Ascoviridae, Asfaviridae, Aspiviridae, Astroviridae, Autographiviridae, Avsunviroidae, Baccilladnaviridae, Baculoviridae, Barnaviridae, Belpaoviridae, Benyviridae, Betaflexiviridae, Bicaudaviridae, Bidnaviridae, Birnaviridae, Bornaviridae, Botourmiarividae, Bromoviridae, Caliciviridae, Carmotetraviridae, Caulimoviridae, Chaseviridae, Chrysoviridae, Chuviridae, Circoviridae, Clavaviridae,*

Closteroviridae, Coronaviridae, Corticoviridae, Cremegaviridae, Cruliviridae, Cystoviridae, Deltaflexiviridae, Demerecviridae, Cicistroviridae, Drexlerviridae, Endomaviridae, Euroniviridae, Filoviridae, Fimoviridae, Finnalakeviridae, Flaviviridae, Fusselloviridae, Gammaflexiviridae, Geminiviridae, Genomoviridae, Globuloviridae, Gresnaviridae, Guttaviridae, Halspiviridae, Hantaviridae, Hepadnaviridae, Hepeviridae, Herelleviridae, Herpesviridae, Hypoviridae, Hytrosaviridae, Iflaviridae, Inoviridae, Iridoviridae, Kitaviridae, Lavidaviridae, Leishbuviridae, Leviviridae, Lipothrixviridae, Lispiviridae, Luteoviridae, Malacoherperviridae, Marnaviridae, Marseilleviridae, Matonaviridae, Mayoviridae, Medionviridae, Megabirnaviridae, Mesoniviridae, Metaviridae, Microviridae, Mimiviridae, Mitoviridae, Mononiviridae, Mymonaviridae, Myoviridae, Mypoviridae, Nairoviridae, Nanghoshaviridae, Nanhypoviridae, Nanoviridae, Narnaviridae, Nimaviridae, Nodaviridae, Nudiviridae, Nyamiviridae, Olifoviridae, Orthomyxoviridae, Ovaliviridae, Papillomaviridae, Paramyxoviridae, Partitiviridae, Parvoviridae, Peribunyaviridae, Permutotetraviridae, Phasmaviridae, Phenuiviridae, Phycodnaviridae, Picobimaviridae, Picornaviridae, Plasmaviridae, Plectroviridae, Pleolipoviridae, Pneumoviridae, Podoviridae, Polycipiviridae, Polydnaviridae, Polymycoviridae, Polymaviridae, Portogloboviridae, Pospiviroidae, Potyviridae, Poxviridae, Pseudoviridae, Qinviridae, Quadrivirdae, Redondoviridae, Reoviridae, Retroviridae, Rhabdoviridae, Roniviridae, Rudiviridae, Sarthroviridae, Secoviridae, Sinhaliviridae, Siphviridae, Smacoviridae, Solemoviridae, Solinviviridae, Sphaerolipoviridae, Spiraviridae, Sunviridae, Tectiviridae, Thaspiviridae, Tobaniviridae, Togaviridae, Tolecusatellitidae, Tombusviridae, Tospoviridae, Totiviridae, Tristromaviridae, Turniviridae, Tymoviridae, Virgaviridae, Wupedeviridae, Xinmoviridae and Yueviridae.

28. The method of claim 27, wherein the virus belongs to a family *Coronaviridae.*

29. The method of claim 28, wherein the virus belongs to a genus selected from the group consisting of *Alphaletovirus, Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus.*

30. The method of claim 29, wherein the virus belongs to a genus *Betacoronavirus.*

31. The method of claim 30, wherein the virus belongs to a species selected from the group consisting of *Betacoronavirus 1, China Rattus coronavirus HKU24, Human coronavirus HKU1, Murine coronavirus, Myodes coronavirus 2JL14, Bat Hp-betacoronavirus Zhejiang2013, Hedgehog coronavirus 1, Middle East respiratory syndrome-*

related coronavirus, Pipistrellus bat coronavirus HKU5, Tylonycteris bat coronavirus HKU4, Eidolon bat coronavirus C704, Rousettus bat coronavirus GCCDC1, Rousettus bat coronavirus HKU9 and Severe acute respiratory syndrome-related coronavirus.

32. The method of claim 31, wherein the virus belongs to a species *Severe acute respiratory syndrome-related coronavirus.*

33. The method of claim 32, wherein the virus is SARSr-CoV BtKY72, SARS-CoV-2, SARSr-CoV RaTG13, SARS-CoV PC4-227 and SARS-CoV.

34. The method of claim 33, wherein the virus is SARS-CoV-2.

35. The method of claim 34, wherein the subject has COVID-19.

36. The method of claim 27, wherein said virus that belongs to a family *Orthomyxoviridae.*

37. The method of claim 36, wherein said virus belongs to a genus selected from the group consisting of *Alphainfluenzavirus*, *Betainfluenzavirus*, *Deltainfluenzavirus* and *Gammainfluenzavirus.*

38. The method of claim 37, wherein said virus belongs to a species selected from the group consisting of *Influenza A virus*, *Influenza B virus*, *Influenza D virus* and *Influenza C virus.*

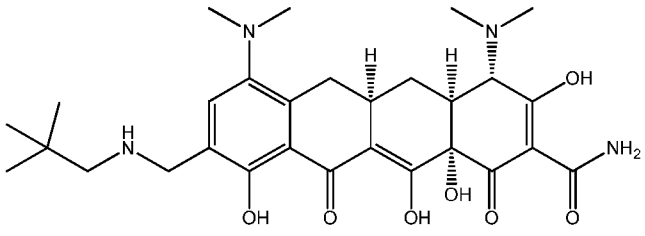
39. The method of claim 25, wherein the subject has a viral disease.

40. The method of claim 39, wherein said viral disease is selected from the group consisting of gastroenteritis, keratoconjunctivitis, pharyngitis, croup, pneumonia, cystitis, hand, food and mouth disease, pleurodynia, meningitis, pericarditis, myocarditis, infectious mononucleosis, hepatitis, hepatic cirrhosis, cytomegalic inclusion disease, AIDS, Dengue fever, influenza, measles, postinfections encephalomyelitis, mumps, common cold, rabies, viral encephalitis, disease caused by West Nile virus and COVID-19.

41. The method of claim 40, wherein said viral disease is COVID-19.

42. The method of claim 40, wherein said viral disease is influenza.

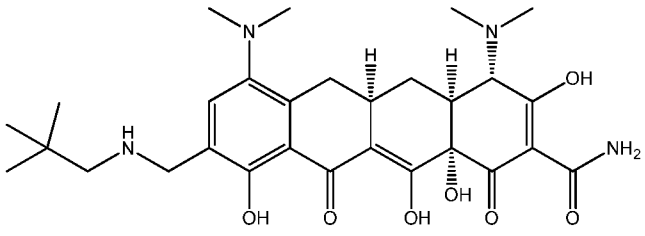
43. A method of modulating an immune response in a subject with a SARS-CoV-2 infection, said method comprising administering to said subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that said immune response in said subject is modulated.

44. A method of modulating an immune response in a subject afflicted with COVID-19, said method comprising administering to said subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that said immune response in said subject is modulated.

45. The method of any one of claims 25-44, wherein administering of the tetracycline compound modulates at least one inflammatory biomarker in said subject.

46. The method of claim 45, wherein said inflammatory biomarker is selected from the group consisting of C-reactive protein (CRP), leukocyte count, neutrophil count, monocyte count, eosinophil count, basophil count, erythrocyte sedimentation count, serum ferritin, white blood cell count (WBC count), serum amyloid A (SAA), procalcitonin (PCT), tumor necrosis factor α (TNF-α), interferon-γ (INF-γ), interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-12 (IL-12), interleukin-15 (IL-15), interleukin-18 (IL-18), interleukin-1β (IL-1β), colony-stimulating factor 2 (CSF 2), colony-

stimulating factor 3 (CSF 3), nitric oxide synthase (iNOS), monokine induced by gamma (MIG), CXCL1 (KC Protein), interferon gamma-induced protein 10 (IP-10), a methyl-accepting chemotaxis protein (MCP), an Intercellular Adhesion Molecule (ICAM), a metalloproteinase, a macrophage inflammatory protein, a complement protein, and a prostaglandin.

47. The method of any one of claims 9, 10, 16, 17, 21, 23, 34, 35, 41, 43 and 44, wherein administering of the tetracycline compound alleviates at least one symptom associated with COVID-19 in said subject.

48. The method of claim 47, wherein the at least one symptom associated with COVID-19 is selected from the group consisting of fever, body ache, muscle and joint pain, dry cough, fatigue, chills, headache, sore throat, shortness of breath, sputum production, hemoptysis, sneezing, runny nose, chest tightness, palpitation, a neurological symptom and a gastrointestinal (GI) symptom.

49. The method of claim 48, wherein said neurological symptom is selected from the group consisting of decreased sense of smell, inability to taste, muscle weakness, tingling or numbness in the hands and feet, dizziness, confusion, delirium, seizure and stroke.

50. The method of claim 48, wherein said GI symptom is selected from the group consisting of loss of appetite, nausea, vomiting, diarrhea and abdominal pain or discomfort.

51. The method of any one of claims 9, 10, 16, 17, 21, 23, 34, 35, 41, 43 and 44, wherein administering of the tetracycline compound prevents at least one complication associated with COVID-19 in said subject.

52. The method of claim 51, wherein said at least one complication associated with COVID-19 is selected from the group consisting of acute respiratory failure, pneumonia, acute respiratory distress syndrome (ARDS), sepsis associated syndrome, acute liver injury, acute cardiac injury, acute kidney injury, disseminated intravascular coagulation (DIC), blood clots and rhabdomyolysis.

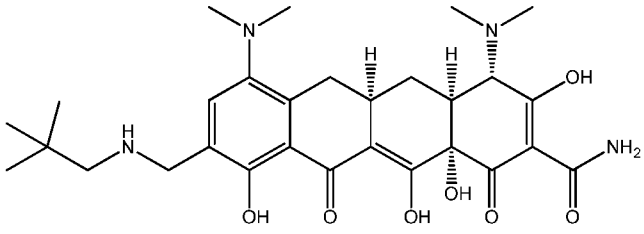
53. The method of claim 52, wherein said pneumonia is secondary bacterial pneumonia.

54. The method of claim 52, wherein said sepsis associated state is systemic inflammatory response syndrome (SIRS).

55. The method of claim 54, wherein said SIRS comprises cytokine storm syndrome (CSS).

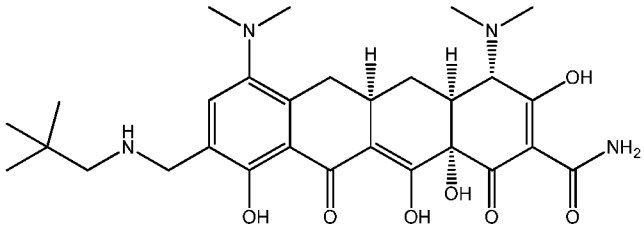
56. The method of claim 52, wherein said sepsis associated state is septic shock.

57. A method of preventing secondary bacterial pneumonia in a subject with a viral infection, said method comprising administering to said subject an effective amount of a tetracycline compound represented by formula (A):


(A),

or a pharmaceutically acceptable salt thereof, such that said secondary bacterial pneumonia in said subject is prevented.

58. A method of reducing the severity of secondary bacterial pneumonia in a subject with a viral infection, said method comprising administering to said subject an effective amount of a tetracycline compound represented by formula (A):


(A),

or a pharmaceutically acceptable salt thereof, such that the severity of said secondary bacterial pneumonia in said subject is reduced.

59. The method of claim 57 or 58, wherein said viral infection is caused by a virus that belongs to a family *Coronaviridae*.

60. The method of claim 59, wherein the virus belongs to a genus selected from the group consisting of *Alphaletovirus, Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus*.

61. The method of claim 60, wherein the virus belongs to a genus *Betacoronavirus*.

62. The method of claim 61, wherein the virus belongs to a species selected from the group consisting of *Betacoronavirus 1, China Rattus coronavirus HKU24, Human coronavirus HKU1, Murine coronavirus, Myodes coronavirus 2JL14, Bat Hp-betacoronavirus Zhejiang2013, Hedgehog coronavirus 1, Middle East respiratory syndrome-related coronavirus, Pipistrellus bat coronavirus HKU5, Tylonycteris bat coronavirus HKU4, Eidolon bat coronavirus C704, Rousettus bat coronavirus GCCDC1, Rousettus bat coronavirus HKU9 and Severe acute respiratory syndrome-related coronavirus*.

63. The method of claim 62, wherein the virus belongs to a species *Severe acute respiratory syndrome-related coronavirus*.

64. The method of claim 63, wherein the virus is SARSr-CoV BtKY72, SARS-CoV-2, SARSr-CoV RaTG13, SARS-CoV PC4-227 and SARS-CoV.

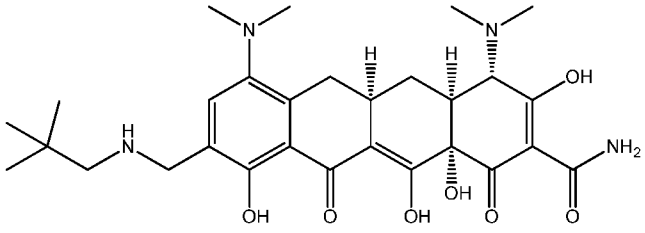
65. The method of claim 64, wherein the virus is SARS-CoV-2.

66. The method of claim 57 or 58, wherein said viral infection is caused by a virus that belongs to a family *Orthomyxoviridae*.

67. The method of claim 66, wherein said virus belongs to a genus selected from the group consisting of *Alphainfluenzavirus*, *Betainfluenzavirus*, *Deltainfluenzavirus* and *Gammainfluenzavirus*.

68. The method of claim 67, wherein said virus belongs to a species selected from the group consisting of *Influenza A virus*, *Influenza B virus*, *Influenza D virus* and *Influenza C virus*.

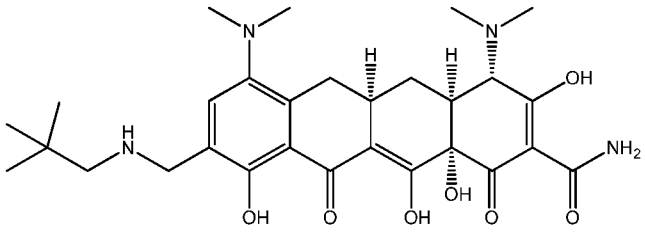
69. A method of preventing secondary bacterial pneumonia in a subject afflicted with a viral disease, said method comprising administering to said subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that said secondary bacterial pneumonia in said subject is prevented.

70. A method of reducing the severity of secondary bacterial pneumonia in a subject afflicted with a viral disease, said method comprising administering to said subject an effective amount of a tetracycline compound represented by formula (A):



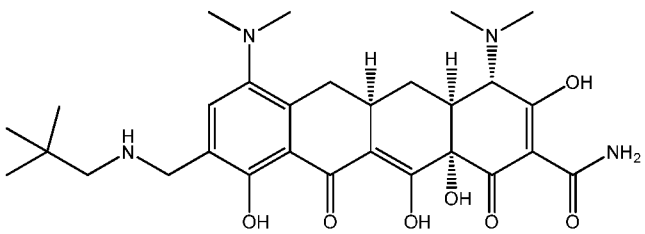
(A),

or a pharmaceutically acceptable salt thereof, such that the severity of said secondary bacterial pneumonia in said subject is reduced.

71. The method of claim 69 or 70, wherein said viral disease is COVID-19.

72. The method of claim 69 or 70, wherein said viral disease in influenza.

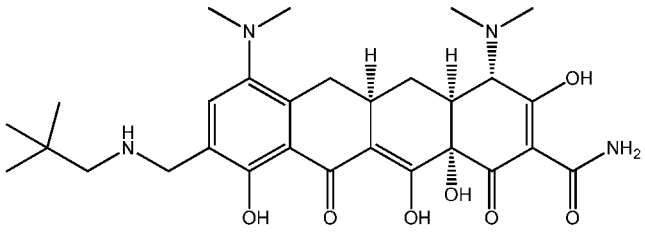
73. A method of preventing secondary bacterial pneumonia in a subject with a SARS-CoV-2 infection, said method comprising administering to said subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that said secondary bacterial pneumonia in said subject is prevented.

74. A method of reducing the severity of secondary bacterial pneumonia in a subject with a SARS-CoV-2 infection, said method comprising administering to said subject an effective amount of a tetracycline compound represented by formula (A):



(A),

or a pharmaceutically acceptable salt thereof, such that the severity of said secondary bacterial pneumonia in said subject is reduced.

75. The method of any one of claims 65, 71, 73 and 74, wherein the administering of the tetracycline compound prevents at least one complication associated with COVID-19.

76. The method of claim 75, wherein said at least one complication associated with COVID-19 is selected from the group consisting of acute respiratory failure, pneumonia, acute respiratory distress syndrome (ARDS), sepsis associated syndrome, acute liver injury, acute cardiac injury, acute kidney injury, disseminated intravascular coagulation (DIC), blood clots and rhabdomyolysis.

77. The method of claim 76, wherein said sepsis associated state is systemic inflammatory response syndrome (SIRS).

78. The method of claim 77, wherein said SIRS comprises cytokine storm syndrome (CSS).

79. The method of claim 76, wherein said sepsis associated state is septic shock.

80. The method of any one of claims 57, 58, 69, 70, 73, 74, wherein said subject has no known bacterial infection.

81. The method of any one of claims 1-80, wherein said tetracycline compound is administered in combination with at least one additional therapeutic agent.

82. The method of claim 81, wherein said at least one additional therapeutic agent is selected from the group consisting of an antiviral agent, an antibacterial agent, an anti-parasitic agent, an immunomodulatory agent and a therapeutic antibody.

83. The method of claim 82, wherein said antiviral agent is selected from the group consisting of remdesivir, favipiravir, umifenovir, azvudine, baloxavir marboxil, danoprevir, lopinavir, ritonavir, sofosbuvir, valacyclovir, darunavir, cobicistat, inosine pranobex, EIDD-2801, BLD-2660, triazavirin, and ribavirin.

84. The method of claim 82, wherein said antibacterial agent is selected from the group consisting of a penicillin, a tetracycline, a cephalosporin, a quinolone, a lincomycin, a macrolide, a sulfonamide, a glycopeptide, an aminoglycoside and a carbapenem.

85. The method of claim 84, wherein said antibacterial agent is a macrolide selected from the group consisting of azithromycin, clarithromycin, erythromycin, spiramycin, teicoplanin, oritavancin, dalbavancin and monensin.

86. The method of claim 82, wherein said antibacterial agent is selected from the group consisting of sulfamethoxazole/trimethoprim, kolimycin, minocycline, doxycycline and azithromycin.

87. The method of claim 82, wherein said antiparasitic agent is selected from the group consisting of chloroquine, hydroxychloroquine, nitazoxanide, mefloquine, levamisole, suramin, and ivermectin.

88. The method of claim 82, wherein said immunomodulatory agent is selected from the group consisting of interferon beta, ciclesonide, colchicine, a corticosteroid, leflunomide, baricitinib, sirolimus, tacrolimus, tetrandrine, tranilast, an NSAID, aescin, anakinra, fingolimod, XPro1595, and a neutralizing antibody against a cytokine associated with a cytokine storm.

89. The method of claim 82, wherein said therapeutic antibody is selected from the group consisting of tocilizumab, sarilumab, bevacizumab, eculizamab, avdoralimab, canakinumab, ravalizumab, clazakizumab, nivolumab, BMS-986253, emapalumab, ixekizumab, leronimab, lenziulumab, ixekizumab, mepolizumab, siltuximab, IFX-1, TJ003234 and an anti-PD-1 antibody.

90. The method of claim 81, wherein said at least one additional therapeutic agent is selected from the group consisting of peginterferon lambda-1a, formoterol, Cd24f, CM4620, LY3127804, OM-85, MRx-4DP0004, recombinant tissue-Plasminogen Activator (rt-PA), viral macrophage inflammatory protein (vMIP), granulocyte-colony stimulating factor (G-CSF), human alpha-1 proteinase inhibitor, human antithrombin-III, human angiotensin-converting enzyme 2, vafidemstat, nafamostat, lenalidomide, Jakotinib, tofacitinib, itraconazole, ruxolitinib, acalabrutinib, estradiol, progesterone, dexmedetomidine, solnatide, etoposide, enoxaparin, vazegepant, linagliptin, sitagliptin, dalargin, hyperbaric oxygen, nitric oxide, ozone, bismuth potassium citrate, chlorine phosphate (Arechin), ramipril, spironolactone, sevoflurane, bromhexine, IB-MECA (methyl 1-[N6-(3-iodobenzyl)-adenin-9-yl]-b-D-ribofuronamide), pyridostigmine, chlorpromazine, ciclesonide, methotrexate, fluvoxamine, losartan, APN01, melatonin, curcumin, metmorfin, angiotensin, imatinib, nintedanib, noscapine, sargramostim, selinexor, isotretinoin, prazosin, defibrotide, brilacidin, griffithsin, an anticoagulant, an anti-hypertensive, famotidine, dipyridamole, sildenafil, avipladil, tradipitant, bezafibrate, fenofibrate, intravenous vitamin C, dapagliflozin, a statin, alteplase, almitrine, deferoxamine, Sn-protoporphyrin IX (SnPPIX), sulfonatoporphyrin(TPPS), polyinosinic:polycytidylic acid, lipoic acid, amiodarone, verapamil, tranexamic acid, dornase alfa, thalidomide, berberine, REGN3048, TZLS-501, AT-001, PUL-042, crocetin, an ACE inhibitor (*e.g.*, captopril), Crostop solution, Croguard syrup, zinc, lithium, heparin, tinzaparin, fondaparinux, clopidogrel, tirofiban, eicosapentaenoic acid, medium-chain triglycerides (MCTs), vitamin A, vitamin D, a derivative of vitamin D, Zofa (Hyssop) syrup, pirfenidone, valsartan, camostat, enoxaparin, intravenous immunoglobulin, extracorporeal blood purification, mesenchymal stem cell therapy, hydrogen-oxygen inhalation, extracorporeal membrane oxygenation (ECMO), hemodialysis, and convalescent plasma.

91. The method of any one of claims 1-90, wherein said subject is a human.

92. The method of claim 91, wherein said subject is over 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 years old or older.

93. The method of claim 91 or 92, wherein said subject has a pre-existing or underlying condition selected from the group consisting of: hypertension, diabetes mellitus, a cardiovascular disease, cancer, chronic kidney disease, liver disease, excess weight and a respiratory disease.

94. The method of claim 93, wherein the respiratory disease comprises chronic lung disease, asthma or lung damage.

95. The method of claim 94, wherein said lung damage is associated with smoking or drug use.

96. The method of any one of claims 91-95, wherein said subject is immunocompromised.

97. The method of claim 96, wherein said subject is immunocompromised due to one of more of the following: undergoing cancer treatment, undergoing organ transplantation, having an immune deficiency, smoking, or prolonged use of immune weakening medication.

98. The method of any one of claims 1-95, wherein said subject is a male.

99. The method of any one of claims 1-98, wherein the tetracycline compound, or a pharmaceutically acceptable salt thereof, is administered parenterally, orally, topically or via an aerosol.

100. The method of claim 99, wherein the tetracycline compound, or a pharmaceutically acceptable salt thereof, is administered parenterally.

101. The method of claim 100, wherein the tetracycline compound, or a pharmaceutically acceptable salt thereof, is administered intravenously.

102. The method of claim 101, wherein the tetracycline compound, or a pharmaceutically acceptable salt thereof, is administered intravenously at a dose of about 100 to about 300 mg.

103. The method of claim 102, wherein the tetracycline compound, or a pharmaceutically acceptable salt, ester or a prodrug thereof, is administered intravenously at a dose of about 100 mg, about 150 mg, about 200 mg, about 250 mg or about 300 mg.

104. The method of claim 99, wherein the tetracycline compound, or a pharmaceutically acceptable salt thereof, is administered orally.

105. The method of claim 104, wherein the tetracycline compound, or a pharmaceutically acceptable salt thereof, is administered orally at a dose of about 150 to about 600 mg.

106. The method of claim 105, wherein the tetracycline compound, or a pharmaceutically acceptable salt thereof, is administered orally at a dose of about 150, about 300 mg, about 450 mg or about 600 mg.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/31608

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/65; C07C 237/26; A61P 31/12 (2021.01)

CPC - A61K 31/65; C07C 237/26; A61P 31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y --- A	US 2014/0309199 A1 (PARATEK PHARMACEUTICALS, INC.) 16 October 2014 (16.10.2014) para [0048], [0121]-[0125], [0143]	1, 19-20, 25-26, 39-40, (45-46)/(25-26,39-40), 57-58, 69-70, 80/(57-58,69-70) --- 2, 27, (45-46)/27 --- 3-14, 16-18, 21, 23-24, 28-38, 41-44,(45-46)/(28-38, 41-44), 47-56, 59-74, 80/(73-74)
Y --- A	WO 2016/025010 A1 (UGWU, Martin) 18 February 2016 (18.02.2016) pg 5, para 7; pg 6, para 2	2, 27, (45-46)/27 --- 3-14, 16-18, 23-24, 28-38, 43-44, (45-46)/(28-38, 43-44), (47-56)/(9,10, 16,17,23,34-35,43-44), 73-74, 80/(73-74)
A	WO 2017/210262 A1 (BARANOVITZ, STEVEN) 07 December 2017 (07.12.2017) pg 7, para 2; pg 30, para 5 to pg 45, para 1	3-14, 16-18, 21, 23-24, 28-38, 41-44,(45-46)/(28-38, 41-44), 47-56, 59-74, 80/(73-74)

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 August 2021	SEP 15 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/31608

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2015/0190415 A1 (LEWIS et al.) 09 July 2015 (09.07.2015) para [0008], [0041]-[0042]	3-14, 16-18, 21, 23-24, 28-38, 41-44,(45-46)/(28-38, 41-44), 47-56, 59-74, 80/(73-74)
A	US 8,318,706 B2 (KIM et al.) 27 November 2012 (27.11.2012) Entire Document	1-14, 16-21, 23-74, 80

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/31608

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 15, 22, 75-79 and 81-106
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.