objectives for treating and managing COVID-19 disease are numerous and complex, spanning an enormous range of pathogenic, immunologic and inflammatory insults mediated by COVID-19, that include ARDS/SARS, CSS, PIMS, ESHS, DIC in severe cases.

To address these needs and overcome attendant obstacles will require discovery and development of potent and innovative tools, including multi-activity and multi-targeting drugs and therapies, for example drugs capable of impairing viral functions and regulating hyperimmune and hyperinflammatory responses, while enhancing, or at a minimum not impairing, beneficial host immune and inflammatory capabilities and responses. Additionally, these objectives will be most profitably met by developing novel combinations of complementary drugs and treatment methods that similarly reach multiple targets and elicit multiple (e.g., antiviral, pro-immune and anti-inflammatory) effects. Successful approaches to combatting COVID-19 and its diverse pathogenic sequelae will be further optimized for individual patients by timing and metering treatment forms, dosages and modalities relative to discrete indicia of disease etiology presented on a patient-specific basis.

SUMMARY

The disclosure achieves the foregoing objects and satisfies additional objects and advantages through the novel and potent use of "TPA" compounds and related compositions and methods to treat and/or prevent an Acute Respiratory Distress Syndrome (ARDS) in a mammalian subject, including Severe Acute Respiratory Syndrome (SARS) in humans mediated by COVID-19 and other SARS coronaviruses. Related examples of the disclosure employ clinically effective TPA compounds, compositions and methods to prevent and/or treat hyperimmune and hyperinflammatory conditions, including "Cytokine Storm Syndrome" (CSS) generally, and a host of other hyperinflammatory diseases, including but not limited to Pediatric Inflammatory Multisystem Syndrome (PIMS) associated with COVID-19 disease, the related childhood condition known as Kawasaki disease, Extrapulmonary Systemic Hyperinflammation Syndrome (ESHS), and vascular congestive and thrombotic conditions caused by hyperinflammation, such as Disseminated Intravascular Coagulation (DIC), thrombosis, stroke, thrombocytopenia, and gangrene.

In one aspect, the present disclosure refers to use of an anti-viral effective amount of a TPA (12-O-tetradecanoylphorbol-13-acetate) compound in the manufacture of a clinically therapeutic or prophylactic medicament for treating or preventing a severe acute respiratory syndrome (SARS) coronavirus infection and acute respiratory distress syndrome (ARDS) in a mammalian subject with elevated risk of SARS coronavirus infection, or presenting with active SARS coronavirus infection, to prevent or reduce SARS viral infection and/or reduce or eliminate SARS viral load detectable in the subject.

In another aspect, the present disclosure refers to use of a pharmaceutical composition or kit in the manufacture of a medicament for preventing or treating acute respiratory distress syndrome (ARDS) in a mammalian subject, wherein the pharmaceutical composition or kit comprises an anti-ARDS effective TPA compound formulated or packaged with a secondary therapeutic or prophylactic drug or agent selected from anti-IL-6 drugs, biologic agents kinase modulating drugs and severe acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus vaccine agents.

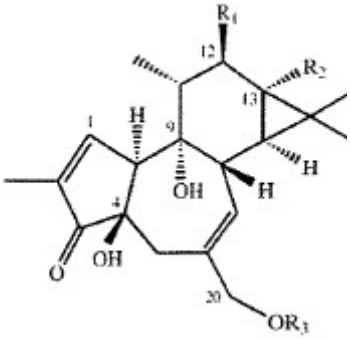
In another aspect, the present disclosure refers to use of a pharmaceutical composition or kit in the manufacture of a medicament for preventing or treating acute respiratory distress syndrome (ARDS) in a mammalian subject, wherein the pharmaceutical composition or kit comprises an anti-ARDS effective TPA compound formulated or packaged with a secondary therapeutic or prophylactic drug or agent selected from: an interferon drug or agent; an intravenous formulated immunoglobulin; a SARS-CoV-2-specific neutralizing antibody, Fab fragment or antibody binding domain; a C5a-specific antibody, Fab fragment or antibody binding domain; thalidomide; fingolimod; anti-angiogenic drugs; hydroxychloroquine; and glucocorticoids, and combinations thereof.

Additional examples of the disclosure employ TPA compounds, compositions and methods to effectively limit or treat a wide range of cellular, tissue and organ injuries that

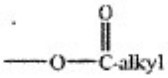
attend ARDS, SARS, CSS, PIMS, ESHS, DIC and other immune and inflammatory injuries or disease states that can attend these conditions.

Further examples of the disclosure are directed to compositions and methods employing a TPA compound to treat and/or prevent COVID-19 disease and related adverse conditions and symptoms in humans caused by a SARS coronavirus (e.g., SARS-CoV, SARS-CoV-2 (COVID-19) and Middle East Respiratory Syndrome coronavirus (MERS-CoV)). In exemplary examples, the disclosure provides clinically effective TPA compounds, compositions and methods that prevent and/or treat ARDS/SARS in severe COVID-19 disease subjects. In other exemplary examples, compositions and method of the disclosure employ a TPA compound or composition to effectively treat and/or prevent hyperimmune and hyperinflammatory conditions, and associated cellular, tissue and organ injury and dysfunction, attending severe COVID-19 disease, including CSS, PIMS, ESHS, DIC and other immune and inflammatory injuries or disease states that may attend these conditions, such as vascular congestive and thrombotic conditions, including but not limited to Disseminated Intravascular Coagulation (DIC), thrombosis, stroke, thrombocytopenia, and gangrene.

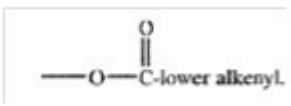
Effective TPA compounds within the methods and compositions of the disclosure include phorbol esters and derivatives according to Formula I, below:



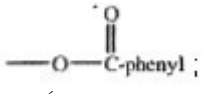
Formula I

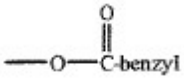
wherein R_1 and R_2 may be hydrogen; hydroxyl; 

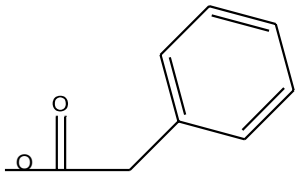
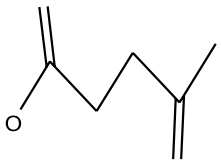
, wherein the alkyl

group contains 1 to 15 carbon atoms; 

, wherein a lower

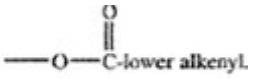
alkenyl group contains between 1 to 7 carbon at 

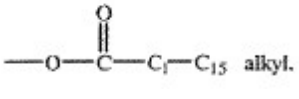
; 

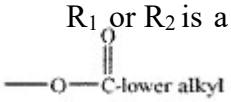
; 
;  and

wherein R_3 may be hydrogen or 

.

In some examples, at least one of R_1 and R_2 are other than hydrogen and R_3 is hydrogen or 

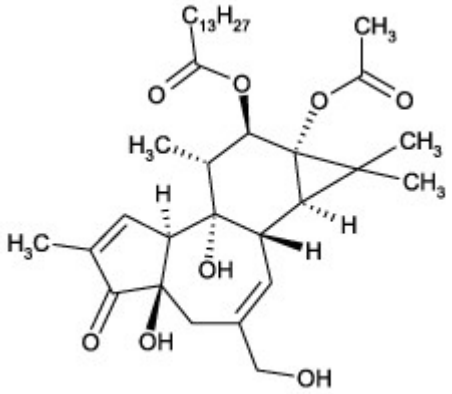
and substituted derivatives thereof. In other examples, either R_1 or R_2 is 

and the remaining R_1 or R_2 is a 

, wherein a lower alkyl is between 1 and 7 carbons, and R_3 is hydrogen.

The alkyl, alkenyl, phenyl and benzyl groups of the formulas herein may be unsubstituted or substituted with halogens, preferably, chlorine, fluorine or bromine, nitro, amino, and/or similar type radicals.

In other examples, the disclosure employs exemplary phorbol esters, of Formula II, below:



Formula II.

Phorbol esters for use within the compositions and methods of the disclosure will be understood to include pharmaceutically acceptable active analogs and derivatives of the Formula I and Formula II compounds, including rational designed chemical analogs and derivatives with selected substitutions, deletions or additions of functional groups applied to a parent compound structure within Formula I or Formula II, as well as salts, isomers, enantiomers, polymorphs, solvates, hydrates, and/or prodrugs of said compounds.

DETAILED DESCRIPTION
OF EXEMPLARY EMBODIMENTS OF THE INVENTION

The following description is provided to illustrate fundamental means and principles of the invention, through explanation of exemplary embodiments. No limitation of the invention is intended by this description. Persons of ordinary skill in the art will appreciate that alterations, modifications, substitutions, refinements and further applications of the objects, materials and principles described here fall within the inventive scope of this disclosure and the appended claims.

The instant invention provides “TPA compounds” as drug agents, and for use in drug combinations and methods, to mediate novel, diverse and often multi-functional therapeutic effects. The TPA compounds and related compositions and methods of the invention are effective to treat and prevent a diverse array of refractory disease conditions mediated by aberrant, hyperimmune and hyperinflammatory responses in humans and other mammals. TPA compounds, compositions and methods of the invention potently exert one or more effective activities, including antiviral, anti-inflammatory, and immune-regulatory

What is Claimed:

1. Use of an anti-viral effective amount of a TPA (12-O-tetradecanoylphorbol-13-acetate) compound in the manufacture of a clinically therapeutic or prophylactic medicament for treating or preventing a severe acute respiratory syndrome (SARS) coronavirus infection and acute respiratory distress syndrome (ARDS) in a mammalian subject with elevated risk of SARS coronavirus infection, or presenting with active SARS coronavirus infection, to prevent or reduce SARS viral infection and/or reduce or eliminate SARS viral load detectable in the subject.

2. The use of claim 1, wherein the SARS coronavirus is a human SARS (hSARS) coronavirus selected from SARS-CoV-2 (COVID-19), and SARS-CoV coronaviruses.

3. The use of claim 2, wherein the hSARS coronavirus is SARS-CoV-2 (COVID-19).

4. The use of claim 1 or 2, wherein the anti-viral TPA compound is manufactured in the medicament for eliciting an anti-viral response sufficient to prevent or reduce SARS-CoV-2 viral infection and/or reduce or eliminate SARS viral load compound, and to concurrently prevent or reduce one or more clinical symptoms of COVID-19 disease.

5. The use of claim 1 or 2, wherein the TPA compound is manufactured in an amount and dosage form for reducing or eliminating one or more indicia of SARS coronavirus infection severity selected from: 1) viral load or titer in an upper or lower respiratory cell, tissue or sample of the subject; 2) viral load or titer in a non-respiratory, ACE-2 positive cell, tissue or sample of the subject, or in a blood plasma of the subject; 3) viral attachment and/or entry into lung or other tissues/cells; 4) viral replication in a lung or other ACE-2 positive cell, tissue or organ of the subject; and/or 5) viral shedding from an upper respiratory tract tissue or sample of an infected subject, each of said indices determinable by observing or measuring an incidence or value of the subject index in an *in vitro* sample from one or more TPA-treated subjects in comparison to incidence or value of the same index in one or more comparable, placebo-treated control subject(s).

6. The use of claim 1, wherein the SARS coronavirus is a human SARS (hSARS) coronavirus selected from SARS-CoV-2 (COVID-19), and SARS-CoV, and wherein the TPA compound is manufactured in the medicament for reducing hSARS viral load or titer in a an upper and/or lower respiratory tract of the subject.

7. The use of claim 1, wherein the SARS virus is a human SARS (hSARS) coronavirus selected from SARS-CoV-2 (COVID-19), and SARS-CoV, and wherein the TPA compound is manufactured in the medicament for reducing hSARS viral load or titer in a non-respiratory, ACE-2 positive cell, tissue or organ of the subject.

8. The use of claim 1, wherein the SARS virus is SARS-CoV-2 (COVID-19), and wherein the anti-viral TPA compound is manufactured in the medicament for eliciting an anti-viral response in the subject that prevents or reduces SARS-CoV-2 viral infection and/or reduces or eliminates SARS viral load, as determined by SARS-CoV-2 DNA or other quantitative measure of SARS-CoV-2 levels in nasopharyngeal swab samples taken pre- and post-treatment from infected subjects, or by comparison of suitable test and control samples.

9. The use of claim 8, wherein viral load as determined by SARS-CoV-2 DNA or other quantitative measure of SARS-CoV-2 viral load in nasopharyngeal swab samples, compared between pre- and post-treatment samples from an individual or group of treated patient(s), or between treated and placebo-treated control subjects, is decreased by an average of 25-50% or 75-95% or more among treated subjects.

10. The use of claim 8, wherein viral load as determined by SARS-CoV-2 DNA or other quantitative measure of SARS-CoV-2 load in nasopharyngeal swab samples from subjects screened as positive for SARS-CoV-2 infection before TPA treatment, is decreased within two weeks after TPA treatment by 100% (corresponding to total clearance of detectable SARS-CoV-2 virus in the upper respiratory tract, indicative of a non-contagious status) in at least 50% of TPA-treated subjects.

11. Use of a pharmaceutical composition or kit in the manufacture of a medicament for preventing or treating acute respiratory distress syndrome (ARDS) in a mammalian subject, wherein the pharmaceutical composition or kit comprises an anti-ARDS effective TPA compound formulated or packaged with a secondary therapeutic or prophylactic drug or agent selected from anti-IL-6 drugs, biologic agents kinase modulating drugs and severe acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus vaccine agents.

12. The use of claim 11, wherein the anti-IL-6 drug or biologic agent is an anti-IL-6 monoclonal antibody or Fab fragment, a soluble IL-6 receptor or receptor analog, or a cognate anti-IL-6 specific binding or deactivating domain thereof.

13. The use of claim 11, wherein the anti-IL-6 drug or biologic is selected from siltuximab, sarilumab (Kevzara), and tocilizumab (TCZ).

14. The use of claim 11, wherein the anti-IL-6 drug or biologic is an anti-IL-6 drug that blocks or inhibits IL-6 directly, or indirectly inhibits, lowers, or alters a pro-inflammatory activity of IL-6, wherein the anti-IL-6 drug is andrographolide.

15. The use of claim 11, wherein the kinase modulating drug or agent directly or indirectly inhibits, lowers, activates or alters an immune or inflammatory activity of one or more kinases involved in mediating or suppressing inflammatory responses, or regulating differentiation, proliferation, activation, inflammatory cytokine synthesis, and/or apoptotic activity of immune and/or inflammatory effector cells, including lymphocytes, monocyte/macrophage cells and/or neutrophils, wherein the kinase modulator drug or agent modulates a mitogen activated protein kinase (MAPK), janus kinase (JAK) and/or protein kinase C (PKC).

16. Use of a pharmaceutical composition or kit in the manufacture of a medicament for preventing or treating acute respiratory distress syndrome (ARDS) in a mammalian subject, wherein the pharmaceutical composition or kit comprises an anti-ARDS effective TPA compound formulated or packaged with a secondary therapeutic or prophylactic drug or agent

selected from: an interferon drug or agent; an intravenous formulated immunoglobulin; a SARS-CoV-2-specific neutralizing antibody, Fab fragment or antibody binding domain; a C5a-specific antibody, Fab fragment or antibody binding domain; thalidomide; fingolimod; anti-angiogenic drugs; hydroxychloroquine; and glucocorticoids, and combinations thereof.

21. The use of claim 1, which is effective to prevent, reduce or eliminate of one or more ARDS disease condition(s) and/or symptom(s) selected from 1) dyspnea; 2) hyper-elevated level(s) of one or more pro-inflammatory cytokine(s) in the lung; 3) hyper-elevated level(s) of monocyte/macrophage cells and/or neutrophils in a lung parenchyma and/or a pulmonary alveolar compartment; 4) degradation or disruption of a pulmonary endothelial and/or epithelial barrier(s); 5) elevated indicia of oxidative stress in lung tissue, determinable by elevated levels of reactive oxygen species (ROS) in the lung; and/or 6) one or more pathogenic symptom(s) of lung injury selected from hyper-inflammation, fibrosis, diffuse alveolar damage (DAD), macrophage and/or neutrophil infiltration into the lung parenchyma, macrophage and/or neutrophil infiltration into pulmonary capillaries, deposition of extensive neutrophil extracellular traps (NETs) in a lung interstitium or parenchyma, pulmonary and/or coronary vessel thromboses, and vasculitis in a treated subject in comparison to the same ARDS disease indicator(s)/value(s) measured and determined in comparable, placebo-treated control subjects.

22. The use of claim 1, wherein the TPA compound is effective to prevent or reduce the extent of an ARDS-associated lung injury selected from hyper-inflammation, fibrosis, diffuse alveolar damage (DAD), macrophage and/or neutrophil infiltration into the lung parenchyma, macrophage and/or neutrophil infiltration into pulmonary capillaries, deposition of extensive neutrophil extracellular traps (NETs) in a lung interstitium or parenchyma, pulmonary and/or coronary vessel thromboses, and vasculitis in treated subjects.

23. The use of claim 1, wherein the ARDS is caused by a severe acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus, and wherein the TPA compound is to be administered before an elevated-risk or known-infected subject manifests one or more index(ices) of severe COVID-19 disease selected from: 1) fever lasting over 2 days; 2) lower respiratory symptoms of pulmonary congestion, tightness, shortness of breath and/or hypoxemia;

3) a condition or symptom associated with ARDS selected from: cytokine storm syndrome (CSS); Extrapulmonary Systemic Hyperinflammation Syndrome (ESHS), and/or 4) any other condition or symptom mediated by a severe hyper-immune or hyper-inflammatory response in the subject, including Pediatric Inflammatory Multisystem Syndrome (PIMS), vascular congestive and thrombotic conditions, Disseminated Intravascular Coagulation (DIC), thrombosis, stroke, and/or thrombocytopenia.

24. The use of claim 4, wherein the one or more clinical symptoms of COVID-19 disease include one or more symptoms of acute respiratory distress syndrome (ARDS), selected from: 1) dyspnea; 2) hyper-elevated level(s) of one or more pro-inflammatory cytokine(s) in the lung; 3) hyper-elevated level(s) of monocyte/macrophage cells and/or neutrophils in a lung parenchyma and/or a pulmonary alveolar compartment; 4) degradation or disruption of a pulmonary endothelial and/or epithelial barrier(s); 5) elevated indicia of oxidative stress in lung tissue, determinable by elevated levels of reactive oxygen species (ROS) in the lung; and/or 6) one or more pathogenic symptom(s) of lung injury selected from hyper-inflammation, fibrosis, diffuse alveolar damage (DAD), macrophage and/or neutrophil infiltration into the lung parenchyma, macrophage and/or neutrophil infiltration into pulmonary capillaries, deposition of extensive neutrophil extracellular traps (NETs) in a lung interstitium or parenchyma, pulmonary and/or coronary vessel thromboses, and vasculitis in a treated subject in comparison to the same ARDS disease indicator(s)/value(s) measured and determined in comparable, placebo-treated control subjects.