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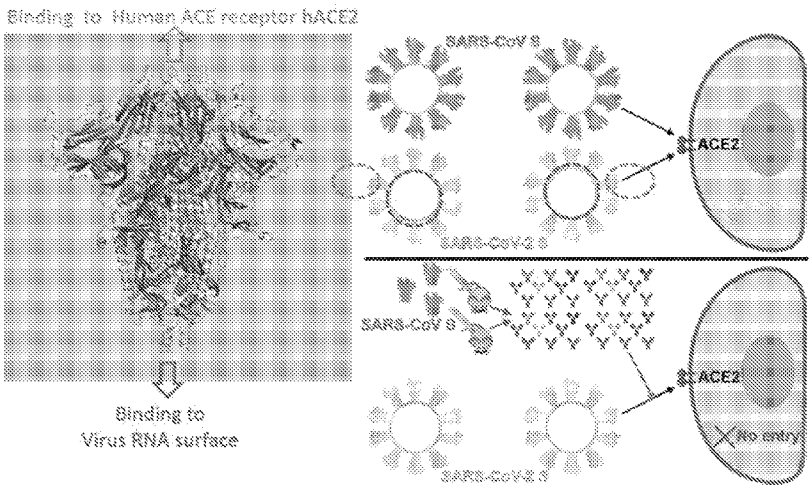

FIGURE 1

(57) Abstract: The present invention provides effective and safe therapeutics and methods thereof for various health conditions associated with infection by the viruses of the *Coronaviridae* family. Specifically, the invention provides novel therapeutics based on combinations of anti-microbial agents and immunomodulators against SARS-CoV-2 (COVID-19).

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MOLECULES THAT TARGET PROTEINS OF CORONAVIRUSES AND USES THEREOF AS ANTI-VIRAL "COCKTAIL"

FIELD OF THE INVENTION

The invention relates to anti-viral compositions and method of using the same. Specifically, the invention related to compositions having antiviral activity against viruses of the *Coronaviridae* family and method of using the same.

BACKGROUND OF THE INVENTION

Coronaviruses are a diverse group of viruses infecting many different animals, and they can cause mild to severe respiratory infections in humans. In 2002 and 2012, respectively, two highly pathogenic coronaviruses with zoonotic origin, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), emerged in humans and caused fatal respiratory illness, making emerging coronaviruses a new public health concern in the twenty-first century.

At the end of 2019, a novel coronavirus designated as SARS-CoV-2 emerged in the city of Wuhan, China, and caused an outbreak of unusual viral pneumonia. Being highly transmissible, this novel coronavirus disease, also known as coronavirus disease 2019 (COVID-19), has spread fast all over the world. It has overwhelmingly surpassed SARS and MERS in terms of both the number of infected people and the spatial range of epidemic areas. The ongoing outbreak of COVID-19 has posed an extraordinary threat to global public health.

By metagenomic RNA sequencing and virus isolation from bronchoalveolar lavage fluid (BALF) samples from patients with severe pneumonia, independent teams of Chinese scientists identified that the causative agent of this emerging disease is a betacoronavirus that had never been seen before. On 9 January 2020, the result of this etiological identification was publicly announced. The first genome sequence of the novel coronavirus was published on the Virological website on 10 January 2020, and more nearly complete genome sequences determined by different research institutes were then released via the GISAID database on 12 January.

As a novel betacoronavirus, SARS-CoV-2 shares 79% genome sequence identity with SARS-CoV and 50% with MERS-CoV24. Its genome organization is shared with other betacoronaviruses. Most of the proteins encoded by SARS-CoV-2 have a similar length to the corresponding proteins in SARS-CoV. Of the four structural genes, SARS-CoV-2 shares more than 90% amino acid identity with SARS-CoV except for the spike (S) gene, which diverges.

SARS-CoV-2 uses the same receptor as SARS-CoV, angiotensin-converting enzyme 2 (ACE2). Besides human ACE2 (hACE2), SARS-CoV-2 also recognizes ACE2 from pig, ferret, rhesus monkey, civet, cat, pangolin, rabbit, and dog. The broad receptor usage of SARS-CoV-2 implies that it may have a wide host range, and the varied efficiency of ACE2 usage in different animals may indicate their different susceptibilities to SARS-CoV-2 infection.

At this stage, molecular mechanisms of SARS-CoV-2 infection pathogenesis and virus-host interactions remain largely unclear, and there are no proven effective therapeutics and treatment protocols for COVID-19, although some treatments have shown certain benefits in subpopulations of patients.

Thus, it is clear that the world population is exhausted and anxious to find effective and accessible preventive tools, therapeutics, and treatment protocols against COVID-19 and its variants.

SUMMARY OF THE INVENTION

It is a principal object of the present invention to provide effective and safe therapeutics for various health conditions associated with infection by the viruses of the *Coronaviridae* family.

The invention provides a method of treating a condition associated with an infection by a virus of the Coronaviridae family, in a subject in need of such treatment, the method comprising administering to the subject a therapeutically effective amount of

a. at least one agent having an anti-microbial activity, and
b. at least one at least one immunomodulator,

to thereby effectively treat the condition associated with the infection by the virus of the *Coronaviridae* family.

The invention further provides a method of slowing and/or preventing progression of a condition associated with an infection by a virus of the *Coronaviridae* family in a subject, comprising administering to the subject

a. at least one agent having an anti-microbial activity, and
b. at least one at least one immunomodulator,

in an amount effective to slow and/or prevent progression of said condition.

The invention further provides a method of reducing a viral load in a subject infected by a virus of the *Coronaviridae* family, comprising administering to the subject

a. at least one agent having an anti-microbial activity, and
b. at least one at least one immunomodulator,

in an amount effective to reduce the viral load.

The invention further provides a method of reducing clinical manifestations of an infection by a virus of the *Coronaviridae* family in a subject in need, comprising administering to the subject

a. at least one agent having an anti-microbial activity, and
b. at least one at least one immunomodulator,

in an amount effective to reduce the clinical manifestations.

The invention further provides a method of reducing at least one surrogate marker associated with an infection by a virus of the *Coronaviridae* family in a subject diagnosed with said infection, comprising administering to said subject

a. at least one agent having an anti-microbial activity, and
b. at least one at least one immunomodulator,

in an amount effective to reduce the at least one surrogate marker.

The invention further provides a method of reducing at least one biomarker associated with an infection by a virus of the *Coronaviridae* family in a subject diagnosed with said infection, comprising administering to said subject

a. at least one agent having an anti-microbial activity, and
b. at least one at least one immunomodulator,

in an amount effective to reduce the at least one biomarker.

The invention further provides a therapeutic combination suitable for administration to a subject in need, comprising:

a. at least one agent having an anti-microbial activity, and
b. at least one at least one immunomodulator,

wherein the subject in need is diagnosed with an infection by a virus of the *Coronaviridae* family.

The invention further provides a pharmaceutical composition comprising

a. at least one agent having an anti-microbial activity, and
b. at least one at least one immunomodulator,
c. at least one pharmaceutically acceptable carrier

The invention further provides a method for treating a subject afflicted with a condition associated with an infection by a virus of the *Coronaviridae* family with a pharmaceutical composition of the invention, comprising the steps of: a) administering a therapeutic amount of the pharmaceutical composition to the subject; b) determining whether the subject is a responder by determining the gene expression profile of the subject, and comparing the gene expression profile to a reference gene expression profile to identify the subject as a responder; and c) continuing the administration if the subject

is identified as a responder, or modifying treatment of the subject if the subject is not identified as a responder.

The invention further provides a method for treating a human subject presenting clinical manifestations associated with infection by a virus of the *Coronaviridae* family with a pharmaceutical composition of the invention, comprising the steps of:(i) determining the gene expression profile of the subject;(ii) identifying the subject as a predicted responder if the gene expression profile is indicative of subject being a responder; and(iii) administering the pharmaceutical composition to the subject only if the subject is identified as a predicted responder.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig.1 is a schematic view of Corona viruses enter human cells;

Fig.2 is an exemplary embodiment of the interface of a first agent: antibiotics having RNA-binding site and Clarithromycin or Azithromycin binding to the pocket;

Fig.3 is an exemplary embodiment of multi-target attack of spike glyco-protein by antibiotics; and

Fig.4 is an exemplary embodiment of Azithromycin dose of 500mg per day and multi-target attack of spike glyco-protein by antibiotics and anti-viral drugs.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is now described more fully hereinafter with reference to the accompanying examples, in which embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather these embodiments are provided so that this disclosure will be thorough and complete and will fully convey the scope of the invention to those skilled in the art.

According to some embodiments, the invention provides method of treating a condition associated with an infection by a virus of the *Coronaviridae* family, in a subject in need of such treatment, the method comprising administering to the subject a therapeutically effective amount of

a. at least one agent having an anti-microbial activity, and

b. at least one immunomodulator,

to thereby effectively treat the condition associated with the infection by the virus of the *Coronaviridae* family.

In the context of the embodiments of the invention the term "antimicrobial agent", refers, without limitation, to drugs, chemicals, or other substances that either kill or slow the growth of microbes. Among the antimicrobial agents of the invention are antibacterial drugs, antifungal agents, and antiparasitic drugs. In one embodiment, the non-limiting list of agents having anti-microbial activity includes Azithromycin, Boromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Ivermectin, Josamycin, Midecamycin, Miocamycin, Oleandomycin, Rokitamycin, Roxithromycin, Spiramycin, Troleandomycin, Doxycycline, and Tylosin. In the context of the embodiments of the invention, the term "immunomodulator" refers, without limitation to agents that change the composition and/or function of immune system or immune cells. In one embodiment, the immunomodulator is a corticosteroid. In another embodiment, the non-limiting list immunomodulators of the invention includes Desoxycortone (desoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Fludrocortisone, Fludrocortisone acetate, Methylprednisolone, Methylprednisolone esters, Prednisolone, Prednisolone esters, Prednisone, Cortisone, Cortisone acetate, Cortodoxone (cortexolone, 11-deoxycortisol), Desoxycortone (deoxycortone, cortexone, 11-deoxycorticosterone), Desoxycortone esters,

Hydrocortisone (cortisol), Hydrocortisone esters, Prebediolone acetate, Pregnenolone, Pregnenolone acetate, Pregnenolone succinate, Cortisol-like and related (16-unsubstituted): Chloroprednisone, Cloprednol, Difluprednate, Fludrocortisone, Flugestone acetate (flurogestone acetate), Fluocinolone, Fluorometholone, Fluorometholone acetate, Fluperolone, Fluperolone acetate, Fluprednisolone, Fluprednisolone esters, Loteprednol, Medrysone, Methylprednisolone, Methylprednisolone esters, Prednicarbate, Prednisolone, Prednisone, Tixocortol, Tixocortol pivalate, Methasones and related (16-substituted): Alclometasone, Beclometasone, Beclometasone esters, Betamethasone, Betamethasone esters, Clobetasol, Clobetasol propionate, Clobetasone, Clocortolone, Clocortolone esters, Cortivazol, Desoximetasone, Dexamethasone, Dexamethasone esters, Diflorasone, Diflucortolone, Diflucortolone valerate, Fluclorolone, Flumetasone, Fluocortin, Fluocortolone, Fluocortolone esters, Fluprednidene acetate, Fluticasone, Fluticasone furoate, Fluticasone propionate, Halometasone, Meprednisone, Mometasone, Mometasone furoate, Paramethasone, Prednylidene, Rimexolone, Triamcinolone, and Ulobetasol (halobetasol).

According to some embodiments of the above method, the therapeutically effective amount of the at least one agent having an anti-microbial activity is from 10mg/day to 5000mg/day. In one embodiment, the therapeutically effective amount of the at least one agent having an anti-microbial activity is 25mg/day to 5000mg/day; 50mg/day to 5000mg/day; 70mg/day to 5000mg/day; 100mg/day to 5000mg/day; 150mg/day to 5000mg/day; 170mg/day to 5000mg/day; 200mg/day to 5000mg/day; 250mg/day to 5000mg/day; 300mg/day to 5000mg/day; 350mg/day to 5000mg/day; 400mg/day to 5000mg/day; 500mg/day to 5000 mg/day; 750mg/day to 5000 mg/day; 1000mg/day to 5000 mg/day; 1200mg/day to 5000 mg/day; 1400mg/day to 5000 mg/day; 1700mg/day to 5000 mg/day; 1850mg/day to 5000 mg/day; 2000mg/day to 5000 mg/day;

2200mg/day to 5000 mg/day; 2400mg/day to 5000 mg/day; 2600mg/day to 5000 mg/day. In one embodiment, the therapeutically effective amount of the at least one agent having an anti-microbial activity is 100mg/day to 1000mg/day; 150mg/day to 950 mg/day; 200mg/day to 900 mg/day; 250mg/day to 850mg/day; 300mg/day to 800mg/day; 350mg/day to 750mg/day; 400mg/day to 700mg/day. In one embodiment, the therapeutically effective amount of the at least one agent having an anti-microbial activity is 50mg/day; 100mg/day; 150 mg/day; 200 mg/day; 250 mg/day; 300 mg/day; 325mg/day; 350mg/day; 375mg/day; 400mg/day; 450mg/day; 475mg/day; 500mg/day; 550mg/day; 600mg/day; 650mg/day; 700mg/day; 750mg/day; 800mg/day; 850mg/day; 900mg/day; 1000mg/day.

According to some embodiments of the above method, the therapeutically effective amount of the at least one immunomodulator is from 0.1 mg/day to 50mg/day. In one embodiment, the therapeutically effective amount of the at least one immunomodulator is 0.25 mg/day to 50mg/day; 0.5 mg/day to 50mg/day; 0.75 mg/day to 50mg/day; 1 mg/day to 50mg/day; 1.25 mg/day to 50mg/day; 1.5mg/day to 50mg/day; 1.75mg/day to 50mg/day; 2mg/day to 50mg/day; 2.25mg/day to 50mg/day; 2.5mg/day to 50mg/day; 2.75mg/day to 50mg/day; 3mg/day to 50mg/day; 3.5mg/day to 50mg/day; 4mg/day to 50mg/day; 4.5mg/day to 50mg/day; 5mg/day to 50mg/day; 5.5mg/day to 50mg/day; 6mg/day to 50mg/day; 6.5mg/day to 50mg/day; 7mg/day to 50mg/day; 7.5mg/day to 50mg/day; 8mg/day to 50mg/day; 8.5mg/day to 50mg/day; 9mg/day to 50mg/day; 9.5mg/day to 50mg/day; 10mg/day to 50mg/day. In one embodiment, the therapeutically effective amount of the at least one immunomodulator is 1mg/day to 15mg/day; 1.5mg/day to 14.5 mg/day; 2mg/day to 14 mg/day; 2.5mg/day to 13.5 mg/day; 3mg/day to 13mg/day; 4mg/day to 12 mg/day; 5mg/day to 11mg/day; 6mg/day to 10mg/day. In one embodiment, the therapeutically effective amount of the at least one immunomodulator is 1mg/day; 2mg/day; 2.5 mg/day; 3mg/day;

3.5mg/day; 4mg/day; 4.5mg/day; 5mg/day; 5.5mg/day; 6mg/day; 6.5mg/day; 7mg/day; 7.5mg/day; 8mg/day; 8.5mg/day; 9mg/day; 9.5mg/day; 10mg/day; 10.5mg/day; 11mg/day; 11.5mg/day; 12mg/day; 12.5mg/day; 13mg/day; 13.5mg/day; 14mg/day; 14.5mg/day; 15mg/day.

According to some embodiment of the above method, the anti-microbial agent is azithromycin, and the immunomodulator is dexamethasone or dexamethasone phosphate.

According to some embodiment of the above method, the daily dose of the anti-microbial agent and/or immunomodulator can be administered at once, or, alternatively can be split into several administration and/or can be given according to any desired regimen. In one embodiment, the anti-microbial agent and the immunomodulator are administered simultaneously. In one embodiment, the anti-microbial agent and the immunomodulator are administered independently of each other.

According to some embodiments of the above method, the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19), SARS-CoV, MERS, OC43, 229E, NL63, OC43, and HKU1. In one embodiment, the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19).

According to some embodiments of the above method, the subject is a mammalian subject. As used herein, the term "mammalian" is interchangeable with "mammal". In one embodiment, the mammalian subject is a human subject.

According to some embodiments of the above method, the non-limiting list of conditions associated with an infection by a virus of the *Coronaviridae* family includes acute respiratory distress syndrome (ARDS), common cold, pneumonia, bronchitis, severe acute respiratory syndrome, and Middle East respiratory syndrome.

According to some embodiments, the above method further comprises administering to the subject a therapeutically

effective amount of at least one antiviral agent. In the context of the embodiments of the invention, the term "agent having an anti-viral activity" refers, without limitation, to an agent that kills a virus or that suppresses its ability to replicate and, hence, inhibits its capability to multiply and/or reproduce. It can be interchangeably referred as anti-viral drug or anti-viral substance or anti-viral compound. According to some embodiments of the above method, the dosing regimen of the antiviral agent is any state-of-the-art regimen and any administration regime. A non-limiting list of antiviral agents includes acyclovir, gancyclovir, valganciclovir, valacyclovir, famciclovir, penciclovir, vidarabine, cidofovir, ribavirin, adefovir, entecavir, favipiravir, brincidofovir, Idoxuridine, trifluridine, tipiracil, edoxudine, brivudine, FV-100, sorivudine, cytarabine, lamivudine, lobucavir, telbivudine, clevudine, tenofovir disoproxil, tenofovir alafenamide, and zidovudine.

According to some embodiments, the invention provides a method of slowing and/or preventing progression of a condition associated with an infection by a virus of the *Coronaviridae* family in a subject, comprising administering to the subject

a. at least one agent having an anti-microbial activity, and

b. at least one immunomodulator,

in an amount effective to prevent said condition. As used herein, the phrase "slowing and/or preventing progression" refers, without limitation, to the influence of the treatment on the clinical course of the disease. For example, illness severity of SARS-CoV-2 (COVID-19) ranges from mild to critical, while mild to moderate disease is categorized as mild symptoms up to mild pneumonia; severe disease has manifestations of dyspnea, hypoxia, or more than 50% lung involvement on imaging; and critical disease has manifestations of respiratory failure,

shock, or multiorgan system dysfunction, which may result in death (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html). In the context of the invention, the proposed therapy is aimed at slowing and/or preventing the transition from mild to severe and to critical illness. The "slowing and/or preventing" progression of the condition according to the embodiments of the above method may be measured using any appropriate questionary, method, scale, diagnostic tool, or any other means that are known in the art or acceptable by the relevant functions and professionals. The term "preventing" might but does not necessarily mean recovery from the illness. As such, the term "preventing" relates to the situation when the patient does not present symptoms and/or signs and/or manifestations of the next "stage" of illness severity as defined by the appropriate and acceptable parameters for the specific disease condition. The term "slowing", or attenuating is can, without limitation, prolong the time of transition into the next "stage" of illness severity, thus providing greater window of opportunity for extensive care and recovery.

According to some embodiments of the above method, the non-limiting list of conditions associated with an infection by a virus of the *Coronaviridae* family includes SARS-CoV-2 (COVID-19), SARS-CoV, MERS, OC43, 229E, NL63, OC43, and HKU1. In one embodiment the condition is SARS-CoV-2 (COVID-19).

According to some embodiments of the above method, the non-limiting list of agents having anti-microbial activity includes Azithromycin, Boromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Ivermectin, Josamycin, Midecamycin, Miocamycin, Oleandomycin, Rokitamycin, Roxithromycin, Spiramycin, Troleandomycin, Doxycycline, and Tylosin. According to some embodiments of the above method, the non-limiting list of immunomodulators includes Desoxycortone

(desoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Fludrocortisone, Fludrocortisone acetate, Methylprednisolone, Methylprednisolone esters, Prednisolone, Prednisolone esters, Prednisone, Cortisone, Cortisone acetate, Cortodoxone (cortexolone, 11-deoxycortisol), Desoxycortone (deoxycortone, cortexone, 11-deoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Prebediolone acetate, Pregnenolone, Pregnenolone acetate, Pregnenolone succinate, Cortisol-like and related (16-unsubstituted): Chloroprednisone, Cloprednol, Difluprednate, Fludrocortisone, Flugestone acetate (flurogestone acetate), Fluocinolone, Fluorometholone, Fluorometholone acetate, Fluperolone, Fluperolone acetate, Fluprednisolone, Fluprednisolone esters, Loteprednol, Medrysone, Methylprednisolone, Methylprednisolone esters, Prednicarbate, Prednisolone, Prednisone, Tixocortol, Tixocortol pivalate, Methasones and related (16-substituted): Alclometasone, Beclometasone, Beclometasone esters, Betamethasone, Betamethasone esters, Clobetasol, Clobetasol propionate, Clobetasone, Clocortolone, Clocortolone esters, Cortivazol, Desoximetasone, Dexamethasone, Dexamethasone esters, Diflorasone, Diflucortolone, Diflucortolone valerate, Fluclorolone, Flumetasone, Fluocortin, Fluocortolone, Fluocortolone esters, Fluprednidene acetate, Fluticasone, Fluticasone furoate, Fluticasone propionate, Halometasone, Meprednisone, Mometasone, Mometasone furoate, Paramethasone, Prednylidene, Rimexolone, Triamcinolone, and Ulobetasol (halobetasol). In one embodiment, the anti-microbial agent is azithromycin, and the immunomodulator is dexamethasone.

According to some embodiments of the above method, the effective amount of the at least one agent having an anti-microbial activity is from 10mg/day to 5000mg/day. In one embodiment, the effective amount of the at least one agent having an anti-microbial activity is 25mg/day to 5000mg/day; 50mg/day to

5000mg/day; 70mg/day to 5000mg/day; 100mg/day to 5000mg/day; 150mg/day to 5000mg/day; 170mg/day to 5000mg/day; 200mg/day to 5000mg/day; 250mg/day to 5000mg/day; 300mg/day to 5000mg/day; 350mg/day to 5000mg/day; 400mg/day to 5000mg/day; 500mg/day to 5000 mg/day; 750mg/day to 5000 mg/day; 1000mg/day to 5000 mg/day; 1200mg/day to 5000 mg/day; 1400mg/day to 5000 mg/day; 1700mg/day to 5000 mg/day; 1850mg/day to 5000 mg/day; 2000mg/day to 5000 mg/day; 2200mg/day to 5000 mg/day; 2400mg/day to 5000 mg/day; 2600mg/day to 5000 mg/day. In one embodiment, the effective amount of the at least one agent having an anti-microbial activity is 100mg/day to 1000mg/day; 150mg/day to 950 mg/day; 200mg/day to 900 mg/day; 250mg/day to 850mg/day; 300mg/day to 800mg/day; 350mg/day to 750mg/day; 400mg/day to 700mg/day. In one embodiment, the effective amount of the at least one agent having an anti-microbial activity is 50mg/day; 100mg/day; 150 mg/day; 200 mg/day; 250 mg/day; 300 mg/day; 325mg/day; 350mg/day; 375mg/day; 400mg/day; 450mg/day; 475mg/day; 500mg/day; 550mg/day; 600mg/day; 650mg/day; 700mg/day; 750mg/day; 800mg/day; 850mg/day; 900mg/day; 1000mg/day.

According to some embodiments of the above method, the effective amount of the at least one immunomodulator is from 0.1 mg/day to 50mg/day. In one embodiment, the effective amount of the at least one immunomodulator is 0.25 mg/day to 50mg/day; 0.5 mg/day to 50mg/day; 0.75 mg/day to 50mg/day; 1 mg/day to 50mg/day; 1.25 mg/day to 50mg/day; 1.5mg/day to 50mg/day; 1.75mg/day to 50mg/day; 2mg/day to 50mg/day; 2.25mg/day to 50mg/day; 2.5mg/day to 50mg/day; 2.75mg/day to 50mg/day; 3mg/day to 50mg/day; 3.5mg/day to 50mg/day; 4mg/day to 50mg/day; 4.5mg/day to 50mg/day; 5mg/day to 50mg/day; 5.5mg/day to 50mg/day; 6mg/day to 50mg/day; 6.5mg/day to 50mg/day; 7mg/day to 50mg/day; 7.5mg/day to 50mg/day; 8mg/day to 50mg/day; 8.5mg/day to 50mg/day; 9mg/day to 50mg/day; 9.5mg/day to 50mg/day; 10mg/day to 50mg/day. In one embodiment, the effective amount of the at

least one immunomodulator is 1mg/day to 15mg/day; 1.5mg/day to 14.5 mg/day; 2mg/day to 14 mg/day; 2.5mg/day to 13.5 mg/day; 3mg/day to 13mg/day; 4mg/day to 12 mg/day; 5mg/day to 11mg/day; 6mg/day to 10mg/day. In one embodiment, the effective amount of the at least one immunomodulator is 1mg/day; 2mg/day; 2.5 mg/day; 3mg/day; 3.5mg/day; 4mg/day; 4.5mg/day; 5mg/day; 5.5mg/day; 6mg/day; 6.5mg/day; 7mg/day; 7.5mg/day; 8mg/day; 8.5mg/day; 9mg/day; 9.5mg/day; 10mg/day; 10.5mg/day; 11mg/day; 11.5mg/day; 12mg/day; 12.5mg/day; 13mg/day; 13.5mg/day; 14mg/day; 14.5mg/day; 15mg/day.

According to some embodiment of the above method, the daily dose of the anti-microbial agent and/or immunomodulator can be administered at once, or, alternatively can be split into several administration and/or can be given according to any desired regimen. In one embodiment, the anti-microbial agent and the immunomodulator are administered simultaneously. In one embodiment, the anti-microbial agent and the immunomodulator are administered independently of each other.

According to some embodiments of the above method, the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19), SARS-CoV, MERS, OC43, 229E, NL63, OC43, and HKU1. In one embodiment, the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19).

According to some embodiments, the above method further comprises administering to the subject an effective amount of at least one antiviral agent. A non-limiting list of antiviral agents includes acyclovir, gancyclovir, valganciclovir, valacyclovir, famciclovir, penciclovir, vidarabine, cidofovir, ribavirin, adefovir, entecavir, favipiravir, brincidofovir, Idoxuridine, trifluridine, tipiracil, edoxudine, brivudine, FV-100, sorivudine, cytarabine, lamivudine, lobucavir, telbivudine, clevudine, tenofovir disoproxil, tenofovir alafenamide, and zidovudine. Any acceptable dose and

administration regimen of the antiviral agent according to the embodiments of the invention can be used.

According to some embodiments, the invention provides method of reducing clinical manifestations of an infection by a virus of the *Coronaviridae* family in a subject in need, comprising administering to the subject

a. at least one agent having an anti-microbial activity, and

b. at least one immunomodulator,

in an amount effective to reduce the clinical manifestations. As used herein, the term "clinical manifestations" refers, without limitation, to signs and symptoms of the disease that can be either objective, when observed by a physician, or subjective, when perceived by the patient.

According to some embodiments of the above method, the non-limiting list of agents having anti-microbial activity includes Azithromycin, Boromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Ivermectin, Josamycin, Midecamycin, Miocamycin, Oleandomycin, Rokitamycin, Roxithromycin, Spiramycin, Troleandomycin, Doxycycline, and Tylosin. According to some embodiments of the above method, the non-limiting list of immunomodulators includes Desoxycortone (desoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Fludrocortisone, Fludrocortisone acetate, Methylprednisolone, Methylprednisolone esters, Prednisolone, Prednisolone esters, Prednisone, Cortisone, Cortisone acetate, Cortodoxone (cortexolone, 11-deoxycortisol), Desoxycortone (deoxycortone, cortexone, 11-deoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Prebediolone acetate, Pregnenolone, Pregnenolone acetate, Pregnenolone succinate, Cortisol-like and related (16-unsubstituted): Chloroprednisone,

Cloprednol, Difluprednate, Fludrocortisone, Flugestone acetate (flurogestone acetate), Fluocinolone, Fluorometholone, Fluorometholone acetate, Fluperolone, Fluperolone acetate, Fluprednisolone, Fluprednisolone esters, Loteprednol, Medrysone, Methylprednisolone, Methylprednisolone esters, Prednicarbate, Prednisolone, Prednisone, Tixocortol, Tixocortol pivalate, Methasones and related (16-substituted): Alclometasone, Beclometasone, Beclometasone esters, Betamethasone, Betamethasone esters, Clobetasol, Clobetasol propionate, Clobetasone, Clocortolone, Clocortolone esters, Cortivazol, Desoximetasone, Dexamethasone, Dexamethasone esters, Diflorasone, Diflucortolone, Diflucortolone valerate, Fluclorolone, Flumetasone, Fluocortin, Fluocortolone, Fluocortolone esters, Fluprednidene acetate, Fluticasone, Fluticasone furoate, Fluticasone propionate, Halometasone, Meprednisone, Mometasone, Mometasone furoate, Paramethasone, Prednylidene, Rimexolone, Triamcinolone, and Ulobetasol (halobetasol). In one embodiment, the anti-microbial agent is azithromycin, and the immunomodulator is dexamethasone.

According to some embodiments of the above method, the effective amount of the at least one agent having an anti-microbial activity is from 10mg/day to 5000mg/day. In one embodiment, the effective amount of the at least one agent having an anti-microbial activity is 25mg/day to 5000mg/day; 50mg/day to 5000mg/day; 70mg/day to 5000mg/day; 100mg/day to 5000mg/day; 150mg/day to 5000mg/day; 170mg/day to 5000mg/day; 200mg/day to 5000mg/day; 250mg/day to 5000mg/day; 300mg/day to 5000mg/day; 350mg/day to 5000mg/day; 400mg/day to 5000mg/day; 500mg/day to 5000 mg/day; 750mg/day to 5000 mg/day; 1000mg/day to 5000 mg/day; 1200mg/day to 5000 mg/day; 1400mg/day to 5000 mg/day; 1700mg/day to 5000 mg/day; 1850mg/day to 5000 mg/day; 2000mg/day to 5000 mg/day; 2200mg/day to 5000 mg/day; 2400mg/day to 5000 mg/day; 2600mg/day to 5000 mg/day. In one embodiment, the effective amount of the at least one agent having an anti-

microbial activity is 100mg/day to 1000mg/day; 150mg/day to 950 mg/day; 200mg/day to 900 mg/day; 250mg/day to 850mg/day; 300mg/day to 800mg/day; 350mg/day to 750mg/day; 400mg/day to 700mg/day. In one embodiment, the therapeutically effective amount of the at least one agent having an anti-microbial activity is 50mg/day; 100mg/day; 150 mg/day; 200 mg/day; 250 mg/day; 300 mg/day; 325mg/day; 350mg/day; 375mg/day; 400mg/day; 450mg/day; 475mg/day; 500mg/day; 550mg/day; 600mg/day; 650mg/day; 700mg/day; 750mg/day; 800mg/day; 850mg/day; 900mg/day; 1000mg/day.

According to some embodiments of the above method, the effective amount of the at least one immunomodulator is from 0.1 mg/day to 50mg/day. In one embodiment, the effective amount of the at least one immunomodulator is 0.25 mg/day to 50mg/day; 0.5 mg/day to 50mg/day; 0.75 mg/day to 50mg/day; 1 mg/day to 50mg/day; 1.25 mg/day to 50mg/day; 1.5mg/day to 50mg/day; 1.75mg/day to 50mg/day; 2mg/day to 50mg/day; 2.25mg/day to 50mg/day; 2.5mg/day to 50mg/day; 2.75mg/day to 50mg/day; 3mg/day to 50mg/day; 3.5mg/day to 50mg/day; 4mg/day to 50mg/day; 4.5mg/day to 50mg/day; 5mg/day to 50mg/day; 5.5mg/day to 50mg/day; 6mg/day to 50mg/day; 6.5mg/day to 50mg/day; 7mg/day to 50mg/day; 7.5mg/day to 50mg/day; 8mg/day to 50mg/day; 8.5mg/day to 50mg/day; 9mg/day to 50mg/day; 9.5mg/day to 50mg/day; 10mg/day to 50mg/day. In one embodiment, the effective amount of the at least one immunomodulator is 1mg/day to 15mg/day; 1.5mg/day to 14.5 mg/day; 2mg/day to 14 mg/day; 2.5mg/day to 13.5 mg/day; 3mg/day to 13mg/day; 4mg/day to 12 mg/day; 5mg/day to 11mg/day; 6mg/day to 10mg/day. In one embodiment, the effective amount of the at least one immunomodulator is 1mg/day; 2mg/day; 2.5 mg/day; 3mg/day; 3.5mg/day; 4mg/day; 4.5mg/day; 5mg/day; 5.5mg/day; 6mg/day; 6.5mg/day; 7mg/day; 7.5mg/day; 8mg/day; 8.5mg/day; 9mg/day; 9.5mg/day; 10mg/day; 10.5mg/day; 11mg/day; 11.5mg/day; 12mg/day; 12.5mg/day; 13mg/day; 13.5mg/day; 14mg/day; 14.5mg/day; 15mg/day.

According to some embodiment of the above method, the daily dose of the anti-microbial agent and/or immunomodulator can be administered at once, or, alternatively can be split into several administration and/or can be given according to any desired regimen. In one embodiment, the anti-microbial agent and the immunomodulator are administered simultaneously. In one embodiment, the anti-microbial agent and the immunomodulator are administered independently of each other, each as a separate medicament.

According to some embodiments of the above method, the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19), SARS-CoV, MERS, OC43, 229E, NL63, OC43, and HKU1. In one embodiment, the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19).

According to some embodiments, the above method further comprises administering to the subject an effective amount of at least one antiviral agent. A non-limiting list of antiviral agents includes acyclovir, gancyclovir, valganciclovir, valacyclovir, famciclovir, penciclovir, vidarabine, cidofovir, ribavirin, adefovir, entecavir, favipiravir, brincidofovir, Idoxuridine, trifluridine, tipiracil, edoxudine, brivudine, FV-100, sorivudine, cytarabine, lamivudine, lobucavir, telbivudine, clevudine, tenofovir disoproxil, tenofovir alafenamide, and zidovudine. Any acceptable dose and administration regimen of the antiviral agent according to the embodiments of the invention can be used.

According to some embodiments, the invention provides a method of reducing a viral load in a subject infected by a virus of the *Coronaviridae* family, comprising administering to the subject

a. at least one agent having an antimicrobial activity, and

b. at least one immunomodulator,

in an amount effective to reduce the viral load. As used herein, the term "viral load" refers, without limitation, to a numerical expression of the quantity of virus in a given volume of fluid.

According to some embodiments of the above method, the non-limiting list of agents having anti-microbial activity includes Azithromycin, Boromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Ivermectin, Josamycin, Midecamycin, Miocamycin, Oleandomycin, Rokitamycin, Roxithromycin, Spiramycin, Troleandomycin, Doxycycline, and Tylosin. According to some embodiments of the above method, the non-limiting list of immunomodulators includes Desoxycortone (desoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Fludrocortisone, Fludrocortisone acetate, Methylprednisolone, Methylprednisolone esters, Prednisolone, Prednisolone esters, Prednisone, Cortisone, Cortisone acetate, Cortodoxone (cortexolone, 11-deoxycortisol), Desoxycortone (deoxycortone, cortexone, 11-deoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Prebediolone acetate, Pregnenolone, Pregnenolone acetate, Pregnenolone succinate, Cortisol-like and related (16-unsubstituted): Chloroprednisone, Cloprednol, Difluprednate, Fludrocortisone, Flugestone acetate (flurogestone acetate), Fluocinolone, Fluorometholone, Fluorometholone acetate, Fluperolone, Fluperolone acetate, Fluprednisolone, Fluprednisolone esters, Loteprednol, Medrysone, Methylprednisolone, Methylprednisolone esters, Prednicarbate, Prednisolone, Prednisone, Tixocortol, Tixocortol pivalate, Methasones and related (16-substituted): Alclometasone, Beclometasone, Beclometasone esters, Betamethasone, Betamethasone esters, Clobetasol, Clobetasol propionate, Clobetasone, Clocortolone, Clocortolone esters, Cortivazol, Desoximetasone, Dexamethasone, Dexamethasone esters, Diflorasone, Diflucortolone, Diflucortolone valerate,

Fluclorolone, Flumetasone, Fluocortin, Fluocortolone, Fluocortolone esters, Fluprednidene acetate, Fluticasone, Fluticasone furoate, Fluticasone propionate, Halometasone, Meprednisone, Mometasone, Mometasone furoate, Paramethasone, Prednylidene, Rimexolone, Triamcinolone, and Ulobetasol (halobetasol). In one embodiment, the anti-microbial agent is azithromycin, and the immunomodulator is dexamethasone.

According to some embodiments of the above method, the effective amount of the at least one agent having an anti-microbial activity is from 10mg/day to 5000mg/day. In one embodiment, the effective amount of the at least one agent having an anti-microbial activity is 25mg/day to 5000mg/day; 50mg/day to 5000mg/day; 70mg/day to 5000mg/day; 100mg/day to 5000mg/day; 150mg/day to 5000mg/day; 170mg/day to 5000mg/day; 200mg/day to 5000mg/day; 250mg/day to 5000mg/day; 300mg/day to 5000mg/day; 350mg/day to 5000mg/day; 400mg/day to 5000mg/day; 500mg/day to 5000 mg/day; 750mg/day to 5000 mg/day; 1000mg/day to 5000 mg/day; 1200mg/day to 5000 mg/day; 1400mg/day to 5000 mg/day; 1700mg/day to 5000 mg/day; 1850mg/day to 5000 mg/day; 2000mg/day to 5000 mg/day; 2200mg/day to 5000 mg/day; 2400mg/day to 5000 mg/day; 2600mg/day to 5000 mg/day. In one embodiment, the effective amount of the at least one agent having an anti-microbial activity is 100mg/day to 1000mg/day; 150mg/day to 950 mg/day; 200mg/day to 900 mg/day; 250mg/day to 850mg/day; 300mg/day to 800mg/day; 350mg/day to 750mg/day; 400mg/day to 700mg/day. In one embodiment, the effective amount of the at least one agent having an anti-microbial activity is 50mg/day; 100mg/day; 150 mg/day; 200 mg/day; 250 mg/day; 300 mg/day; 325mg/day; 350mg/day; 375mg/day; 400mg/day; 450mg/day; 475mg/day; 500mg/day; 550mg/day; 600mg/day; 650mg/day; 700mg/day; 750mg/day; 800mg/day; 850mg/day; 900mg/day; 1000mg/day.

According to some embodiments of the above method, the effective amount of the at least one immunomodulator is from 0.1 mg/day to 50mg/day. In one embodiment, the effective amount of the at least one immunomodulator is 0.25 mg/day to 50mg/day; 0.5 mg/day to 50mg/day; 0.75 mg/day to 50mg/day; 1 mg/day to 50mg/day; 1.25 mg/day to 50mg/day; 1.5mg/day to 50mg/day; 1.75mg/day to 50mg/day; 2mg/day to 50mg/day; 2.25mg/day to 50mg/day; 2.5mg/day to 50mg/day; 2.75mg/day to 50mg/day; 3mg/day to 50mg/day; 3.5mg/day to 50mg/day; 4mg/day to 50mg/day; 4.5mg/day to 50mg/day; 5mg/day to 50mg/day; 5.5mg/day to 50mg/day; 6mg/day to 50mg/day; 6.5mg/day to 50mg/day; 7mg/day to 50mg/day; 7.5mg/day to 50mg/day; 8mg/day to 50mg/day; 8.5mg/day to 50mg/day; 9mg/day to 50mg/day; 9.5mg/day to 50mg/day; 10mg/day to 50mg/day. In one embodiment, the effective amount of the at least one immunomodulator is 1mg/day to 15mg/day; 1.5mg/day to 14.5 mg/day; 2mg/day to 14 mg/day; 2.5mg/day to 13.5 mg/day; 3mg/day to 13mg/day; 4mg/day to 12 mg/day; 5mg/day to 11mg/day; 6mg/day to 10mg/day. In one embodiment, the effective amount of the at least one immunomodulator is 1mg/day; 2mg/day; 2.5 mg/day; 3mg/day; 3.5mg/day; 4mg/day; 4.5mg/day; 5mg/day; 5.5mg/day; 6mg/day; 6.5mg/day; 7mg/day; 7.5mg/day; 8mg/day; 8.5mg/day; 9mg/day; 9.5mg/day; 10mg/day; 10.5mg/day; 11mg/day; 11.5mg/day; 12mg/day; 12.5mg/day; 13mg/day; 13.5mg/day; 14mg/day; 14.5mg/day; 15mg/day.

According to some embodiment of the above method, the daily dose of the anti-microbial agent and/or immunomodulator can be administered at once, or, alternatively can be split into several administration and/or can be given according to any desired regimen. In one embodiment, the anti-microbial agent and the immunomodulator are administered simultaneously. In one embodiment, the anti-microbial agent and the immunomodulator are administered independently of each other, each as a separate medicament.

According to some embodiments of the above method, the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19), SARS-CoV, MERS, OC43, 229E, NL63, OC43, and HKU1. In one embodiment, the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19).

According to some embodiments, the above method further comprises administering to the subject an effective amount of at least one antiviral agent. A non-limiting list of antiviral agents includes acyclovir, gancyclovir, valganciclovir, valacyclovir, famciclovir, penciclovir, vidarabine, cidofovir, ribavirin, adefovir, entecavir, favipiravir, brincidofovir, Idoxuridine, trifluridine, tipiracil, edoxudine, brivudine, FV-100, sorivudine, cytarabine, lamivudine, lobucavir, telbivudine, clevudine, tenofovir disoproxil, tenofovir alafenamide, and zidovudine. Any acceptable dose and administration regimen of the antiviral agent according to the embodiments of the invention can be used.

According to some embodiments of the above method, the viral log is reduced by at least 1.3 log to 10 log. According to some embodiments of the above method, the viral log is reduced by at least 1.3 log, 1.5 log, 1.7 log, 2 log, 2.25 log, 2.5 log, 2.75 log, 3 log, 3.25 log, 3.75log, 4 log, 4.25 log, 4.5 log, 4.75 log, 5 log, 5.25 log, 5.5 log, 5.75 log, 6 log; 6.25 log, 6.5 log, 6.75 log, 7 log, 7.25 log, 7.5 log, 7.75 log, 8 log, 8.25 log, 8.5 log, 8.75 log, 9 log, 9.25 log, 9.5 log, 9.75 log, 10 log.

According to some embodiments, the invention provides a method of reducing at least one surrogate marker associated with an infection by a virus of the *Coronaviridae* family in a subject diagnosed with said infection, comprising administering to said subject

a. at least one agent having an anti-microbial activity, and

b. at least one immunomodulator,

in an amount effective to reduce the at least one surrogate marker. As used herein, the term "surrogate marker" refers, without limitation, to a measure of effect of a specific treatment that may correlate with a real clinical endpoint but does not necessarily have a guaranteed relationship. In the context of the invention, the unlimited list of possible surrogate markers includes genomic marker, antigen marker, antibody, and a combination thereof.

According to some embodiments, the invention provides a method of reducing at least one biomarker associated with an infection by a virus of the *Coronaviridae* family in a subject diagnosed with said infection, comprising administering to said subject

a. at least one agent having an anti-microbial activity, and

b. at least one immunomodulator,

in an amount effective to reduce the at least one biomarker. As used herein, the term "biomarker" refers, without limitation, to a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention. This definition encompasses therapeutic interventions and can be derived from molecular, histologic, radiographic, or physiologic characteristics (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5813875/). A non-limiting list of the biomarkers of the invention includes SLP1, IDO1, SLC7A11, PTGS2, MR1, PNP, ABCG2, CXCL8, MMP1, ARG1, CCL2, BCL2L1, CTSB, HEXB, ARSA, and MAN2B2 and/or other upregulated or downregulated genes.

According to some embodiments, the invention provides therapeutic combination suitable for administration to a subject in need, comprising:

a. at least one agent having an anti-microbial activity, and

b. at least one immunomodulator,

wherein the subject in need is diagnosed with an infection by a virus of the *Coronaviridae* family. As used herein, the term "therapeutic combination" is meant to be understood, without limitation, as a combination of a number of components: at least one agent having an anti-microbial activity with at least one immunomodulator that is administered to a subject in need to provide a desirable therapeutic effect. In the combination according to the embodiments of the invention, the at least two components can be given in a single formulation or as a separate medicament; they can be administered simultaneously, or alternatively, can have each a specific dosing regimen and/or administration regime. The combination according to the embodiments of the invention cam be a synergistic combination, while the combined effect is larger than the additive effect of each individual drug. In one embodiment, the combination has an additive effect on the clinical outcome.

According to some embodiments of the above combination, the non-limiting list of agents having anti-microbial activity includes Azithromycin, Boromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Ivermectin, Josamycin, Midecamycin, Miocamycin, Oleandomycin, Rokitamycin, Roxithromycin, Spiramycin, Troleandomycin, Doxycycline, and Tylosin. According to some embodiments of the above combination, the non-limiting list of immunomodulators includes Desoxycortone (desoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Fludrocortisone, Fludrocortisone acetate, Methylprednisolone, Methylprednisolone esters, Prednisolone, Prednisolone esters, Prednisone, Cortisone, Cortisone acetate, Cortodoxone (cortexolone, 11-deoxycortisol), Desoxycortone (deoxycortone, cortexone, 11-

deoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Prebediolone acetate, Pregnenolone, Pregnenolone acetate, Pregnenolone succinate, Cortisol-like and related (16-unsubstituted): Chloroprednisone, Cloprednol, Difluprednate, Fludrocortisone, Flugestone acetate (flurogestone acetate), Fluocinolone, Fluorometholone, Fluorometholone acetate, Fluperolone, Fluperolone acetate, Fluprednisolone, Fluprednisolone esters, Loteprednol, Medrysone, Methylprednisolone, Methylprednisolone esters, Prednicarbate, Prednisolone, Prednisone, Tixocortol, Tixocortol pivalate, Methasones and related (16-substituted): Alclometasone, Beclometasone, Beclometasone esters, Betamethasone, Betamethasone esters, Clobetasol, Clobetasol propionate, Clobetasone, Clocortolone, Clocortolone esters, Cortivazol, Desoximetasone, Dexamethasone, Dexamethasone esters, Diflorasone, Diflucortolone, Diflucortolone valerate, Fluclorolone, Flumetasone, Fluocortin, Fluocortolone, Fluocortolone esters, Fluprednidene acetate, Fluticasone, Fluticasone furoate, Fluticasone propionate, Halometasone, Meprednisone, Mometasone, Mometasone furoate, Paramethasone, Prednylidene, Rimexolone, Triamcinolone, and Ulobetasol (halobetasol). In one embodiment, the anti-microbial agent is azithromycin, and the immunomodulator is dexamethasone.

According to some embodiments of the above combination, the effective amount of the at least one agent having an anti-microbial activity is from 10mg/day to 5000mg/day. In one embodiment, the effective amount of the at least one agent having an anti-microbial activity is 25mg/day to 5000mg/day; 50mg/day to 5000mg/day; 70mg/day to 5000mg/day; 100mg/day to 5000mg/day; 150mg/day to 5000mg/day; 170mg/day to 5000mg/day; 200mg/day to 5000mg/day; 250mg/day to 5000mg/day; 300mg/day to 5000mg/day; 350mg/day to 5000mg/day; 400mg/day to 5000mg/day; 500mg/day to 5000 mg/day; 750mg/day to 5000 mg/day; 1000mg/day to 5000 mg/day; 1200mg/day to 5000 mg/day; 1400mg/day to 5000 mg/day;

1700mg/day to 5000 mg/day; 1850mg/day to 5000 mg/day; 2000mg/day to 5000 mg/day; 2200mg/day to 5000 mg/day; 2400mg/day to 5000 mg/day; 2600mg/day to 5000 mg/day. In one embodiment, the effective amount of the at least one agent having an anti-microbial activity is 100mg/day to 1000mg/day; 150mg/day to 950 mg/day; 200mg/day to 900 mg/day; 250mg/day to 850mg/day; 300mg/day to 800mg/day; 350mg/day to 750mg/day; 400mg/day to 700mg/day. In one embodiment, the effective amount of the at least one agent having an anti-microbial activity is 50mg/day; 100mg/day; 150 mg/day; 200 mg/day; 250 mg/day; 300 mg/day; 325mg/day; 350mg/day; 375mg/day; 400mg/day; 450mg/day; 475mg/day; 500mg/day; 550mg/day; 600mg/day; 650mg/day; 700mg/day; 750mg/day; 800mg/day; 850mg/day; 900mg/day; 1000mg/day.

According to some embodiments of the above combination, the effective amount of the at least one immunomodulator is from 0.1 mg/day to 50mg/day. In one embodiment, the effective amount of the at least one immunomodulator is 0.25 mg/day to 50mg/day; 0.5 mg/day to 50mg/day; 0.75 mg/day to 50mg/day; 1 mg/day to 50mg/day; 1.25 mg/day to 50mg/day; 1.5mg/day to 50mg/day; 1.75mg/day to 50mg/day; 2mg/day to 50mg/day; 2.25mg/day to 50mg/day; 2.5mg/day to 50mg/day; 2.75mg/day to 50mg/day; 3mg/day to 50mg/day; 3.5mg/day to 50mg/day; 4mg/day to 50mg/day; 4.5mg/day to 50mg/day; 5mg/day to 50mg/day; 5.5mg/day to 50mg/day; 6mg/day to 50mg/day; 6.5mg/day to 50mg/day; 7mg/day to 50mg/day; 7.5mg/day to 50mg/day; 8mg/day to 50mg/day; 8.5mg/day to 50mg/day; 9mg/day to 50mg/day; 9.5mg/day to 50mg/day; 10mg/day to 50mg/day. In one embodiment, the effective amount of the at least one immunomodulator is 1mg/day to 15mg/day; 1.5mg/day to 14.5 mg/day; 2mg/day to 14 mg/day; 2.5mg/day to 13.5 mg/day; 3mg/day to 13mg/day; 4mg/day to 12 mg/day; 5mg/day to 11mg/day; 6mg/day to 10mg/day. In one embodiment, the effective amount of the at least one immunomodulator is 1mg/day; 2mg/day; 2.5 mg/day; 3mg/day;

3.5mg/day; 4mg/day; 4.5mg/day; 5mg/day; 5.5mg/day; 6mg/day; 6.5mg/day; 7mg/day; 7.5mg/day; 8mg/day; 8.5mg/day; 9mg/day; 9.5mg/day; 10mg/day; 10.5mg/day; 11mg/day; 11.5mg/day; 12mg/day; 12.5mg/day; 13mg/day; 13.5mg/day; 14mg/day; 14.5mg/day; 15mg/day.

According to some embodiments, the above combination further comprises an effective amount of at least one antiviral agent. A non-limiting list of antiviral agents includes acyclovir, gancyclovir, valganciclovir, valacyclovir, famciclovir, penciclovir, vidarabine, cidofovir, ribavirin, adefovir, entecavir, favipiravir, brincidofovir, Idoxuridine, trifluridine, tipiracil, edoxudine, brivudine, FV-100, sorivudine, cytarabine, lamivudine, lobucavir, telbivudine, clevudine, tenofovir disoproxil, tenofovir alafenamide, and zidovudine. Any acceptable dose and administration regimen of the antiviral agent according to the embodiments of the invention can be used.

According to some embodiments of the above combination, the virus of the *Coronaviridae* family is selected from the group consisting of SARS-CoV-2 (COVID-19), SARS-CoV, MERS, OC43, 229E, NL63, OC43, and HKU1. In one embodiment, the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19).

According to some embodiments, the invention provides a pharmaceutical composition comprising

a. at least one at least one agent having an anti-microbial activity,

b. at least one immunomodulator, and

c. at least one pharmaceutically acceptable carrier

According to some embodiments of the above pharmaceutical composition, the non-limiting list of agents having anti-

microbial activity includes Azithromycin, Boromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Ivermectin, Josamycin, Midecamycin, Miocamycin, Oleandomycin, Rokitamycin, Roxithromycin, Spiramycin, Troleandomycin, Doxycycline, and Tylosin. According to some embodiments of the above pharmaceutical composition, the non-limiting list of immunomodulators includes Desoxycortone (desoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Fludrocortisone, Fludrocortisone acetate, Methylprednisolone, Methylprednisolone esters, Prednisolone, Prednisolone esters, Prednisone, Cortisone, Cortisone acetate, Cortodoxone (cortexolone, 11-deoxycortisol), Desoxycortone (deoxycortone, cortexone, 11-deoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Prebediolone acetate, Pregnenolone, Pregnenolone acetate, Pregnenolone succinate, Cortisol-like and related (16-unsubstituted): Chloroprednisone, Cloprednol, Difluprednate, Fludrocortisone, Flugestone acetate (flurogestone acetate), Fluocinolone, Fluorometholone, Fluorometholone acetate, Fluperolone, Fluperolone acetate, Fluprednisolone, Fluprednisolone esters, Loteprednol, Medrysone, Methylprednisolone, Methylprednisolone esters, Prednicarbate, Prednisolone, Prednisone, Tixocortol, Tixocortol pivalate, Methasones and related (16-substituted): Alclometasone, Beclometasone, Beclometasone esters, Betamethasone, Betamethasone esters, Clobetasol, Clobetasol propionate, Clobetasone, Clocortolone, Clocortolone esters, Cortivazol, Desoximetasone, Dexamethasone, Dexamethasone esters, Diflorasone, Diflucortolone, Diflucortolone valerate, Fluclorolone, Flumetasone, Fluocortin, Fluocortolone, Fluocortolone esters, Fluprednidene acetate, Fluticasone, Fluticasone furoate, Fluticasone propionate, Halometasone, Meprednisone, Mometasone, Mometasone furoate, Paramethasone, Prednylidene, Rimexolone, Triamcinolone, and Ulobetasol

(halobetasol). In one embodiment, the anti-microbial agent is azithromycin, and the immunomodulator is dexamethasone.

According to some embodiments of the above pharmaceutical composition, the effective amount of the at least one agent having an anti-microbial activity is from 10mg/day to 5000mg/day. In one embodiment, the effective amount of the at least one agent having an anti-microbial activity is 25mg/day to 5000mg/day; 50mg/day to 5000mg/day; 70mg/day to 5000mg/day; 100mg/day to 5000mg/day; 150mg/day to 5000mg/day; 170mg/day to 5000mg/day; 200mg/day to 5000mg/day; 250mg/day to 5000mg/day; 300mg/day to 5000mg/day; 350mg/day to 5000mg/day; 400mg/day to 5000mg/day; 500mg/day to 5000 mg/day; 750mg/day to 5000 mg/day; 1000mg/day to 5000 mg/day; 1200mg/day to 5000 mg/day; 1400mg/day to 5000 mg/day; 1700mg/day to 5000 mg/day; 1850mg/day to 5000 mg/day; 2000mg/day to 5000 mg/day; 2200mg/day to 5000 mg/day; 2400mg/day to 5000 mg/day; 2600mg/day to 5000 mg/day. In one embodiment, the effective amount of the at least one agent having an anti-microbial activity is 100mg/day to 1000mg/day; 150mg/day to 950 mg/day; 200mg/day to 900 mg/day; 250mg/day to 850mg/day; 300mg/day to 800mg/day; 350mg/day to 750mg/day; 400mg/day to 700mg/day. In one embodiment, the therapeutically effective amount of the at least agent having an anti-microbial activity is 50mg/day; 100mg/day; 150 mg/day; 200 mg/day; 250 mg/day; 300 mg/day; 325mg/day; 350mg/day; 375mg/day; 400mg/day; 450mg/day; 475mg/day; 500mg/day; 550mg/day; 600mg/day; 650mg/day; 700mg/day; 750mg/day; 800mg/day; 850mg/day; 900mg/day; 1000mg/day.

According to some embodiments of the above pharmaceutical composition, the effective amount of the at least one immunomodulator is from 0.1 mg/day to 50mg/day. In one embodiment, the effective amount of the at least one immunomodulator is 0.25 mg/day to 50mg/day; 0.5 mg/day to 50mg/day; 0.75 mg/day to 50mg/day; 1 mg/day to 50mg/day; 1.25

mg/day to 50mg/day; 1.5mg/day to 50mg/day; 1.75mg/day to 50mg/day; 2mg/day to 50mg/day; 2.25mg/day to 50mg/day; 2.5mg/day to 50mg/day; 2.75mg/day to 50mg/day; 3mg/day to 50mg/day; 3.5mg/day to 50mg/day; 4mg/day to 50mg/day; 4.5mg/day to 50mg/day; 5mg/day to 50mg/day; 5.5mg/day to 50mg/day; 6mg/day to 50mg/day; 6.5mg/day to 50mg/day; 7mg/day to 50mg/day; 7.5mg/day to 50mg/day; 8mg/day to 50mg/day; 8.5mg/day to 50mg/day; 9mg/day to 50mg/day; 9.5mg/day to 50mg/day; 10mg/day to 50mg/day. In one embodiment, the effective amount of the at least one immunomodulator is 1mg/day to 15mg/day; 1.5mg/day to 14.5 mg/day; 2mg/day to 14 mg/day; 2.5mg/day to 13.5 mg/day; 3mg/day to 13mg/day; 4mg/day to 12 mg/day; 5mg/day to 11mg/day; 6mg/day to 10mg/day. In one embodiment, the effective amount of the at least one immunomodulator is 1mg/day; 2mg/day; 2.5 mg/day; 3mg/day; 3.5mg/day; 4mg/day; 4.5mg/day; 5mg/day; 5.5mg/day; 6mg/day; 6.5mg/day; 7mg/day; 7.5mg/day; 8mg/day; 8.5mg/day; 9mg/day; 9.5mg/day; 10mg/day; 10.5mg/day; 11mg/day; 11.5mg/day; 12mg/day; 12.5mg/day; 13mg/day; 13.5mg/day; 14mg/day; 14.5mg/day; 15mg/day.

According to some embodiments, the above pharmaceutical composition further comprises an effective amount of at least one antiviral agent. A non-limiting list of antiviral agents includes acyclovir, gancyclovir, valganciclovir, valacyclovir, famciclovir, penciclovir, vidarabine, cidofovir, ribavirin, adefovir, entecavir, favipiravir, brincidofovir, Idoxuridine, trifluridine, tipiracil, edoxudine, brivudine, FV-100, sorivudine, cytarabine, lamivudine, lobucavir, telbivudine, clevudine, tenofovir disoproxil, tenofovir alafenamide, and zidovudine. Any acceptable dose and administration regimen of the antiviral agent according to the embodiments of the invention can be used.

According to some embodiments of the above combination, the virus of the *Coronaviridae* family is selected from the group

consisting of SARS-CoV-2 (COVID-19), SARS-CoV, MERS, OC43, 229E, NL63, OC43, and HKU1. In one embodiment, the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19).

The pharmaceutical composition according to the embodiments of the invention may be a fixed dosage form composition. In one embodiment, the pharmaceutical composition is a solid composition, a liquid composition, or a semi-solid composition. In another embodiment, the pharmaceutical composition is designed for oral administration, intra-muscular administration, intravenous administration, intraperitoneal administration, intranasal administration, intramucosal administration, or transdermal administration. In yet another embodiment, the pharmaceutical composition is in the form of a tablet, a capsule, a powder, a powder for suspension, a powder for reconstitution, granules, a syrup, a suspension, a suppository, a patch, and a dispersion.

According to some embodiments, the invention provides the above pharmaceutical compositions for use as a medicament.

According to some embodiments, the invention provides the above pharmaceutical compositions for use in the treatment of a condition associated with an infection by a virus of the *Coronaviridae* family, in a subject in need of such treatment. According to some embodiments, the condition associated with the infection by a virus of the *Coronaviridae* family is selected from the group consisting of acute respiratory distress syndrome (ARDS), common cold, pneumonia, bronchitis, severe acute respiratory syndrome, and Middle East respiratory syndrome.

According to some embodiments, the invention provides method for treating a subject afflicted with a condition associated with an infection by a virus of the *Coronaviridae* family with a pharmaceutical compositions according to the embodiments of the invention, comprising the steps of: a) administering a

therapeutic amount of the pharmaceutical composition to the subject; b) determining whether the subject is a responder by determining the gene expression profile of the subject, and comparing the gene expression profile to a reference gene expression profile to identify the subject as a responder; and c) continuing the administration if the subject is identified as a responder, or modifying treatment of the subject if the subject is not identified as a responder. As used herein the term "responder" is meant to be understood, without limitation, as a subject who, based on his gene expression profile, namely specific biomarkers, is likely to respond to the proposed treatment. For example, genetic profile of the Responder is characterized by upregulation and/or downregulation of certain genes, while genetic profile of the Non-Responder is characterized by different pattern of gene expression. The reason for the differentiated response can be a result of various cellular pathway and processes. The change in genetic profile may be triggered, without limitation, by administration of the proposed therapeutics and/or by the infection itself. The variability in the response of different people to viral infection and may lead to differential gene expression and different response to therapeutic tool. The opposite is also possible, while administration of similar therapeutics to different people may lead to different gene expression pattern which becomes a determinant of the clinical outcome.

According to some embodiments, the invention further provides a method for treating a human subject presenting clinical manifestations associated with infection by a virus of the *Coronaviridae* family with pharmaceutical compositions according to the embodiments of the invention, comprising the steps of:(i) determining the gene expression profile of the subject;(ii) identifying the subject as a predicted responder if the gene expression profile is indicative of subject being a responder;

and(iii) administering the pharmaceutical composition to the subject only if the subject is identified as a predicted responder

According to some embodiments of the above methods, compositions and combinations, a non-limiting list of clinical manifestations according to the embodiments of the invention includes fever, cough, dyspnea, hypoxia, more than 50% lung involvement on imaging, respiratory failure, shock, multiorgan system dysfunction, malaise, fatigue, sputum/secretion, neurological symptoms, dermatological manifestations, anorexia, myalgia, sneezing, sore throat, rhinitis, goosebumps, headache, chest pain and diarrhea.

Examples

Example 1: Homology modeling of SARS-CoV-2 Targets.

Methods

The sequencing data of COVID-19 were retrieved from Genbank database under the FASTA format for analysis. Homology modelling was performed using Swiss model webserver (http://swissmodel.expasy.org/). Swiss model was used for 3D structure prediction and also template selection. The best homology models were selected according to Global Model Quality Estimation (GMQE) and QMEAN statistical parameters. The prediction of ligand binding site for few proteins in the modelled protein structure was made using 3DLigandSite server (http://www.sbg.bio.ic.ac.uk/3dligandsite/). Quality and accuracy with validation of the predicted models were analyzed performing RAMPAGE for Ramachandran plot analysis.

Procedure

Homology modelling of protein targets for antiviral/antibiotics, in particular, of spike glycoprotein (S protein) from SARS-CoVid-2, and RNA-dependent RNA-polymerase (RdRp), was performed

based on known templates with similar structure/function. For template selection, the target sequence was searched against Protein Data Bank (PDB) database using PSI-BLAST tool and threading server Protein Homology/analogY Recognition Engine (PHYRE) (17). Based on BLAST and PHYRE analysis, a number of proteins from Viruses/Bacteria/ Fungi were retrieved as top-score hits. In order to get available 3D structures with ligand/drug bound sites as templates for modelling potential targets on SARS-CoV-2, we data-mined the Protein Data Bank with FDA approved antibiotics, namely, Doxycycline, Azithromycine, Clarithromycine, Amikacin, Tobramycine, etc. as queries. Structures were further studied and compared using different structure superimposing servers Vector Alignment Search Tool (VAST), PDBefold, Combinatorial Extension (CE), and threading servers PHYRE, 3D-Position Specific Scoring Matrix (3DPSSM). Hits with bound antibiotics/antiviral drugs were selected, and multiple structure-based sequence alignments were performed. Based on these alignments, structures from PDB were selected as multiple templates and used for further modelling based on SWISS-MODEL, MODELLER, and iTASSER protocols.

The models were further evaluated using Ramachandran plot, ERRAT (Protein structure verification web server) and ProSA (Protein Structure Analysis).

Quality assessment of protein models

The global and per-residue model quality has been assessed using the QMEAN scoring function.

Docking

Docking grids were generated using the receptor grid generation module in AutoDock4 application. Grids were generated with OPLS-like force field, keeping the default values of van der Waals scaling factor set to 0.8 and charge cutoff set to 0.15. The binding sites were defined at the (1) SARS-CoVid-2 spike glycoprotein/hACE and (2) virus RNA interfaces, respectively.

For RdRp, the center of ATP-binding region was used for the definition of bindingsite. Cubicboxes of 35Å dimension centre don these binding sites were generated for each docking model.

The modules from OpenBabel suite and Chimera v1.11.2 were used to prepare ligand molecules for docking. When available, 3D structures of antiviral/antibiotics molecules were taken from PDB (such as Doxycycline, Azithromycine, Clarithromycine, Amikacin, Tobramycine, etc.). All possible ionization states and tautomers were generated and prepared for docking study. Molecular conformers were generated and docked to the areas identified as binding sites, using AutoDock4 and AutoDock Vina docking protocols. Docking strategy included writing per-residue interaction energy values in order to determine key residues involved in antibiotics binding and selectivity. All molecules from our library of FDA approved antiviral/antibiotics were docked to Site1 and Site2 regions (as identified by FTMap), and these docking conformations with the best scores were analyzed. Compounds which showed favorable interactions and good AutoDock Vina score, were then selected for further mechanism-of-action analysis.

Results

Targeting SARS-CoV-2 spike glycoprotein

A multi-target attack was defined on the SARS-CoV-2 spike glycoprotein to three possible binding sites: RNA binding site with the viral RNA, the SARS-CoV-2 surface binding to the human cell receptor ACE2 binding site (Figure 1).

First, all the anti-pneumonia agents, particularly, antibiotics we collected (Table 1). Most interesting there were molecules with a mechanism of actions to RNA, such as a binding to the 50S subunit of the bacterial ribosome, thus, inhibiting translation of mRNA. Such antibiotics are known to have RNA binding property and may prevent virus from two functions: (1) virus particle re-assembly by binding of the S-glycoprotein to the viral surface,

and (2) binding of this glycoprotein to human/host ACE2 receptor (Figures 2-4).

Table 1. antibiotics drugs candidates:

ACC_id: drugbank.ca/drugs/	Generic Name	ACTIVE INGREDIENT	UNII:	CAS Number	ACC_salt_id: drugbank.ca/salts/
DB01137	Levofloxacin	Levofloxacin hemihydrate	6GNT3Y5LMF	138199-71-0	DBSALT001001
DB01211	Clarithromycin	Clarithromycin citrate	16K08R7NG0	848130-51-8	DBSALT002306
DB01137	Levofloxacin	Levofloxacin hemihydrate	6GNT3Y5LMF	138199-71-0	DBSALT001001
DB01212	Ceftriaxone	Ceftriaxone sodium	023Z5BR09K	104376-79-6	DBSALT001213
DB00207	Azithromycin	Azithromycin dihydrate	5FD1131I7S	117772-70-0	DBSALT000882
DB00207	Azithromycin	Azithromycin monohydrate	JTE4MNN1MD	121470-24-4	DBSALT001208
DB01060	Amoxicillin	Amoxicillin sodium	544Y3D6MYH	34642-77-8	DBSALT000868
DB01060	Amoxicillin	Amoxycillin trihydrate	804826J2HU	61336-70-7	DBSALT000867
DB00254	Doxycycline	Doxycycline calcium	8ZL07I20SB	94088-85-4	DBSALT001217
DB00254	Doxycycline	Doxycycline hyclate	19XTS3T51U	24390-14-5	DBSALT000896
DB00254	Doxycycline	Doxycycline hydrochloride	4182Z6T2ET	10592-13-9	DBSALT000897
DB00254	Doxycycline	Doxycycline monohydrate	N12000U13O	17086-28-1	DBSALT001956
DB00218	Moxifloxacin	Moxifloxacin hydrochloride	C53598599T	186826-86-8	DBSALT000387
DB00218	Moxifloxacin	Moxifloxacin hydrochloride monohydrate	B8956S8609	192927-63-2	DBSALT002560
DB00537	Ciprofloxacin	Ciprofloxacin hydrochloride	0MP32MFP6C	93107-08-5	DBSALT000293
DB01190	Clindamycin	Clindamycin hydrochloride	T20OQ1YN1W	21462-39-5	DBSALT001163
DB01190	Clindamycin	Clindamycin palmitate hydrochloride	VN9A8JM7M7	25507-04-4	DBSALT001215
DB01190	Clindamycin	Clindamycin phosphate	EH6D7113I8	24729-96-2	DBSALT000778
DB00535	Cefdinir	Cefdinir monohydrate	6E7SN358SE	213978-34-8	DBSALT001745
DB00766	Clavulanic	Clavulanate potassium	Q42OMW3AT8	61177-45-5	DBSALT001302
DB00440	Trimethoprim	Trimethoprim hydrochloride	9XE000OU9B	60834-30-2	DBSALT001480
DB00440	Trimethoprim	Trimethoprim sulfate	E377MF8EQ8	56585-33-2	DBSALT001471
DB00493	Cefotaxime	Cefotaxime sodium	258J72S7TZ	64485-93-4	DBSALT000547
DB01015	Sulfamethoxazole	Trimethoprim			
DB00916	Metronidazole	Metronidazole hydrochloride	76JC1633UF	69198-10-3	DBSALT000362
DB01112	Cefuroxime	Cefuroxime axetil	Z49QDT0J8Z	64544-07-6	DBSALT001355

DB01112	Cefuroxime	Cefuroxime sodium	R8A7M9MY61	56238-63-2	DBSALT001160
DB01327	Cefazolin	Cefazolin sodium	P380M0454Z	27164-46-1	DBSALT000310
DB00512	Vancomycin	Vancomycin hydrochloride	71WO621TJD	1404-93-9	DBSALT000300
DB01413	Cefepime	Cefepime hydrochloride	I8X1O0607P	123171-59-5	DBSALT000920
DB00438	Ceftazidime	Ceftazidime pentahydrate	9M416Z9QNR	78439-06-2	DBSALT001024
DB00438	Ceftazidime	Ceftazidime sodium	CMC30V039K	73547-61-2	DBSALT001474
DB00601	Linezolid	Linezolid	ISQ9I6J12J	165800-03-3	
DB00479	Amikacin	Amikacin sulfate	N6M33094FD	39831-55-5	DBSALT000351
DB01606	Tazobactam	Tazobactam sodium	UXA545ABTT	89785-84-2	DBSALT001475
DB01416	Cefpodoxime	Cefpodoxime proxetil	2TB00A1Z7N	87239-81-4	DBSALT001354
DB01416	Cefpodoxime	Cefpodoxime sodium	3ULP5169B3	82619-04-3	DBSALT001810
DB01597	Cilastatin	Cilastatin sodium	5428WXZ74M	81129-83-1	DBSALT001295
DB01598	Imipenem	Imipenem monohydrate	71OTZ9ZE0A	74431-23-5	DBSALT002429
DB00199	Erythromycin	Erythromycin estolate	XRJ2P631HP	3521-62-8	DBSALT001358
DB00199	Erythromycin	Erythromycin ethylsuccinate	1014KSJ86F	1264-62-6	DBSALT001220
DB00199	Erythromycin	Erythromycin gluceptate	2AY21R0U64	23067-13-2	DBSALT001340
DB00199	Erythromycin	Erythromycin lactobionate	33H58I7GLQ	3847-29-8	DBSALT001219
DB00199	Erythromycin	Erythromycin phosphate	I8T8KU14X7	4501-00-2	DBSALT001624
DB00199	Erythromycin	Erythromycin stearate	LXW024X05M	643-22-1	DBSALT001221
DB00199	Erythromycin	Erythromycin sulfate	KVW9N83AME	7184-72-7	DBSALT002260
DB00199	Erythromycin	Erythromycin thiocyanate	Y7A95YRI88	7704-67-8	DBSALT001625
DB00319	Piperacillin	Piperacillin sodium	M98T69Q7HP	59703-84-3	DBSALT001067
DB00684	Tobramycin	Tobramycin hydrochloride	01IX3OU168	95188-93-5	DBSALT002273
DB00684	Tobramycin	Tobramycin sulfate	HJT0RXD7JK	49842-07-1	DBSALT000317
DB00671	Cefixime	Cefixime trihydrate	97I1C92E55	125110-14-7	DBSALT001818
DB00485	Dicloxacillin	Dicloxacillin sodium	4HZT2V9KX0	13412-64-1	DBSALT001622
DB00485	Dicloxacillin	Dicloxacillin sodium anhydrous	4CKS6MOL6Z	343-55-5	DBSALT000495
DB00417	Phenoxymethylpenicillin	Phenoxymethylpenicillin benzathine	3T4EMH59ZU	5928-84-7	DBSALT001952
DB00417	Phenoxymethylpenicillin	Phenoxymethylpenicillin potassium	146T0TU1JB	132-98-9	DBSALT000299

Second, the anti-viral agents and anti-viral drugs were collected (Table 2) with a mechanism of action against viruses,

in particular, Rimantadine and other Amantadines (Table 2). The exact mechanism of action of Rimantadine is not understood. This agent appears to exert its antiviral effect against Influenza A virus by interfering with the function of the trans-membrane domain of the viral M2 protein, thereby preventing the uncoating of the virus and subsequent release of infectious (Figure 5). It might be effective against corona virus (Figure 5). Third, we proposed natural agents that may bind virus, particularly secondary metabolites found in plants, for example, in roots of Salvadora persica (Figure 5).

Table 2. antiviral drugs candidates:

ACC_id: drugbank.ca/drugs/	Generic Name	ACTIVE INGREDIENT	UNII:	CAS Number
DB00787	Acyclovir	Acyclovir sodium	927L42J563	69657-51-8
DB00495	Zidovudine		4B9XT59T7S	30516-87-1
DB00194	Vidarabine		3XQD2MEW34	24356-66-9
DB00249	Idoxuridine		LGP81V5245	54-42-2
DB00632	Docosanol		9G1OE216XY	661-19-8
DB06759	Fomivirsen	Fomivirsen sodium	3Z6W3S36X5	160369-77-7
DB13421	Edoxudine		15ZQM81Y3R	15176-29-1
DB00432	Trifluridine		RMW9V5RW38	70-00-8
DB00787	Acyclovir	Acyclovir sodium	927L42J563	69657-51-8
DB01266	Sinecatechins		T432289GYZ	188265-33-0
DB13156	Inosine pranobex		W1SO0V223F	36703-88-5
DB13288	Tromantadine		H191JFG8WA	53783-83-8
DB01004	Ganciclovir	Ganciclovir sodium	02L083W284	107910-75-8
DB00008	Peginterferon alfa-2a		Q46947FE7K	198153-51-4
DB00011	Interferon alfa-n1		41697D4Z5C	74899-72-2
DB00022	Peginterferon alfa-2b	Interferon alfa-2b	43K1W2T1M6	98530-12-2
DB00060	Interferon beta-1a		XRO4566Q4R	145258-61-3
DB00069	Interferon alfacon-1		56588OP40D	118390-30-0
DB00109	Enfuvirtide		19OWO1T3ZE	159519-65-0
DB00110	Palivizumab		DQ448MW7KS	188039-54-5

DB00198	Oseltamivir	Oseltamivir phosphate	4A3O49NGEZ	204255-11-8
DB00220	Nelfinavir	Nelfinavir mesylate	98D603VP8V	159989-65-8
DB00224	Indinavir	Indinavir monohydrate	5W6YA9PKKH	180683-37-8
DB00224	Indinavir	Indinavir sulfate	771H53976Q	157810-81-6
DB00238	Nevirapine	Nevirapine hemihydrate	B7XF2TD73C	220988-26-1
DB00299	Penciclovir	ri	P06226385L	97845-62-0
DB00300	Tenofovir disoproxil	Tenofovir disoproxil fumarate	OTT9J7900I	202138-50-9
DB00369	Cidofovir	Cidofovir dihydrate	JIL713Q00N	149394-66-1
DB00426	Famciclovir	Penciclovir	359HUE8FJC	39809-25-1
DB00442	Entecavir	Entecavir monohydrate	5968Y6H45M	209216-23-9
DB00442	Entecavir	Entecavir triphosphate		
DB00478	Rimantadine	Rimantadine hydrochloride	JEI07OOS8Y	1501-84-4
DB00495	Zidovudine		4B9XT59T7S	30516-87-1
DB00503	Ritonavir		O3J8G9O825	155213-67-5
DB00529	Foscarnet	Foscarnet sodium	8C5OQ81LWT	63585-09-1
DB00558	Zanamivir		L6O3XI777I	139110-80-8
DB00577	Valaciclovir	Valaciclovir hydrochloride	G447S0T1VC	124832-27-5
DB00625	Efavirenz		JE6H2O27P8	154598-52-4
DB00649	Stavudine		BO9LE4QFZF	3056-17-5
DB00701	Amprenavir		5S0W860XNR	161814-49-9
DB00705	Delavirdine	Delavirdine mesylate	421105KRQE	147221-93-0
DB00709	Lamivudine		2T8Q726O95	134678-17-4
DB00718	Adefovir dipivoxil	Adefovir	6GQP90I798	106941-25-7
DB00811	Ribavirin		49717AWG6K	36791-04-5
DB00879	Emtricitabine		G70B4ETF4S	143491-57-0
DB00900	Didanosine		K3GDH6OH08	69655-05-6
DB00915	Amantadine	Amantadine hydrochloride	M6Q1EO9TD0	665-66-7
DB00915	Amantadine	Amantadine sulfate	9921T5P019	31377-23-8
DB00932	Tipranavir	Tipranavir disodium	9BAN2XG1ZW	191150-83-1
DB00943	Zalcitabine		6L3XT8CB3I	7481-89-2

Example 2: Antiviral cocktail based on Acyclovir and Dexamethasone Phosphate against COVID-19.

Based on the described above key anti-viral mechanism on the structural level, a new pharmaceutical combination was designed, aimed to enhance the pharmaco-therapeutic potential of Acyclovir in the treatment of patients infected by SARS-CoV-2. This includes Dexamethasone phosphate acting as the phosphate donor for Acyclovir biotransformation. An additional phosphate donor was antibiotic Fosfomycin the phosphoenolpyruvate analogue with the phosphate group bound to epoxypropyl moiety. Fosfomycin is old well-tolerated antimicrobial drug. According to our structure- based modeling results, this small molecule may enter inter-helical pores of viral surface proteins, in particular, the S-glycoprotein and thus may be in the pharmacological synergism with acyclovir action by being the phosphate donor. This biochemical and pharmacological synergism of the Acyclovir & Dexamethasole and Acyclovir & Fosfomycin compositions provided with promising opportunity in the current urgent need of novel methods to stop the outburst of the SARS-CoV-2.

Example 3: POC Testing for Human Coronavirus OC43 (hCoV-OC43) Attenuation by Azythromycin & Dexamethasone Phosphate Liquid Formula

The aim of the study was POC testing of the antiviral potential of a formula containing azithromycin and dexamethasone phosphate, on human coronavirus OC43 (hCoV-OC43), by cytopathogenic effect (CPE) monitoring and cell viability assay.

Samples

1. One vial of 10mg azithromycin
2. One vial of 10mg dexamethasone phosphate, 98%

Samples were stored at 4°C.

Materials

1. Human MRC5 cells (lung fibroblasts; ATCC, Cat # CCL-171)
2. L-Alanyl-L-Glutamine Solution (200 mM; Biological Industries, Cat # 03-022-1B) 4.3. Penicillin-Streptomycin Solution (Biological Industries, Cat # 03-031-1B)
3. Fetal Bovine Serum (FBS; Biological Industries, Cat # 04-127-1A)
4. MEM-NEAA Medium (Biological Industries, Cat # 01-040-1A)
5. Human coronavirus OC43 (hCoV-OC43; stock titer: 6.36x106 TCID50/ml)
6. Consumables:15mltube(Corning,Cat#430055),filtertips(Axygen,Cat#TF-300-R-S,TF-200R- S), filter tips (Thermo Fisher, Cat # 94052410), 96-well plate (Greiner Bio One, Cat # 655180), sterile 1.5 ml microcentrifuge tubes (SARSTEDT Cat# 72.690), Minisart syringe filter (0.2 Œ°m; Sartorius, Cat # 17597-K)

Methods and experimental procedures

Cytotoxicity test:

Sample preparation: MRC5 cells were grown in MEM medium (4.5) supplemented with 2mM L-Alanyl-L-Glutamine, 1% Penicillin-Streptomycin and 10% FBS, in an incubator at 37°C and 5% CO_2. On the day of the experiment 1.1mg dexamethasone phosphate were dissolved in 1ml 0.1M NaOH (to reach a final concentration of 100µM/mL). 1.3mg azithromycin were dissolved in 10ml 0.1MNaOH to reach a concentration of 13µM/mL. Next, the two solutions were mixed 1:1 to a final volume of 2ml, to generate a stock solution with final concentration 1mM dexamethasone phosphate and 0.13mM of azithromycin in 1mL. The 2ml stock solution was filter sterilized through a Minisart syringe filter (0.2µm filter;).Following filtration, the formula was diluted four (4) times to provide 4 concentrations as follows:

- 1.3µM azithromycin, 200µM dexamethasone phosphate

- 0.64µM azithromycin, 100µM dexamethasone phosphate
- 0.32µM azithromycin, 50µM dexamethasone phosphate
- 0.16µM azithromycin, 25µM dexamethasone phosphate

All dilutions were performed in MEM medium supplemented with 2mM L-Alanyl- LGlutamine, 1% Penicillin-Streptomycin and 10% FBS. Table 3 summarizes the azithromycin-dexamethasone phosphate formula preparation and its dilutions.

Table 3. azithromycin-dexamethasone phosphate formulas preparation and its dilutions.:

Substance	Stock	Final concentrations placed on cells (in MEM)			
		I (1:5 of stock)	II (1:2 of I)	III (1:2 of II)	IV (1:2 of III)
Azithromycin	1.3mg azithromycin (in 10ml 0.1MNaOH concentration of 13µM/mL)	1.3µM	0.64 µM	0.32 µM	0.16µM
Dexamethasone phosphate	1 mM (in 0.1M NaOH)	200µM	100µM	50µM	25µM

Experimental procedure

On the day of the experiment, the cell growth medium was removed and 250µl of each of the four (4) dilutions prepared (5.1.1) were added, each in a triplicate, to the cells instead of the removed medium. In parallel, in the same 96-well plate, three (3) additional wells (triplicate) were used as negative control (NC-tox) for the viability assay, in which the media was replaced by 250µl sterile MEM, containing no azithromycin-dexamethasone phosphate formula. Following media replacement in the MRC5 96-well plate, cells were incubated for six (6) days at 37°C and 5% CO_2, and monitored every 24 hours under the microscope. Cell viability was determined by MTT assay on day six (6) of incubation.

MTT viability assay

On day 6 of the test, the growth medium was removed from each well. Next, 5 mg/ml MTT compound (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, in PBS) was diluted 1:7.5 in MEM, and 150µl of the diluted MTT were added per well as

replacement medium. The plate was then incubated for 2 hours at 37OC and 5% CO2. Following incubation, medium + MTT was removed, and 100µl DMSO were added per well. The plate was incubated for 15 minutes at room temperature following DMSO addition and was read by SPECTRAFluor Plus plate reader (Tecan) at 560nm.

MTT assay results are presented below in Table 4

Azithromycin-dexamethasone phosphate formula - antiviral activity experiment

Sample preparation

MRC5 cells were plated in a 96-well plate, and grown as described above. On the day of the experiment (day 1) cells were either infected with hCoV-OC43 at TCID50 = 3.16x103 for the treatment testing (Tr), or with seven 10-fold serial dilutions of hCoV-OC43 (each in 4 replicates), starting at TCID50 = $3.16x10^6$ to serve as viral infection calibration curve. All viral infections were performed in MEM medium supplemented with 2mM L-Alanyl-L-Glutamine, 1% Penicillin Streptomycin and 2% FBS, and the plate was then placed in an incubator at 35°C and 5% CO_2. Twenty-four (24) hours post-infection, on day 2, 1.3µM azithromycin, azithromycin -dexamethasone phosphate formula stock solution was prepared in the same procedure elaborated in section 5.1.1 (final concentrations: 1mM azithromycin, 1mM dexamethasone phosphate). The formula stock solution was filter sterilized through a Minisart syringe filter (0.2µm filter; 4.7), and was then diluted to provide 4 concentrations as follows:

- 1.3µM azithromycin, 200µM dexamethasone phosphate
- 0.64µM azithromycin, 100µM dexamethasone phosphate
- 0.32µM azithromycin, 50µM dexamethasone phosphate
- 0.16µM azithromycin, 25µM dexamethasone phosphate

The stock was then kept at 4°C. All dilutions were performed in MEM medium supplemented with 2mM L-Alanyl-L-Glutamine, 1% Penicillin-Streptomycin, and 2% FBS.

Experimental procedure

Day 2 of the experiment: following formula dilutions, the cells were monitored under the microscope. Next, the growth medium of MRC5 cells 96-well plate was removed, and 125µl of each of the four (4) dilutions prepared were added, each in a triplicate, to cells infected the day before instead of the removed medium (treatment; Tr). In parallel, in the same 96-well plate, 125µl of each of the four (4) dilutions prepared were added, each in a triplicate, to wells of uninfected cells instead of the removed medium (negative control; NC). For the calibration curve, in each replicate of 4 wells, 125µl of sterile MEM medium were added, to cells infected the day before instead of the removed medium. Four (4) additional wells of uninfected cells (as replicates) were used as negative control (NC-c) for the calibration curve viability assay, to which 125µl of sterile MEM medium were added. The MRC5 96-well plate was then returned to the incubator for 3 additional days at 35OC and 5% CO2, and monitored every 24 hours under the microscope. Cell viability was determined by MTT assay on day 6 of the experiment.

Day 3 of the experiment: twenty-four (24) hours post-medium replacement in the MRC5 plate, the cells were monitored under the microscope. Next, the formula stock solution was removed from 4OC, and dilutions were made to produce the same 4 concentrations as in section. To the Tr wells, additional 125µl treatment of each of the four formula dilutions were added, each in a triplicate, of cells infected on day 1 of the experiment. To the NC wells additional 125µl treatment of each of the four formula dilutions were added, each in a triplicate, of cells uninfected on day 1 of the experiment. To the calibration curve wells and the NC-c wells additional 125µl of sterile MEM medium

were added. The MRC5 96-well plate was then returned to the incubator for 3 additional days at 35OC and 5% CO_2,and monitored every 24 hours under the microscope. Cell viability was determined by MTT assay on day 6 of the experiment.

MTT viability assay

on day 6 of the experiment, the growth medium was removed from each well. Next, the procedure as described in section was performed. MTT assay results are presented in Table 4.

Table 4. Cytotoxicity test results - % cell viability upon 6-day treatment with the acyclovir- dexamethasone phosphate formula:

Formula concentration	% Cell viability
I- Az 1.3 µM / D.ph 200 µM	100
II- Az 0.64 µM / D.ph 100 µM	100
III- Az 0.32 µM / D.ph 50 µM	112
IV- Az 0.16 µM / D.ph 25 µM	105
Az 1.3 µM/ NO D.ph	100

Az: azithromycin, D.ph: dexamethasone phosphate NC-tox: negative control (i.e cells incubated with MEM medium only) Az 1.3 µM/ NO D.ph cells incubated with azithromycin % Cell viability: indicating viable cells per sample. Cell viability per each sample was calculated as percentage of the average MTT result of each triplicate, from the average of NC wells MTT results, which was regarded as representing 100% cell viability.

Results and conclusion

The results displayed indicate that the tested formula, as tested in the current study, does hamper hCoV-OC43 infectivity and reduce viral load by 1.6 log following 2 dose treatment, and incubation for 3 days following treatment (as indicated in Table 5). Furthermore, based on our microscope monitoring during the

6 days of the experiment, we have observed viral cytopathogenic effects (CPE) using the in all wells of the cells infected with hCoVOC43 and then twice treated with the acyclovir-dexamethasone phosphate formula. These results should be repeated. The CPE started 3 days post-viral infection of the cells, and was observed to a similar extent following all 4 treatments of the formula (i.e., in all 4 concentrations). In conclusion, in this study, 4 concentrations of a liquid formula were tested as antiviral treatment post cell infection with hCoV-OC43. To that end, we employed a direct method assaying cell viability following their infection with the virus and their treatment in a double dose of the tested formula. Results of this study indicate that the tested treatment increase the viability of MRC5 cells. Additional experiment is presented in Table

Azithromycin-dexamethasone phosphate formula antiviral activity experiment – CPE & MTT assay results (CPE and MTT assay results, as presented in Table 5):

Table 5. azithromycin-dexamethasone phosphate formula antiviral activity experiment – CPE & MTT assay results

Treated cells formula concentration	Initial viral $TCID_{50}$	% Cell viability	Viral log reduction	CPE / outset day
Az 1.3 µM / D.ph 100µM	**3.16E+03**	**30**	**1.6**	**+ - - / day 4, +-- / day 6**
Az 0.64 µM / D.ph 50µM	3.16E+03	20	1.2	minor / day 4, +-- / day 6
Az 0.32 µM / D.ph 25µM	3.16E+03	20	1.2	minor / day 4, ++- / day 6
Az 0.16 µM / D.ph 12.5µM	3.16E+03	20	1.2	minor / day 4, ++- / day 6
Az 1.3 µM / NO D.ph	**3.16E+03**	**22**	**1.3**	**minor / day 4, ++-/ day 6**

% Cell viability: indicating viable cells per sample. Cell viability per each sample was calculated as percentage of the average MTT result of each treatment concentration + hCoV-OC43 infection, from the average of MTT result of the same treatment concentration with no hCoV-OC43 infection. Initial

viral TCID50: the viral inoculum used to infect the cells on day 1 of the experiment.

Viral log reduction: is calculated by dividing the initial viral TCID50 by the end viral TCID50 in each sample. CPE / outset day: the viral cytopathogenic effects as observed under the microscope during the 6 days of experiment. '+++' = massive CPE, '++-' = mild CPE, '+--' = minimal CPE. Day indicates the outset day of observed CPE. No anti-viral activity was observed for D.ph using 100 µM concentration.

The results indicate that the tested formula, as tested in the current study, does hamper hCoV-OC43 infectivity and reduce viral load by 1.6 log following 2 dose treatment, and incubation for 3 days following treatment. Furthermore, based on our microscope monitoring during the 6 days of the experiment, viral cytopathogenic effects (CPE) were observed in all wells of the cells infected with hCoVOC43 and then twice treated with the azithromycin-dexamethasone phosphate formula. The CPE started 3 days post-viral infection of the cells, and was observed to a similar extent following all 4 treatments of the formula (i.e. in all 4 concentrations).

In conclusion, in this study, 4 concentrations of a liquid formula containing azithromycin and dexamethasone phosphate were tested as antiviral treatment post cell infection with hCoV-OC43. To that end, we employed a direct method assaying cell viability following their infection with the virus and their treatment in a double dose of the tested formula. Results of this study indicate that the tested treatment increase the viability of MRC5 cells by 10%.

Example 4: Genomic biomarkers for composition suitability analyses

CXCL8 (also referred to as IL-8) is a chemokine considered a potential prognostic biomarker for acute respiratory distress syndrome (ARDS) clinical course. CXCL8 plays a vital role in the early control of respiratory tract infection due to its chemotactic activity for neutrophils and monocytes. The activity of CXCL8 is strongly reliant on the transcription factor AP-1 and is associated with the spike and nucleocapsid proteins of

SARS-CoV-2. CXCL8 stimulates the formation of the highly immunogenic and toxic neutrophil extracellular traps (NETs) that lead to inflammation and apoptosis of epithelial/endothelial cells. Using the differential gene expression analysis and comparative profiling of transcriptome data, we observed that CXCL8 is consistently up-regulated in the bronchoalveolar lavage fluid (BALF) of severe COVID-19 patients. Hence, CXCL8 could be used as a biomarker for severe COVID-19 cases as they are not found to be up-regulated in case of mild COVID-19 cases. Therefore, inhibitors of CXCL8 could be considered as possible therapeutic modalities for severe COVID-19. Based on the previous studies, we collected the FDA-approved drugs that could be effective against the CXCL8. Based on the structural analysis, we found Acyclovir and Azithromycin are the most effective FDA-approved drugs that could be used for controlling the expression of CXCL8. Our studies suggest that a combination of these two drugs could be useful for treating severe COVID-19 cases to reduce the chances of ARDS.

Table 6:

Non-severe COVID-19 (DE based on PBMC data)

Chemical Name	Gene name	Category
Acyclovir	HLA-DRB6	Upregulated
Acyclovir	PNP	Upregulated
Acyclovir	PTGS2	Downregulated
Acyclovir, Azithromycin	CXCL8	Downregulated
Azithromycin	CTSB	Upregulated
Azithromycin	HEXB	Upregulated
Azithromycin	AOC1	Downregulated

Table 7:

Severe COVID-19 (DE based on BALF data)

Chemical Name	Gene name	Category
Acyclovir	SLPI	Upregulated
Acyclovir	IDO1	Upregulated
Acyclovir	SLC7A11	Upregulated
Acyclovir	PTGS2	Upregulated
Acyclovir	MR1	Downregulated
Acyclovir	PNP	Downregulated
Acyclovir	ABCG2	Downregulated
Acyclovir, Azithromycin	CXCL8	Upregulated
Azithromycin	MMP1	Upregulated
Azithromycin	ARG1	Upregulated
Azithromycin	CCL2	Upregulated
Azithromycin	BCL2L1	Downregulated
Azithromycin	CTSB	Downregulated
Azithromycin	HEXB	Downregulated
Azithromycin	ARSA	Downregulated
Azithromycin	MAN2B2	Downregulated

Commons differentially expressed genes between severe and non-severe COVID-19 cases are highlighted. We can see three genes which are upregulated in the non-severe cases are found to downregulated in severe cases while two genes which are downregulated in non-severe cases are found to upregulated in severe cases.

Example 5: Clinical trial evaluating safety and efficacy of the combination of azithromycin & dexamethasone phosphate on clinical manifestation of COVID-19 infection

A clinical study to asses safety and efficacy of administration of the combination of azithromycin and dexamethasone in moderate COVID-19 patients requiring supplemental oxygen via nasal cannula is conducted. The clinical trial is divided into two phases: phase I including approximately 10 patients and phase II, double blinded study including about 50-100 moderate COVID-19 patients. A at least one endpoint of the study is assessing antiviral effect of the combination versus standard of care treatment.

The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used herein, the singular forms "a," "an" and "the" are intended to include plural forms as well, unless the context clearly indicates otherwise. It will be further understood that the terms "comprises" or "comprising," when used in this specification, specify the presence of stated features, integers, steps, operations, elements components and/or groups or combinations thereof, but do not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components and/or groups or combinations thereof. As used herein the terms "comprises", "comprising", "includes", "including", “having” and their conjugates mean "including but not limited to". The term “consisting of” means “including and limited to”.

As used herein, the term "and/or" includes any and all possible combinations or one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

Unless otherwise defined, all terms (including technical and scientific terms) used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. It will be further understood that terms, such as those defined in commonly used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the specification and claims and should not be interpreted in an idealized or overly formal sense unless expressly so defined herein. Well-known functions or constructions may not be described in detail for brevity and/or clarity.

It will be understood that, although the terms first, second, etc., may be used herein to describe various elements, components, regions, layers and/or sections, these elements, components, regions, layers and/or sections should not be limited by these terms. Rather, these terms are only used to distinguish one element, component, region, layer and/or section, from another element, component, region, layer and/or section.

Certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those

embodiments, unless the embodiment is inoperative without those elements.

Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

Whenever the term "about" is used, it is meant to refer to a measurable value such as an amount, a temporal duration, and the like, and is meant to encompass variations of ±20%, ±10%, ±5%, ±1%, or ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known

manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

As used herein the term "patient" or "subject" is meant to include any mammal. A "mammal," as used herein, refers to any animal classified as a mammal, including but not limited to, humans, experimental animals including monkeys, rats, mice, and guinea pigs, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, and the like.

As used herein, a "pharmaceutically acceptable" carrier or excipient is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

"Treating" or "treatment" of a disease as used herein includes: preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease; inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms, or relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

A "therapeutically-effective amount" or an "effective amount" means the amount of a compound or a dosage form that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically-effective amount" will vary depending on the compound, the disease, and its severity and the age, weight, etc., of the subject to be treated.

As used herein the term "Pharmaceutically-acceptable salt" refers to salts which retain the biological effectiveness and properties of compounds which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts refer to

pharmaceutically acceptable salts of the compounds, which salts are derived from a variety of organic and inorganic counter ions well known in the art.

The pharmaceutical dosage forms may be prepared as medicaments to be administered orally. Suitable forms for oral administration include, without limitation, tablets, capsules, solutions, syrups and suspensions; such as ready-to-use syrups and suspensions, or reconstituted from solid dosage form such as, without limitation, dry powder. The dosage form may contain suitable binders, lubricants, coloring agents, flavoring agents, flow-inducing agents, stabilizing agents, solubilizing agents, antioxidants, buffering agent, chelating agents, and fillers, all collectively or individually fall under the definition of the term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient".

In the pharmaceutical composition, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert filler such as gelatin, agar, starch, methyl cellulose, mannitol, xylitol, sorbitol, maltodextrin and the like. Suitable binders include starch, gelatin, natural sugars such as corn starch, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, povidone, cellulose based soluble polymers such as but not limited to hydroxypropylomethylcellulose, hydroxypropylcellulose, polyethylene glycol, and the like. Glidants used in these dosage forms include sodium benzoate, sodium acetate, polyethylene glycole, and the like. Stabilizing (antimicrobial) agents include benzoic acid, and salts thereof, parahydroxybenzoate and salts thereof, sorbic acid and salts thereof and the like. Stabilizing (physical) agents include viscosity enhancing polymers such as hydroxyethyl cellulose, xanthan gum and the like.

All publications, patent applications, patents, and other references mentioned in the disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. In case of conflict, the patent specification, including definitions, will prevail. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. Throughout this application various publications, published patent applications and published patents are referenced.

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather the scope of the present invention is defined by the appended claims and includes both combinations and sub-combinations of the various features described hereinabove as well as variations and modifications thereof, which would occur to persons skilled in the art upon reading the foregoing description. While certain features of the invention have been illustrated and described herein, many modifications, substitutions, changes, and equivalents may occur to those skilled in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention. Various embodiments have been presented. Each of these embodiments may of course include features from other embodiments presented, and embodiments not specifically described may include various features described herein.

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Claims:

1. A method of treating a condition associated with an infection by a virus of the *Coronaviridae* family, in a subject in need of such treatment, the method comprising administering to the subject a therapeutically effective amount of

   a. at least one agent having an anti-microbial activity, and

   b. at least one immunomodulator,

   to thereby effectively treat the condition associated with the infection by the virus of the *Coronaviridae* family.

2. The method of claim 1, wherein the at least one agent having an anti-microbial activity is a macrolide.

3. The method of claim 1 or 2, wherein the at least one agent having an anti-microbial activity is selected from the group consisting of Azithromycin, Boromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Ivermectin, Josamycin, Midecamycin, Miocamycin, Oleandomycin, Rokitamycin, Roxithromycin, Spiramycin, Troleandomycin, Doxycycline, and Tylosin.

4. The method of any one of claims 1 to 3, wherein the at least one immunomodulator is a corticosteroid.

5. The method of any one of claims 1 to 3, wherein the at least one immunomodulator is selected from the group consisting of Desoxycortone (desoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol),

Hydrocortisone esters, Fludrocortisone, Fludrocortisone acetate, Methylprednisolone, Methylprednisolone esters, Prednisolone, Prednisolone esters, Prednisone, Cortisone, Cortisone acetate, Cortodoxone (cortexolone, 11-deoxycortisol), Desoxycortone (deoxycortone, cortexone, 11-deoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Prebediolone acetate, Pregnenolone, Pregnenolone acetate, Pregnenolone succinate, Cortisol-like and related (16-unsubstituted): Chloroprednisone, Cloprednol, Difluprednate, Fludrocortisone, Flugestone acetate (flurogestone acetate), Fluocinolone, Fluorometholone, Fluorometholone acetate, Fluperolone, Fluperolone acetate, Fluprednisolone, Fluprednisolone esters, Loteprednol, Medrysone, Methylprednisolone, Methylprednisolone esters, Prednicarbate, Prednisolone, Prednisone, Tixocortol, Tixocortol pivalate, Methasones and related (16-substituted): Alclometasone, Beclometasone, Beclometasone esters, Betamethasone, Betamethasone esters, Clobetasol, Clobetasol propionate, Clobetasone, Clocortolone, Clocortolone esters, Cortivazol, Desoximetasone, Dexamethasone, Dexamethasone esters, Diflorasone, Diflucortolone, Diflucortolone valerate, Fluclorolone, Flumetasone, Fluocortin, Fluocortolone, Fluocortolone esters, Fluprednidene acetate, Fluticasone, Fluticasone furoate, Fluticasone propionate, Halometasone, Meprednisone, Mometasone, Mometasone furoate, Paramethasone, Prednylidene, Rimexolone, Triamcinolone, and Ulobetasol (halobetasol).

6. The method of any one of claims 1 to 5, wherein the therapeutically effective amount of the at least one agent

having the anti-microbial activity is from 10mg/day to 5000 mg/day.

7. The method of any one of claims 1 to 6, wherein the therapeutically effective amount of the at least one immunomodulator is from 0.1 mg/day to 50mg/day.

8. The method of any one of claims 1 to 7, wherein the virus of the Coronaviridae family is SARS-CoV-2 (COVID-19), SARS-CoV, MERS, OC43, 229E, NL63, OC43, and HKU1.

9. The method of claim 8, wherein the virus of the Coronaviridae family is SARS-CoV-2 (COVID-19).

10. The method of any one of claims 1 to 9, wherein the subject is a mammalian subject.

11. The method of claim 10, wherein the mammalian subject is a human subject.

12. The method of any one of claims 1 to 11, wherein the condition associated with an infection by a virus of the Coronaviridae family is selected from the group consisting of acute respiratory distress syndrome (ARDS), pneumonia, common cold, bronchitis, severe acute respiratory syndrome, and Middle East respiratory syndrome.

13. The method of any one of claims 1 to 12, further comprising administering to the subject a therapeutically effective amount of at least one agent having anti-viral activity.

14. The method of claim 13, wherein the agent having anti-viral activity is selected from the group consisting of

acyclovir, gancyclovir, valganciclovir, valacyclovir, famciclovir, penciclovir, vidarabine, cidofovir, ribavirin, adefovir, entecavir, favipiravir, brincidofovir, Idoxuridine, trifluridine, tipiracil, edoxudine, brivudine, FV-100, sorivudine, cytarabine, lamivudine, lobucavir, telbivudine, clevudine, tenofovir disoproxil, tenofovir alafenamide, and zidovudine.

15. A method of slowing and/or preventing progression of a condition associated with an infection by a virus of the Coronaviridae family in a subject, comprising administering to the subject

    a. at least one agent having an anti-microbial activity, and

    b. at least one immunomodulator,

    in an amount effective to slow and/or prevent progression of said condition.

16. The method of claim 15, wherein the at least one agent having an anti-microbial activity is a macrolide.

17. The method of claim 15, wherein the at least one agent having an anti-microbial activity is selected from the group consisting of Azithromycin, Boromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Ivermectin, Josamycin, Midecamycin, Miocamycin, Oleandomycin, Rokitamycin, Roxithromycin, Spiramycin, Troleandomycin, Doxycycline, and Tylosin.

18. The method of any one of claims 15 to 17, wherein the at least one immunomodulator is a corticosteroid.

19. The method of any one of claims 15 to 18, wherein the at least one immunomodulator is selected from the group consisting of Desoxycortone (desoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Fludrocortisone, Fludrocortisone acetate, Methylprednisolone, Methylprednisolone esters, Prednisolone, Prednisolone esters, Prednisone, Cortisone, Cortisone acetate, Cortodoxone (cortexolone, 11-deoxycortisol), Desoxycortone (deoxycortone, cortexone, 11-deoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Prebediolone acetate, Pregnenolone, Pregnenolone acetate, Pregnenolone succinate, Cortisol-like and related (16-unsubstituted): Chloroprednisone, Cloprednol, Difluprednate, Fludrocortisone, Flugestone acetate (flurogestone acetate), Fluocinolone, Fluorometholone, Fluorometholone acetate, Fluperolone, Fluperolone acetate, Fluprednisolone, Fluprednisolone esters, Loteprednol, Medrysone, Methylprednisolone, Methylprednisolone esters, Prednicarbate, Prednisolone, Prednisone, Tixocortol, Tixocortol pivalate, Methasones and related (16-substituted): Alclometasone, Beclometasone, Beclometasone esters, Betamethasone, Betamethasone esters, Clobetasol, Clobetasol propionate, Clobetasone, Clocortolone, Clocortolone esters, Cortivazol, Desoximetasone, Dexamethasone, Dexamethasone esters, Diflorasone, Diflucortolone, Diflucortolone valerate, Fluclorolone, Flumetasone, Fluocortin, Fluocortolone, Fluocortolone esters, Fluprednidene acetate, Fluticasone, Fluticasone furoate, Fluticasone propionate, Halometasone, Meprednisone, Mometasone,

Mometasone furoate, Paramethasone, Prednylidene, Rimexolone, Triamcinolone, and Ulobetasol (halobetasol).

20. The method of any one of claims 15 to 19, wherein the effective amount of the at least one agent having the anti-microbial activity is from 10mg/day to 5000mg/day.

21. The method of any one of claims 15 to 20, wherein the effective amount of the at least one immunomodulator is from 0.1 mg/day to 50mg/day

22. The method of any one of claims 15 to 21, wherein the virus of the Coronaviridae family is selected from the group consisting of SARS-CoV-2 (COVID-19), SARS-CoV, MERS, OC43, 229E, NL63, OC43, and HKU1.

23. The method of claim 22, wherein the virus of the Coronaviridae family is SARS-CoV-2 (COVID-19).

24. The method of any one of claims 15 to 23, wherein the subject is a mammalian subject.

25. The method of claim 24, wherein the subject is a human subject.

26. The method of any one of claims 15 to 25, wherein the condition associated with an infection by a virus of the Coronaviridae family is selected from the group consisting of acute respiratory distress syndrome (ARDS), common cold, pneumonia, bronchitis, severe acute respiratory syndrome, and Middle East respiratory syndrome.

27. The method of any one of claims 15 to 26, further comprising administering to the subject an effective amount of at least one agent having anti-viral activity.

28. The method of claim 27, wherein the agent having anti-viral activity is selected from the group consisting of acyclovir, gancyclovir, valganciclovir, valacyclovir, famciclovir, penciclovir, vidarabine, cidofovir, ribavirin, adefovir, entecavir, favipiravir, brincidofovir, Idoxuridine, trifluridine, tipiracil, edoxudine, brivudine, FV-100, sorivudine, cytarabine, lamivudine, lobucavir, telbivudine, clevudine, tenofovir disoproxil, tenofovir alafenamide, and zidovudine.

29. A method of reducing clinical manifestations of an infection by a virus of the Coronaviridae family in a subject in need, comprising administering to the subject, of

    a. at least one agent having an anti-microbial activity, and

    b. at least one immunomodulator,

    in an amount effective to reduce the clinical manifestations of said infection.

30. The method of claim 29, wherein the at least one agent having an anti-microbial activity is a Azithromycin, Boromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Ivermectin, Josamycin, Midecamycin, Miocamycin, Oleandomycin, Rokitamycin, Roxithromycin, Spiramycin, Troleandomycin, Doxycycline, and Tylosin.

31. The method of claim 29 or 30, wherein the at least one immunomodulator is a corticosteroid.

32. The method of any one of claims 29 or 30, wherein the at least one immunomodulator is selected from the group consisting of Desoxycortone (desoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Fludrocortisone, Fludrocortisone acetate, Methylprednisolone, Methylprednisolone esters, Prednisolone, Prednisolone esters, Prednisone, Cortisone, Cortisone acetate, Cortodoxone (cortexolone, 11-deoxycortisol), Desoxycortone (deoxycortone, cortexone, 11-deoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Prebediolone acetate, Pregnenolone, Pregnenolone acetate, Pregnenolone succinate, Cortisol-like and related (16-unsubstituted): Chloroprednisone, Cloprednol, Difluprednate, Fludrocortisone, Flugestone acetate (flurogestone acetate), Fluocinolone, Fluorometholone, Fluorometholone acetate, Fluperolone, Fluperolone acetate, Fluprednisolone, Fluprednisolone esters, Loteprednol, Medrysone, Methylprednisolone, Methylprednisolone esters, Prednicarbate, Prednisolone, Prednisone, Tixocortol, Tixocortol pivalate, Methasones and related (16-substituted): Alclometasone, Beclometasone, Beclometasone esters, Betamethasone, Betamethasone esters, Clobetasol, Clobetasol propionate, Clobetasone, Clocortolone, Clocortolone esters, Cortivazol, Desoximetasone, Dexamethasone, Dexamethasone esters, Diflorasone, Diflucortolone, Diflucortolone valerate, Fluclorolone, Flumetasone, Fluocortin, Fluocortolone, Fluocortolone esters, Fluprednidene

acetate, Fluticasone, Fluticasone furoate, Fluticasone propionate, Halometasone, Meprednisone, Mometasone, Mometasone furoate, Paramethasone, Prednylidene, Rimexolone, Triamcinolone, and Ulobetasol (halobetasol).

33. The method of any one of claims 29 to 31, wherein the effective amount of the at least one agent having the anti-microbial activity is from 10mg/day to 5000mg/day.

34. The method of any one of claims 29 to 32, wherein the effective amount of the at least one immunomodulator is from 0.1 mg/day to 50mg/day.

35. The method of any one of claims 29 to 34, wherein the virus of the *Coronaviridae* family is selected from the group consisting of SARS-CoV-2 (COVID-19), SARS-CoV, MERS, OC43, 229E, NL63, OC43, and HKU1.

36. The method of claim 35, wherein the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19).

37. The method of any one of claims 29 to 36, wherein the subject is a mammalian subject.

38. The method of claim 37, wherein the mammalian subject is a human subject.

39. The method of any one of claims 29 to 38, wherein the condition associated with an infection by a virus of the Coronaviridae family is selected from the group consisting of acute respiratory distress syndrome (ARDS), common cold, pneumonia, bronchitis, severe acute respiratory syndrome, and Middle East respiratory syndrome.

40. The method of any one of claims 29 to 39, further comprising administering to the subject an effective amount of at least one agent having anti-viral activity.

41. The method of claim 40, wherein the agent having anti-viral activity is selected from the group consisting of 39. acyclovir, gancyclovir, valganciclovir, valacyclovir, famciclovir, penciclovir, vidarabine, cidofovir, ribavirin, adefovir, entecavir, favipiravir, brincidofovir, Idoxuridine, trifluridine, tipiracil, edoxudine, brivudine, FV-100, sorivudine, cytarabine, lamivudine, lobucavir, telbivudine, clevudine, tenofovir disoproxil, tenofovir alafenamide, and zidovudine.

42. The method of any one of claims 27 to 41, wherein the clinical manifestations are selected from the group consisting of fever, cough, dyspnea, hypoxia, more than 50% lung involvement on imaging, respiratory failure, shock, multiorgan system dysfunction, malaise, fatigue, sputum/secretion, neurological symptoms, dermatological manifestations, anorexia, myalgia, sneezing, sore throat, rhinitis, goosebumps, headache, chest pain and diarrhea.

43. A method of reducing a viral load in a subject infected by a virus of the Coronaviridae family, comprising administering to the subject

    a. at least one agent having an anti-microbial activity, and

    b. at least one immunomodulator,

    in an amount effective to reduce the viral load.

44. The method of claim 43, wherein the viral load is measured in the body fluids of the subject.

45. The method of claim 43 or 44, wherein the subject is a mammalian subject.

46. The method of claim 45, wherein said subject is a human subject.

47. The method of any one of claims 43 to 46, wherein the at least one agent having an anti-microbial activity is a macrolide.

48. The method of claim 43 to 46, wherein the at least one agent having an anti-microbial activity is selected from the group consisting of Azithromycin, Boromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Ivermectin, Josamycin, Midecamycin, Miocamycin, Oleandomycin, Rokitamycin, Roxithromycin, Spiramycin, Troleandomycin, Doxycycline, and Tylosin.

49. The method of any one of claims 43 to 48, wherein the at least one immunomodulator is a corticosteroid.

50. The method of any one of claims 41 to 47, wherein the at least one immunomodulator is selected from the group consisting of Desoxycortone (desoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Fludrocortisone, Fludrocortisone acetate, Methylprednisolone, Methylprednisolone esters, Prednisolone, Prednisolone esters, Prednisone, Cortisone, Cortisone acetate, Cortodoxone (cortexolone, 11-deoxycortisol), Desoxycortone (deoxycortone, cortexone, 11-deoxycorticosterone), Desoxycortone esters,

Hydrocortisone (cortisol), Hydrocortisone esters, Prebediolone acetate, Pregnenolone, Pregnenolone acetate, Pregnenolone succinate, Cortisol-like and related (16-unsubstituted): Chloroprednisone, Cloprednol, Difluprednate, Fludrocortisone, Flugestone acetate (flurogestone acetate), Fluocinolone, Fluorometholone, Fluorometholone acetate, Fluperolone, Fluperolone acetate, Fluprednisolone, Fluprednisolone esters, Loteprednol, Medrysone, Methylprednisolone, Methylprednisolone esters, Prednicarbate, Prednisolone, Prednisone, Tixocortol, Tixocortol pivalate, Methasones and related (16-substituted): Alclometasone, Beclometasone, Beclometasone esters, Betamethasone, Betamethasone esters, Clobetasol, Clobetasol propionate, Clobetasone, Clocortolone, Clocortolone esters, Cortivazol, Desoximetasone, Dexamethasone, Dexamethasone esters, Diflorasone, Diflucortolone, Diflucortolone valerate, Fluclorolone, Flumetasone, Fluocortin, Fluocortolone, Fluocortolone esters, Fluprednidene acetate, Fluticasone, Fluticasone furoate, Fluticasone propionate, Halometasone, Meprednisone, Mometasone, Mometasone furoate, Paramethasone, Prednylidene, Rimexolone, Triamcinolone, and Ulobetasol (halobetasol).

51. The method of any one of claims 43 to 50, wherein the effective amount of the at least one agent having the anti-microbial activity is from 10mg/day to 5000mg/day.

52. The method of any one of claims 43 to 51, wherein the effective amount of the at least one immunomodulator is from 0.1 mg/day to 50mg/day.

53. The method of any one of claims 43 to 52, acute respiratory distress syndrome (ARDS), common cold, pneumonia, bronchitis, severe acute respiratory syndrome, and Middle East respiratory syndrome.

54. The method of any one of claims 43 to 53, wherein the virus of the Coronaviridae family is selected from the group consisting of SARS-CoV-2 (COVID-19), SARS-CoV, MERS, OC43, 229E, NL63, OC43, and HKU1.

55. The method of claim 54, wherein the virus of the Coronaviridae family is SARS-CoV-2 (COVID-19).

56. The method of any one of claims 43 to 55, further comprising administering to the subject an effective amount of at least one agent having anti-viral activity.

57. The method of claim 56, wherein the agent having anti-viral activity is selected from the group consisting of acyclovir, gancyclovir, valganciclovir, valacyclovir, famciclovir, penciclovir, vidarabine, cidofovir, ribavirin, adefovir, entecavir, favipiravir, brincidofovir, Idoxuridine, trifluridine, tipiracil, edoxudine, brivudine, FV-100, sorivudine, cytarabine, lamivudine, lobucavir, telbivudine, clevudine, tenofovir disoproxil, tenofovir alafenamide, and zidovudine.

58. The method of any one of claims 43 to 57, wherein the viral load is reduced by at least 1.3 log.

59. The method of any one of claims 1 to 58, wherein the at least one agent having anti-microbial activity and the at least one immunomodulator are administered simultaneously.

60. The method of claim 59, wherein the at least one agent having anti-microbial activity and the at least one immunomodulator are administered as a fixed dosage form composition.

61. The method of any one of claims 1 to 58, wherein the at least one agent having anti-microbial activity and the at least one immunomodulator are administered independently of each other.

62. A method of reducing at least one surrogate marker associated with an infection by a virus of the Coronaviridae family in a subject diagnosed with said infection, comprising administering to said subject

    a. at least one agent having an anti-microbial activity, and

    b. at least one immunomodulator,

    in an amount an effective to reduce the at least one surrogate marker.

63. A method of reducing at least one biomarker associated with an infection by a virus of the *Coronaviridae* family in a subject diagnosed with said infection, comprising administering to said subject

    a. at least one agent having an anti-microbial activity, and

    b. at least one immunomodulator,

    in an amount an effective to reduce the at least one biomarker.

64. The method of claim 62 or 63, wherein the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19).

65. The method of any one of claims 62 to 64, wherein the at least one agent having an anti-microbial activity is a macrolide.

66. The method of any one of claims 62 to 64, wherein the at least one agent having an anti-microbial activity is selected from the group consisting of Azithromycin, Boromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Ivermectin, Josamycin, Midecamycin, Miocamycin, Oleandomycin, Rokitamycin, Roxithromycin, Spiramycin, Troleandomycin, Doxycycline, and Tylosin.

67. The method of any one of claims 62 to 66, wherein the at least one immunomodulator is a corticosteroid.

68. The method of any one of claims 62 to 66, wherein the at least one immunomodulator is selected from the group consisting of Desoxycortone (desoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Fludrocortisone, Fludrocortisone acetate, Methylprednisolone, Methylprednisolone esters, Prednisolone, Prednisolone esters, Prednisone, Cortisone, Cortisone acetate, Cortodoxone (cortexolone, 11-deoxycortisol), Desoxycortone (deoxycortone, cortexone, 11-deoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Prebediolone acetate, Pregnenolone, Pregnenolone acetate, Pregnenolone succinate, Cortisol-like and related (16-unsubstituted): Chloroprednisone, Cloprednol, Difluprednate, Fludrocortisone, Flugestone

acetate (flurogestone acetate), Fluocinolone, Fluorometholone, Fluorometholone acetate, Fluperolone, Fluperolone acetate, Fluprednisolone, Fluprednisolone esters, Loteprednol, Medrysone, Methylprednisolone, Methylprednisolone esters, Prednicarbate, Prednisolone, Prednisone, Tixocortol, Tixocortol pivalate, Methasones and related (16-substituted): Alclometasone, Beclometasone, Beclometasone esters, Betamethasone, Betamethasone esters, Clobetasol, Clobetasol propionate, Clobetasone, Clocortolone, Clocortolone esters, Cortivazol, Desoximetasone, Dexamethasone, Dexamethasone esters, Diflorasone, Diflucortolone, Diflucortolone valerate, Fluclorolone, Flumetasone, Fluocortin, Fluocortolone, Fluocortolone esters, Fluprednidene acetate, Fluticasone, Fluticasone furoate, Fluticasone propionate, Halometasone, Meprednisone, Mometasone, Mometasone furoate, Paramethasone, Prednylidene, Rimexolone, Triamcinolone, and Ulobetasol (halobetasol).

69. The method of any one of claims 62 to 68, wherein the effective amount of the at least one agent having the anti-microbial activity is from 10mg/day to 5000mg/day.

70. The method of any one of claims 62 to 69, wherein the effective amount of the at least one immunomodulator is from 0.1 mg/day to 50mg/day.

71. The method of any one of claims 62 to 70, further comprising administering to the subject an effective amount of at least one agent having anti-viral activity.

72. The method of claim 67, wherein the agent having anti-viral activity is selected from the group consisting of

acyclovir, gancyclovir, valganciclovir, valacyclovir, famciclovir, penciclovir, vidarabine, cidofovir, ribavirin, adefovir, entecavir, favipiravir, brincidofovir, Idoxuridine, trifluridine, tipiracil, edoxudine, brivudine, FV-100, sorivudine, cytarabine, lamivudine, lobucavir, telbivudine, clevudine, tenofovir disoproxil, tenofovir alafenamide, and zidovudine.

73. A therapeutic combination suitable for administration to a subject in need, comprising:

a. at least one agent having an anti-microbial activity, and

b. at least one immunomodulator,

wherein the subject in need is diagnosed with an infection by a virus of the Coronaviridae family.

74. The combination of claim 73, wherein the at least one agent having an anti-microbial activity is a macrolide.

75. The combination of claim 73 or 74, wherein the at least one agent having an anti-microbial activity is selected from the group consisting of Azithromycin, Boromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Ivermectin, Josamycin, Midecamycin, Miocamycin, Oleandomycin, Rokitamycin, Roxithromycin, Spiramycin, Troleandomycin, Doxycycline, and Tylosin.

76. The combination of any one of claims 73 to 75, wherein the at least one immunomodulator is a corticosteroid.

77. The combination of any one of claims 73 to 75, wherein the at least one immunomodulator is selected from the

group consisting of Desoxycortone (desoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Fludrocortisone, Fludrocortisone acetate, Methylprednisolone, Methylprednisolone esters, Prednisolone, Prednisolone esters, Prednisone, Cortisone, Cortisone acetate, Cortodoxone (cortexolone, 11-deoxycortisol), Desoxycortone (deoxycortone, cortexone, 11-deoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Prebediolone acetate, Pregnenolone, Pregnenolone acetate, Pregnenolone succinate, Cortisol-like and related (16-unsubstituted): Chloroprednisone, Cloprednol, Difluprednate, Fludrocortisone, Flugestone acetate (flurogestone acetate), Fluocinolone, Fluorometholone, Fluorometholone acetate, Fluperolone, Fluperolone acetate, Fluprednisolone, Fluprednisolone esters, Loteprednol, Medrysone, Methylprednisolone, Methylprednisolone esters, Prednicarbate, Prednisolone, Prednisone, Tixocortol, Tixocortol pivalate, Methasones and related (16-substituted): Alclometasone, Beclometasone, Beclometasone esters, Betamethasone, Betamethasone esters, Clobetasol, Clobetasol propionate, Clobetasone, Clocortolone, Clocortolone esters, Cortivazol, Desoximetasone, Dexamethasone, Dexamethasone esters, Diflorasone, Diflucortolone, Diflucortolone valerate, Fluclorolone, Flumetasone, Fluocortin, Fluocortolone, Fluocortolone esters, Fluprednidene acetate, Fluticasone, Fluticasone furoate, Fluticasone propionate, Halometasone, Meprednisone, Mometasone, Mometasone furoate, Paramethasone, Prednylidene, Rimexolone, Triamcinolone, and Ulobetasol (halobetasol).

78. The combination of any one of claims 73 to 77, wherein the effective amount of the at least one agent having the anti-microbial activity is from 10mg/day to 5000mg/day.

79. The combination of any one of claims 73 to 78, wherein the effective amount of the at least one immunomodulator is from 0.1 mg/day to 50mg/day.

80. The combination of any one of claims 73 to 79, wherein the virus of the *Coronaviridae* family is selected from the group consisting of SARS-CoV-2 (COVID-19), SARS-CoV, MERS, OC43, 229E, NL63, OC43, and HKU1.

81. The combination of claim 80, wherein the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19).

82. The combination of any one of claims 73 to 80, wherein the subject is a mammalian subject.

83. The combination of claim 82, wherein the mammalian subject is a human subject.

84. A pharmaceutical composition comprising

    a. at least one at least one agent having an anti-microbial activity,

    b. at least one immunomodulator, and

    c. at least one pharmaceutically acceptable carrier

85. The pharmaceutical composition of claim 84, wherein the at least one agent having an anti-microbial activity is a macrolide.

86. The pharmaceutical composition of claim 84 or 85, wherein the at least one agent having an anti-microbial activity is selected from the group consisting of Azithromycin, Boromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Ivermectin, Josamycin, Midecamycin, Miocamycin, Oleandomycin, Rokitamycin, Roxithromycin, Spiramycin, Troleandomycin, Doxycycline, and Tylosin.

87. The pharmaceutical composition of any one of claims 84 to 86, wherein the at least one immunomodulator is a corticosteroid.

88. The pharmaceutical composition of any one of claims 84 to 86, wherein the at least one immunomodulator is selected from the group consisting of Desoxycortone (desoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Fludrocortisone, Fludrocortisone acetate, Methylprednisolone, Methylprednisolone esters, Prednisolone, Prednisolone esters, Prednisone, Cortisone, Cortisone acetate, Cortodoxone (cortexolone, 11-deoxycortisol), Desoxycortone (deoxycortone, cortexone, 11-deoxycorticosterone), Desoxycortone esters, Hydrocortisone (cortisol), Hydrocortisone esters, Prebediolone acetate, Pregnenolone, Pregnenolone acetate, Pregnenolone succinate, Cortisol-like and related (16-unsubstituted): Chloroprednisone, Cloprednol, Difluprednate, Fludrocortisone, Flugestone acetate (flurogestone acetate), Fluocinolone, Fluorometholone, Fluorometholone acetate, Fluperolone, Fluperolone acetate, Fluprednisolone, Fluprednisolone esters, Loteprednol, Medrysone, Methylprednisolone,

Methylprednisolone esters, Prednicarbate, Prednisolone, Prednisone, Tixocortol, Tixocortol pivalate, Methasones and related (16-substituted): Alclometasone, Beclometasone, Beclometasone esters, Betamethasone, Betamethasone esters, Clobetasol, Clobetasol propionate, Clobetasone, Clocortolone, Clocortolone esters, Cortivazol, Desoximetasone, Dexamethasone, Dexamethasone esters, Diflorasone, Diflucortolone, Diflucortolone valerate, Fluclorolone, Flumetasone, Fluocortin, Fluocortolone, Fluocortolone esters, Fluprednidene acetate, Fluticasone, Fluticasone furoate, Fluticasone propionate, Halometasone, Meprednisone, Mometasone, Mometasone furoate, Paramethasone, Prednylidene, Rimexolone, Triamcinolone, and Ulobetasol (halobetasol).

89. The pharmaceutical composition of any one of claims 84 to 88, wherein the effective amount of the at least one agent having the anti-microbial activity is from 10mg/day to 5000mg/day.

90. The pharmaceutical composition of any one of claims 84 to 89, wherein the effective amount of the at least one immunomodulator is from 0.1 mg/day to 50mg/day.

91. The pharmaceutical composition of any one of claims 84 to 90 which is a fixed dosage form composition.

92. The pharmaceutical composition of any one of claims 84 to 91 for use as a medicament.

93. The pharmaceutical composition of any one of claims 84 to 91 for use in the treatment of a condition associated with an infection by a virus of the *Coronaviridae* family, in a subject in need of such treatment.

94. The pharmaceutical composition of any one of claims 93 to 93, wherein the virus of the *Coronaviridae* family is selected from the group consisting of SARS-CoV-2 (COVID-19), SARS-CoV, MERS, OC43, 229E, NL63, OC43, and HKU1.

95. The pharmaceutical composition of claim 94, wherein the virus of the *Coronaviridae* family is SARA-CoV-2 (COVID-19).

96. The pharmaceutical composition of any one of claims 93 to 95, wherein the subject is a mammalian subject.

97. The pharmaceutical composition of claim 96, wherein the mammalian subject is a human subject.

98. The pharmaceutical composition of any one of claims 93 to 97, wherein the condition associated with the infection by a virus of the Coronaviridae family is selected from the group consisting of acute respiratory distress syndrome (ARDS), common cold, pneumonia, bronchitis, severe acute respiratory syndrome, and Middle East respiratory syndrome.

99. The pharmaceutical composition of any one of claims 93 to 98 further comprising an agent having an anti-viral activity.

100. The pharmaceutical composition of claim 99, wherein the agent having anti-viral activity is selected from the group consisting of acyclovir, gancyclovir, valganciclovir, valacyclovir, famciclovir, penciclovir, vidarabine, cidofovir, ribavirin, adefovir, entecavir, favipiravir, brincidofovir, Idoxuridine, trifluridine, tipiracil, edoxudine, brivudine, FV-100, sorivudine,

cytarabine, lamivudine, lobucavir, telbivudine, clevudine, tenofovir disoproxil, tenofovir alafenamide, and zidovudine.

101. The pharmaceutical composition of any one of claims 84 to 100, selected from solid composition, liquid composition, or semi-solid composition.

102. The pharmaceutical composition of any one of claims 84 to 101, which is designed for oral administration, intra-muscular administraton, intravenous administration, intraperitoneal administration, intranasal administration, intramucosal administration, or transdermal administration.

103. The pharmaceutical composition of any one of claims 84 to 101 in the form of a tablet, a capsule, a powder, a syrup, a suspension, or a dispersion.

104. A method for treating a subject afflicted with a condition associated with an infection by a virus of the *Coronaviridae* family with a pharmaceutical composition of any one of claims 84 to 92, comprising the steps of: a) administering a therapeutic amount of the pharmaceutical composition to the subject; b) determining whether the subject is a responder by determining the gene expression profile of the subject, and comparing the gene expression profile to a reference gene expression profile to identify the subject as a responder; and c) continuing the administration if the subject is identified as a responder, or modifying treatment of the subject if the subject is not identified as a responder.

105. The method of claim 104, wherein the condition is selected from the group consisting of acute respiratory distress syndrome (ARDS), severe pneumonia, and severe acute respiratory syndrome.

106. The method of claim 104 or 105, wherein the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19).

107. A method for treating a human subject presenting clinical manifestations associated with infection by a virus of the *Coronaviridae* family with a pharmaceutical composition of any one of claims 84 to 92, comprising the steps of:(i) determining the gene expression profile of the subject;(ii) identifying the subject as a predicted responder if the gene expression profile is indicative of subject being a responder; and(iii) administering the pharmaceutical composition to the subject only if the subject is identified as a predicted responder.

108. The method of claim 107, wherein the condition is selected from the group consisting of acute respiratory distress syndrome (ARDS), severe pneumonia, and severe acute respiratory syndrome.

109. The method of claim 107 or 108, wherein the virus of the *Coronaviridae* family is SARS-CoV-2 (COVID-19).

110. The method of any one of claims 1 to 72, wherein the at least one agent having an anti-microbial activity is Azithromycin.

111. The method of claim 110, wherein the at least one immunomodulator is dexamethasone.

112. The pharmaceutical composition of any one of claims 84 to 103, wherein the least one agent having an anti-microbial activity is Azithromycin.

113. The pharmaceutical composition of claim 112, wherein the at least one immunomodulator is dexamethasone.

114. The method of any one of claims 104 to 109, wherein the least one agent having an anti-microbial activity is Azithromycin.

115. The method of claim 114, wherein the at least one immunomodulator is dexamethasone.

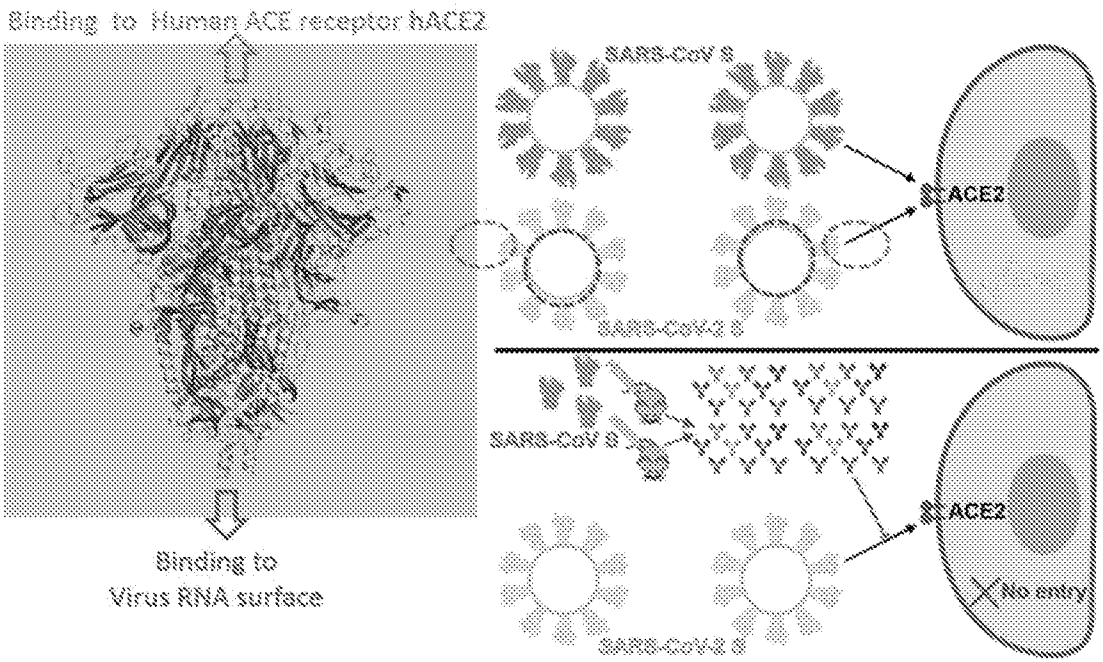
Binding to Human ACE receptor hACE2
SARS-CoV S
SARS-CoV-2 S
ACE2
SARS-CoV S
SARS-CoV-2 S
ACE2
No entry
Binding to
Virus RNA surface

FIGURE 1

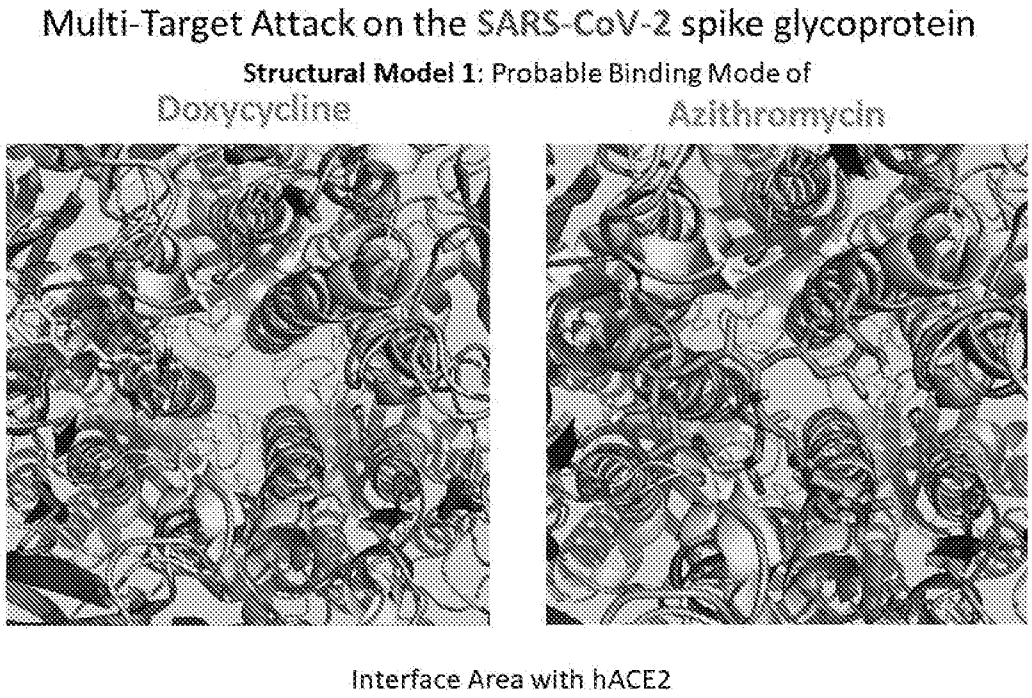
Multi-Target Attack on the SARS-CoV-2 spike glycoprotein
Structural Model 1: Probable Binding Mode of
Doxycycline
Azithromycin
Interface Area with hACE2

FIGURE 2

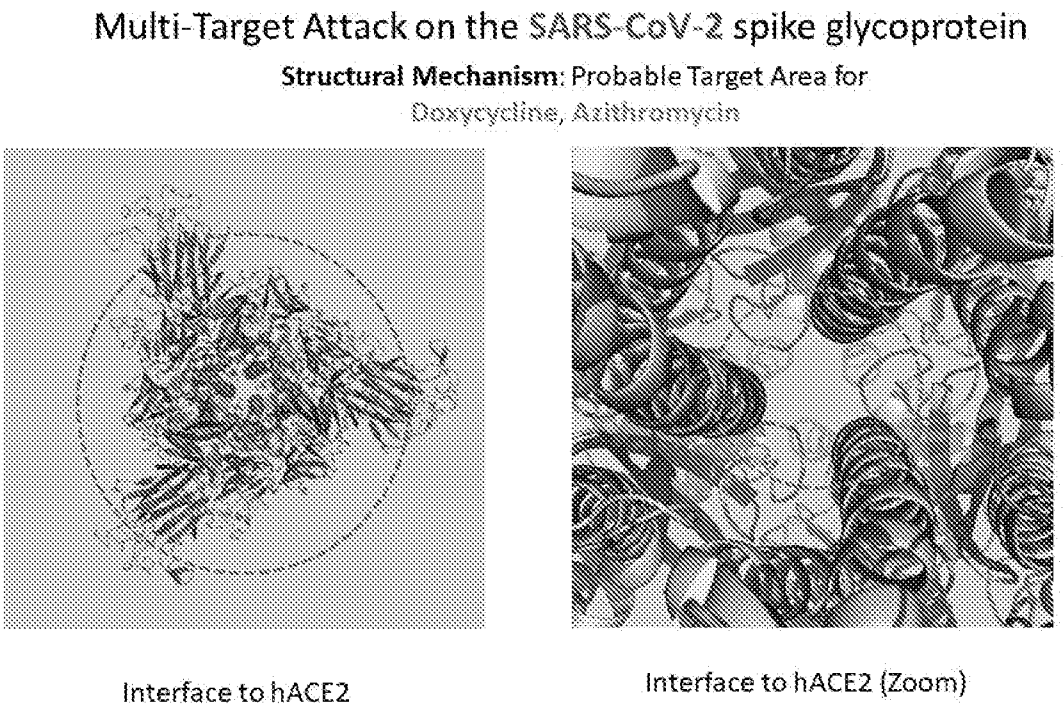
Multi-Target Attack on the SARS-CoV-2 spike glycoprotein
Structural Mechanism: Probable Target Area for
Doxycycline, Azithromycin
Interface to hACE2
Interface to hACE2 (Zoom)

FIGURE 3

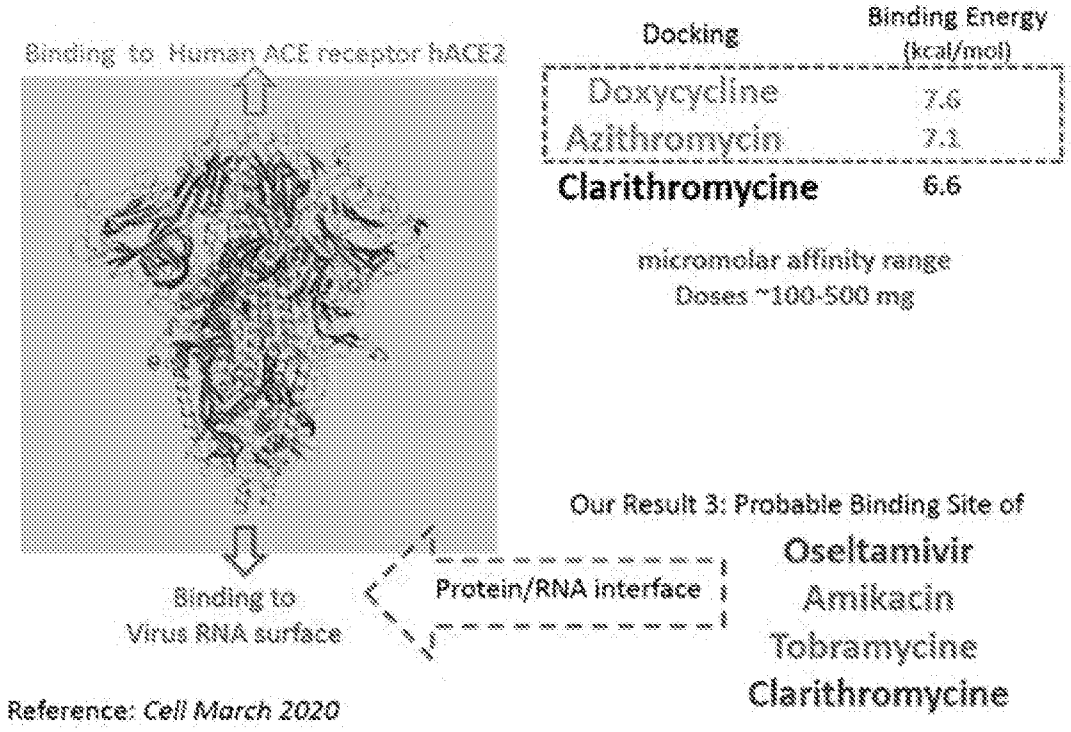
Binding to Human ACE receptor hACE2
Docking
Binding Energy (kcal/mol)
Doxycycline 7.6
Azithromycin 7.1
Clarithromycine 6.6
micromolar affinity range
Doses ~100-500 mg
Our Result 3: Probable Binding Site of
Oseltamivir
Amikacin
Tobramycine
Clarithromycine
Protein/RNA interface
Binding to Virus RNA surface
Reference: Cell March 2020

FIGURE 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2021/050290

A. CLASSIFICATION OF SUBJECT MATTER
IPC (20210101) A61P 31/12, A61P 37/00, A61P 31/04
CPC (20180101) A61P 31/12, A61P 31/04, A61P 37/00
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)
IPC (20210101) A61P 31/12, A61P 37/00, A61P 31/04
CPC (20180101) A61P 31/12, A61P 31/04, A61P 37/00

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Databases consulted: Esp@cenet, Google Patents, Google Scholar, Derwent Innovation
Search terms used: Coronaviridae, coronavirus, corona, antimicrobial agent, immunomodulatory, dexamethasone, surrogate marker, biomarker, infection, Morgenstern Milana, Mukherjee, Sumit, Tworowski, Dmitry, A61P 31/12.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7892563 B2 SIBER GEORGE R. [US] 22 Feb 2011 (2011/02/22) Column 7 lines 41-44, column 20 lines 55-56, column 21 lines 9-15, column 23 lines 24-39, column 24 lines 18-62.	1-115

☐ 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
14 Jun 2021	15 Jun 2021

Name and mailing address of the ISA:	Authorized officer
Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Email address: pctoffice@justice.gov.il	FURMANOVICH Elinor Telephone No. 972-73-3927108

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2021/050290

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
US 7892563 B2	22 Feb 2011	US 2004235047 A1	25 Nov 2004
		US 7892563 B2	22 Feb 2011
		AU 2004266111 A1	03 Mar 2005
		AU 2004266111 B2	26 Aug 2010
		AU 2004266111 B8	23 Dec 2010
		BR PI0410467 A	30 May 2006
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		EP 1624850 A4	31 Oct 2007
		IL 171972 D0	10 Apr 2006
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		US 2006263847 A1	23 Nov 2006
		US 7722886 B2	25 May 2010
		WO 2005018535 A2	03 Mar 2005
		WO 2005018535 A3	21 Dec 2006