

What is Claimed:

1. A method for treating or preventing a sudden acute respiratory syndrome (SARS) coronavirus infection in a mammalian subject comprising: administering an anti-viral effective amount of a TPA compound to a subject at elevated risk for SARS coronavirus infection, or presenting with active SARS coronavirus infection, to elicit a significant, clinically therapeutic or prophylactic, anti-viral response in the subject, sufficient to prevent or reduce SARS viral infection and/or reduce or eliminate SARS viral load detectable in the subject.
2. The method of claim 1, wherein the SARS coronavirus is a human SARS (hSARS) coronavirus selected from SARS-CoV-2 (COVID-19), SARS-CoV, and middle east respiratory syndrome (MERS) coronaviruses.
3. The method of claim 2, wherein the hSARS coronavirus is SARS-CoV-2 (COVID-19).
4. The method of claim 1, wherein the anti-viral TPA compound is effective to elicit an anti-viral response in the subject 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 method of claim 1, wherein the TPA compound is administered in an amount and dosage form effective to reduce or eliminate 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 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 method of claim 1, wherein the SARS coronavirus is a human SARS (hSARS) coronavirus selected from SARS-CoV-2 (COVID-19), SARS-CoV, and middle east respiratory syndrome (MERS) coronaviruses, and wherein the TPA compound is effective to reduce hSARS viral load or titer in a an upper and/or lower respiratory tract of the subject.
7. The method of claim 1, wherein the SARS virus is a human SARS (hSARS) coronavirus selected from SARS-CoV-2 (COVID-19), SARS-CoV, and middle east respiratory syndrome

(MERS) coronaviruses, and wherein the TPA compound is effective to reduce hSARS viral load or titer in a non-respiratory, ACE-2 positive cell, tissue or organ of the subject.

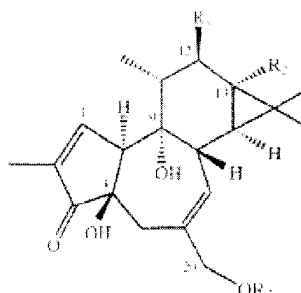
8. The method of claim 1, wherein the SARS virus is SARS-CoV-2 (COVID-19), and wherein the anti-viral TPA compound is effective to elicit an anti-viral response in the subject that prevents or reduces SARS-CoV-2 viral infection and/or reduces or eliminates SARS viral load, as determined by SARS-CoV-2 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 method 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 more among treated subjects.

10. The method 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 75-95% or more among treated subjects.

11. The method 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.

12. The method of claim 1, wherein the anti-viral TPA compound is selected from compounds of Formula I, below, and anti-viral active analogs, derivatives, complexes, conjugates, salts, enantiomers and mixtures thereof:



Formula I

wherein R_1 and R_2 are selected from the group consisting of hydrogen; ---O---C(=O)alkyl ,

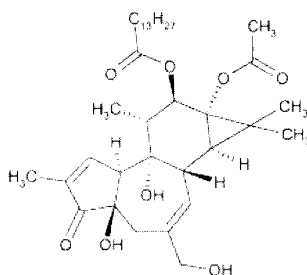
wherein the alkyl group contains 1 to 15 carbon atoms, $\text{---O---C(=O)lower alkenyl}$, $\text{---O---C(=O)phenyl}$,

$\text{---O---C(=O)benzyl}$ and substituted derivatives thereof and R_3 may be hydrogen,

$\text{---O---C(=O)lower alkenyl}$ or substituted derivatives thereof,

wherein the "lower alkyl" or "lower alkenyl" can contain 1-7 carbons and may be straight or branched, and are optionally unsubstituted or substituted by chlorine, fluorine, or another halogen, or nitro, amino or other active functionality.

13. The method of claim 1, wherein the anti-viral TPA compound is selected from Formula I below and anti-viral active analogs, derivatives, complexes, conjugates, salts, enantiomers and mixtures thereof.



Formula II

14. The method of claim 1, wherein the anti-viral TPA compound is a phorbol ester selected from: phorbol 13-butyrate; phorbol 12-decanoate; phorbol 13-decanoate; phorbol 12,13-diacetate; phorbol 13,20-diacetate; phorbol 12,13-dibenzoate; phorbol 12,13-dibutyrate; phorbol 12,13-didecanoate; phorbol 12,13-dihexanoate; phorbol 12,13-dipropionate; phorbol 12-myristate; phorbol 13-myristate; phorbol 12,13,20-triacetate; 12-deoxyphorbol 13-angelate; 12-deoxyphorbol 13-angelate 20-acetate; 12-deoxyphorbol 13-isobutyrate; 12-deoxyphorbol 13-isobutyrate-20-acetate; 12-deoxyphorbol 13-phenylacetate; 12-deoxyphorbol 13-phenylacetate 20-acetate; 12-deoxyphorbol 13-tetradecanoate; phorbol 12-tiglate 13-decanoate; 12-deoxyphorbol 13-acetate; phorbol 12-acetate; phorbol 13-acetate; and anti-viral active analogs, derivatives, complexes, conjugates, salts, enantiomers and mixtures thereof.

15. The method of claim 1, wherein the anti-viral TPA compound is 12-O-tetradecanoylphorbol-13-acetate.

16. The method of claim 1, wherein the SARS virus is SARS-CoV-2 (COVID-19), and wherein the anti-viral TPA compound is first administered within 2 weeks of a subject being initially diagnosed with SARS-CoV-2 infection.

17. The method of claim 1, wherein the SARS virus is SARS-CoV-2 (COVID-19), and wherein the anti-viral TPA compound is first administered 7-10 days after the subject is initially diagnosed with SARS-CoV-2 infection.

18. The method of claim 1, wherein the SARS virus is SARS-CoV-2 (COVID-19), and wherein the anti-viral TPA compound is administered before a subject at 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 acute respiratory distress syndrome (ARDS), including cytokine storm syndrome (CSS); Extrapulmonary Systemic Hyperinflammation Syndrome (ESHS), and/or 4) another condition or symptom associated with 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.

19. The method of claim 1, wherein the anti-viral TPA compound is formulated and administered simultaneously with, or coordinately administered simultaneously or sequentially in

a coordinate, multi-drug prophylactic or treatment protocol with, a secondary therapeutic or prophylactic drug or agent selected from: 1) a conventional anti-viral drug or agent; 2) an anti-ARDS drug or agent; 3) an anti-CSS drug or agent; 4) an anti-PIMS drug or agent; 5) an anti-ESHS drug or agent; 6) an anti-DAD drug or agent; and/or 7) an anti-inflammatory, pro-immune, anti-cytopathic and/or pro-apoptotic drug or agent; and combinations thereof.

20. The method of claim 8, wherein the anti-SARS-CoV2 TPA compound is formulated and administered simultaneously with, or coordinately administered simultaneously or sequentially in a coordinate, multi-drug prophylactic or treatment protocol with, a secondary anti-viral drug or agent.

21. The method of claim 20, wherein the secondary anti-viral drug or agent is selected from: Abacavir, Acyclovir, Adefovir, Amantadine, Ampligen, Amprenavir (Agenerase), Arbidol, Atazanavir, Atripla, Balavir, Baloxavir marboxil (Xofluza), Biktarvy, Boceprevir (Victrelis), Cidofovir, Cobicistat (Tybost), Combivir, Daelatasvir (Daklinza), Darunavir, Delavirdine, Descovy, Didanosine, Docosanol, Dolutegravir, Doravirine (Pifeltro), Ecoliever, Edoxudine, Efavirenz, Elvitegravir, Emtricitabine, Enfuvirtide, Entecavir, Etravirine (Intelence), Fanciclovir, Fomivirsen, Fosamprenavir, Foscarnet, Fosfonet, Fusion inhibitor, Ganciclovir (Cytovene), Ibacitabine, Ibalizumab (Trogarzo), Idoxuridine, Imiquimod, Immunovir, Indinavir, Inosine, Integrase inhibitor, Interferon type I, Interferon type II, Interferon type III, Lamivudine, Letermovir (Prevymis), Lopinavir, Loviride, Maraviroc, Methisazone, Moroxydine, Nelfinavir, Nevirapine, Nexavir, Nitazoxanide, Norvir, Nucleoside analogues, Oseltamivir (Tamiflu), Peginterferon alfa-2a, Peginterferon alfa-2b, Penciclovir, Peramivir (Rapivab), Pleconaril, Podophyllotoxin, Pyrimidine, Raltegravir, Remdesivir, Reverse transcriptase inhibitor, Ribavirin, Rilpivirine (Edurant), Rimantadine, Ritonavir, Saquinavir, Simeprevir (Olysio), Sofosbuvir, Stavudine, Telaprevir, Telbivudine (Tyzeka), Tenofovir alafenamide, Tenofovir disoproxil, Tenofovir, Tipranavir, Trifluridine, Trizivir, Tromantadine, Truvada, Valaciclovir (Valtrex), Valganciclovir, Vicriviroc, Vidarabine, Viramidine, Zalcitabine, Zanamivir (Relenza), and Zidovudine, and combinations thereof.

22. The method of claim 20, wherein the secondary anti-viral drug or agent is an anti-ACE2 drug or agent.

23. The method of claim 20, wherein the secondary anti-viral drug or agent is an anti-inflammatory drug or agent.

24. The method of claim 23, wherein the anti-inflammatory drug or agent is selected from non-steroidal anti-inflammatory drugs (NSAIDs).
25. The method of claim 24, wherein the NSAIDs include: aspirin, celecoxib (Celebrex), diclofenac (Cambia, Cataflam, Voltaren-XR, Zipsor, Zorvolex), diflunisal, etodolac, ibuprofen (Motrin, Advil), indomethacin (Indocin), celecoxib (Celebrex), piroxicam (Feldene), indomethacin (Indocin), meloxicam (Mobic Vivlodex), ketoprofen (Orudis, Ketoprofen ER, Oruvail, Actron), sulindac (Clinoril), diflunisal (Dolobid), nabumetone (Relafen), oxaprozin (Daypro), tolmetin (Tolmetin Sodium, Tolectin), salsalate (Disalcid), fenoprofen (Nalfon), flurbiprofen (Ansaid), ketorolac (Toradol), meclofenamate, mefenamic acid (Ponstel), and combinations thereof.
26. The method of claim 20, wherein the secondary anti-viral drug or agent is a cytokine inhibitor drug or agent.
27. The method of claim 26, wherein the cytokine inhibitor drug or agent is effective to inhibit or lower induction, synthesis, activation and/or circulating level(s) of one or more pro-inflammatory cytokine targets selected from: (IL)-1B; IL-2; IL-6, IL-7; IL-8; IL-9; IL-10; fibroblast growth factor (FGF); granulocyte-macrophage colony stimulating factor (GM-CSF); IFN γ ; granulocyte-colony stimulating factor (G-CSF); interferon- γ -inducible protein (IP10); monocyte chemoattractant protein (MCP1); macrophage inflammatory protein 1 alpha (MIP1A); platelet derived growth factor (PDGF); tumor necrosis factor (TNF α); and vascular endothelial growth factor (VEGF), and combinations thereof.xx
28. The method of claim 27, wherein coordinate multi-drug therapy with the TPA compound and cytokine inhibitor drug is combinatorially effective to yield improved, additive, synergistic and/or potentiating therapeutic benefits (compared to benefits yielded by either drug/agent alone in a same dosage) for reducing induction, synthesis, activation and/or circulating level(s) of one or more pro-inflammatory cytokine targets that are hyper-elevated in association with SARS-CoV-2 infection, COVID-19 disease, ARDS, SARS, CSS, PIMS, ESHS, DAD or another hyper-inflammatory condition mediated or exacerbated by SARS-CoV-2 infection.
29. The method of claim 20, wherein the secondary anti-viral drug or agent is an anti-IL-6 drug or biologic agent.

30. The method of claim 29, 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.
31. The method of claim 30, wherein the anti-IL-6 drug or biologic is selected from siltuximab, sarilumab (Kevzara), and tocilizumab (TCZ).
32. The method of claim 29, 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.
33. The method of claim 32, wherein the anti-IL-6 drug is andrographolide.
34. The method of claim 20, wherein the secondary anti-viral drug or agent is a kinase modulating drug or agent.
35. The method of claim 34, wherein the kinase inhibitor is a 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.
36. The method of claim 35, wherein the kinase modulator drug modulates a mitogen activated protein kinase (MAPK), janus kinase (JAK) and/or protein kinase C (PKC).
37. The method of claim 36, wherein coordinate treatment of COVID-19 disease subjects with the TPA compound and kinase modulator drug clinically reduces one or more disease condition(s) or symptom(s) associated with severe SARS-CoV-2 infection, including one or more condition(s) or symptom(s) associated with ARDS, SARS, CSS, PIMS, ESHS, and DAD.
38. The method of claim 20, wherein the secondary anti-viral drug or agent is an anti-SARS-CoV-2 vaccine agent.
39. The method of claim 20, wherein the secondary anti-viral drug or agent is a composition comprising conditioned natural killer (NK) Cells.
40. The method of claim 20, wherein the secondary anti-viral drug or agent is a composition comprising conditioned mesenchymal stem cells (MSCs).
41. The method of claim 20, wherein the secondary anti-viral drug or agent is a recombinant Interferon.

42. The method of claim 20, wherein the secondary anti-viral drug or agent is an intravenous formulated immunoglobulin.

43. The method of claim 20, wherein the secondary anti-viral drug or agent comprises a SARS-CoV-2-specific neutralizing antibody, Fab fragment or antibody binding domain.

44. The method of claim 20, wherein the secondary anti-viral drug or agent comprises a C5a-specific antibody, Fab fragment or antibody binding domain.

45. The method of claim 20, wherein the secondary anti-viral drug or agent is selected from Thalidomide, Fingolimod, anti-angiogenic drugs, hydroxychloroquine and glucocorticoids.

The method of claim 1, which is anti-virally effective to mediate one or more significant clinical benefits relating to prevention and/or treatment of SARS-CoV-2 viral infection, selected from: 1) preventing or reducing viral infection or titer in the upper respiratory tract; 2) preventing or reducing viral infection or titer the lower respiratory tract; 3) preventing or reducing viral infection or titer in non-respiratory, ACE-2 positive cell and tissues; 4) preventing or reducing viral attachment and entry into lung and other ACE-2 positive cells and tissues; 5) preventing or reducing viral replication in lung and other ACE-2 positive cell and tissues; and/or 7) preventing or reducing viral shedding from an upper respiratory tract of infected subjects.

46. A method for treating an acute respiratory distress syndrome (ARDS) in a mammalian subject, comprising: administering an anti-ARDS effective amount of a TPA composition to said subject, sufficient 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.

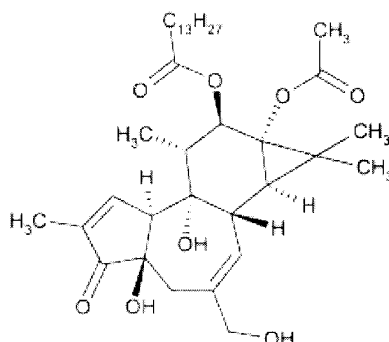
47. The method of claim 46, wherein the ARDS is caused by a respiratory viral or bacterial infection, heat or chemical burn injury to the lungs, pulmonary trauma, or another disease or injury that triggers an immune dysfunction or hyper-inflammatory response that mediates extensive pulmonary injury and dysfunction.
48. The method of claim 46, wherein the ARDS is caused by a sudden acute respiratory syndrome (SARS) coronavirus.
49. The method of claim 48, wherein the SARS coronavirus is a human SARS (hSARS) coronavirus selected from SARS-CoV-2 (COVID-19), SARS-CoV, and middle east respiratory syndrome (MERS) coronaviruses.
50. The method of claim 46, wherein the anti-ARDS TPA compound is effective to prevent or reduce an incidence or severity of dyspnea (labored, short or inadequate breathing), hypoxemia and/or required respirator support in ARDS-affected subjects.
51. The method of claim 46, wherein the anti-ARDS TPA compound is effective to prevent or reduce a hyper-elevated level and/or activity of one or more pro-inflammatory cytokine(s) in the lung, plasma or other cell, tissue or compartment linked to ARDS-associated hyper-inflammation.
52. The method of claim 46, wherein the one or more pro-inflammatory cytokine(s) is/are selected from: (IL)-1B; IL-2; IL-6; IL-7; IL-8; IL-9; IL-10; fibroblast growth factor (FGF); granulocyte-macrophage colony stimulating factor (GM-CSF); IFN γ ; granulocyte-colony stimulating factor (G-CSF); interferon- γ -inducible protein (IP10); monocyte chemoattractant protein (MCP1); macrophage inflammatory protein 1 alpha (MIP1A); platelet derived growth factor (PDGF); tumor necrosis factor (TNF α); and vascular endothelial growth factor (VEGF), and combinations thereof.
53. The method of claim 46, wherein the anti-ARDS TPA compound is effective to prevent or reduce hyper-elevated level(s) of monocyte/macrophage cells and/or neutrophils in a lung parenchyma and/or a pulmonary alveolar compartment in ARDS-affected subjects.
54. The method of claim 53, wherein the anti-ARDS TPA compound is effective to prevent or reduce hyper-elevated levels of neutrophils and deposition of associated neutrophil extracellular traps (NETs) in a lung parenchyma, pulmonary alveolar compartment and/or pulmonary blood vessels in ARDS-affected subjects.

55. The method of claim 46, wherein the anti-ARDS TPA compound is effective to prevent or reduce degradation or disruption of a pulmonary endothelial and/or epithelial barrier(s) in ARDS-affected subjects.

56. The method of claim 46, wherein the anti-ARDS TPA compound is effective to prevent or reduce oxidative stress in lung tissue of ARDS-affected subjects, including by reducing reactive oxygen species (ROS) in the lung.

57. The method of claim 46, wherein the anti-ARDS TPA compound is effective to prevent or reduce the extent of a 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 ARDS-affected subjects.

58. The method of claim 46, wherein the anti-ARDS TPA compound is selected from Formula I below and anti-ARDS active analogs, derivatives, complexes, conjugates, salts, enantiomers and mixtures thereof.



Formula II

59. The method of claim 46, wherein the anti-ARDS TPA compound is a phorbol ester selected from: phorbol 13-butyrate; phorbol 12-decanoate; phorbol 13-decanoate; phorbol 12,13-diacetate; phorbol 13,20-diacetate; phorbol 12,13-dibenzoate; phorbol 12,13-dibutyrate; phorbol 12,13-didecanoate; phorbol 12,13-dihexanoate; phorbol 12,13-dipropionate; phorbol 12-myristate; phorbol 13-myristate; phorbol 12,13,20-triacetate; 12-deoxyphorbol 13-angelate; 12-deoxyphorbol 13-angelate 20-acetate; 12-deoxyphorbol 13-isobutyrate; 12-deoxyphorbol 13-

isobutyrate-20-acetate; 12-deoxyphorbol 13-phenylacetate; 12-deoxyphorbol 13-phenylacetate 20-acetate; 12-deoxyphorbol 13-tetradecanoate; phorbol 12-tigliate 13-decanoate; 12-deoxyphorbol 13-acetate; phorbol 12-acetate; phorbol 13-acetate; and anti-ARDS active analogs, derivatives, complexes, conjugates, salts, enantiomers and mixtures thereof.

60. The method of claim 46, wherein the anti-ARDS TPA compound is 12-O-tetradecanoylphorbol-13-acetate.

61. The method of claim 46, wherein the ARDS is caused by a sudden acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus, and wherein the anti-ARDS TPA compound is first administered within 2 weeks of a subject being initially diagnosed with SARS-CoV-2 infection.

62. The method of claim 46, wherein the ARDS is caused by a sudden acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus, and wherein the anti-ARDS TPA compound is first administered 7-10 days after the subject is initially diagnosed with SARS-CoV-2 infection.

63. The method of claim 46, wherein the ARDS is caused by a sudden acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus, and wherein the anti-ARDS TPA compound is 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.

64. The method of claim 46, wherein the anti-ARDS TPA compound is effective to treat one or more disease condition(s) or symptom(s) associated with (ARDS) selected from 1) lower respiratory symptoms of pulmonary congestion, tightness, shortness of breath and/or hypoxemia; 2) cytokine storm syndrome (CSS); 3) Extrapulmonary Systemic Hyperinflammation Syndrome (ESHS), and/or 4) another 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.

65. The method of claim 46, wherein the anti-ARDS TPA compound is formulated and administered simultaneously with, or coordinately administered simultaneously or sequentially in a coordinate, multi-drug prophylactic or treatment protocol with, a secondary therapeutic or prophylactic drug or agent selected from: 1) a conventional anti-viral drug or agent; 2) a secondary anti-ARDS drug or agent; 3) an anti-CSS drug or agent, 4) an anti-PIMS drug or agent; 5) an anti-ESHS drug or agent; 6) an anti-DAD drug or agent; and/or 7) an anti-inflammatory, pro-immune, anti-cytopathic and/or pro-apoptotic drug or agent; and combinations thereof.

66. The method of claim 65, wherein the ARDS is caused by a sudden acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus, and wherein the anti-ARDS TPA compound is formulated and administered simultaneously with, or coordinately administered simultaneously or sequentially in a coordinate, multi-drug prophylactic or treatment protocol with, a secondary anti-viral drug or agent.

67. The method of claim 66, wherein the secondary anti-viral drug or agent is selected from: Abacavir, Acyclovir, Adefovir, Amantadine, Ampligen, Amprenavir (Agenerase), Arbidol, Atazanavir, Atripla, Balavir, Baloxavir marboxil (Xofluza), Biktarvy, Boceprevir (Victrelis), Cidofovir, Cobicistat (Tybost), Combivir, Daelatasvir (Daklinza), Darunavir, Delavirdine, Descovy, Didanosine, Docosanol, Dolutegravir, Doravirine (Pifeltro), Ecoliever, Edoxudine, Efavirenz, Elvitegravir, Emtricitabine, Enfuvirtide, Entecavir, Etravirine (Intelence), Famciclovir, Fomivirsen, Fosamprenavir, Foscarnet, Fosfonet, Fusion inhibitor, Ganciclovir (Cytovene), Ibacitabine, Ibalizumab (Trogarzo), Idoxuridine, Imiquimod, Immunovir, Indinavir, Inosine, Integrase inhibitor, Interferon type I, Interferon type II, Interferon type III, Lamivudine, Letemovir (Prevymis), Lopinavir, Loviride, Maraviroc, Methisazone, Moroxydine, Nelfinavir, Nevirapine, Nexavir, Nitazoxanide, Norvir, Nucleoside analogues, Oseltamivir (Tamiflu), Peginterferon alfa-2a, Peginterferon alfa-2b, Penciclovir, Peramivir (Rapivab), Pleconaril, Podophyllotoxin, Pyrimidine, Raltegravir, Remdesivir, Reverse transcriptase inhibitor, Ribavirin, Rilpivirine (Edurant), Rimantadine, Ritonavir, Saquinavir, Simeprevir (Olysio), Sofosbuvir, Stavudine, Telaprevir, Telbivudine (Tyzeka), Tenofovir alafenamide, Tenofovir disoproxil, Tenofovir, Tipranavir, Trifluridine, Trizivir, Tromantadine, Truvada, Valaciclovir

(Valtrex), Valganciclovir, Viceriviroc, Vidarabine, Viramidine, Zalcitabine, Zanamivir (Relenza), and Zidovudine, and combinations thereof.

68. The method of claim 65, wherein the secondary drug or agent is an anti-ACE2 drug or agent.

69. The method of claim 65, wherein the secondary drug or agent is an anti-inflammatory drug or agent.

70. The method of claim 69, wherein the anti-inflammatory drug or agent is selected from non-steroidal anti-inflammatory drugs (NSAIDs).

71. The method of claim 70, wherein the NSAIDs include: aspirin, celecoxib (Celebrex), diclofenac (Cambia, Cataflam, Voltaren-XR, Zipsor, Zorvolex), diflunisal, etodolac, ibuprofen (Motrin, Advil), indomethacin (Indocin), celecoxib (Celebrex), piroxicam (Feldene), indomethacin (Indocin), meloxicam (Mobic Vivlodex), ketoprofen (Orudis, Ketoprofen ER, Oruvail, Actron), sulindac (Clinoril), diflunisal (Dolobid), nabumetone (Relafen), oxaprozin (Daypro), tolmetin (Tolmetin Sodium, Tolectin), salsalate (Disalcid), fenoprofen (Nalfon), flurbiprofen (Ansaid), ketorolac (Toradol), meclofenamate, mefenamic acid (Ponstel), and combinations thereof.

72. The method of claim 65, wherein the secondary drug or agent is a cytokine inhibitor drug or agent.

73. The method of claim 72, wherein the cytokine inhibitor drug or agent is effective to inhibit or lower induction, synthesis, activation and/or circulating level(s) of one or more pro-inflammatory cytokine targets selected from: (IL)-1B; IL-2; IL-6, IL-7; IL-8; IL-9; IL-10; fibroblast growth factor (FGF); granulocyte-macrophage colony stimulating factor (GM-CSF); IFN γ ; granulocyte-colony stimulating factor (G-CSF); interferon- γ -inducible protein (IP10); monocyte chemoattractant protein (MCP1); macrophage inflammatory protein 1 alpha (MIP1A); platelet derived growth factor (PDGF); tumor necrosis factor (TNF α); and vascular endothelial growth factor (VEGF), and combinations thereof.

74. The method of claim 72, wherein the ARDS is caused by a sudden acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus, and wherein coordinate multi-drug therapy with the TPA compound and cytokine inhibitor drug is combinatorially effective to yield improved, additive, synergistic and/or potentiating therapeutic benefits (compared to benefits yielded by either drug/agent alone in a same dosage) for reducing induction, synthesis,

activation and/or circulating level(s) of one or more pro-inflammatory cytokine targets that are hyper-elevated in association with SARS-CoV-2 infection, COVID-19 disease, ARDS, SARS, CSS, PIMS, ESHS, DAD or another hyper-inflammatory condition mediated or exacerbated by SARS-CoV-2 infection.

75. The method of claim 65, wherein the secondary drug or agent is an anti-IL-6 drug or biologic agent.

76. The method of claim 75, 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.

77. The method of claim 75, wherein the anti-IL-6 drug or biologic is selected from siltuximab, sarilumab (Kevzara), and tocilizumab (TCZ).

78. The method of claim 75, 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.

79. The method of claim 78, wherein the anti-IL-6 drug is andrographolide.

80. The method of claim 65, wherein the secondary drug or agent is a kinase modulating drug or agent.

81. The method of claim 80, 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.

82. The method of claim 81, wherein the kinase modulator drug or agent modulates a mitogen activated protein kinase (MAPK), janus kinase (JAK) and/or protein kinase C (PKC).

83. The method of claim 65, wherein the ARDS is caused by a sudden acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus, and wherein the coordinate treatment of COVID-19 disease subjects with the TPA compound and kinase modulator drug clinically reduces one or more disease condition(s) or symptom(s) associated with severe SARS-CoV-2 infection, including one or more condition(s) or symptom(s) associated with ARDS, SARS, CSS, PIMS, ESHS, and DAD.

84. The method of claim 65, wherein the ARDS is caused by a sudden acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus, and wherein the secondary drug or agent is an anti-SARS-CoV-2 vaccine agent.
85. The method of claim 65, wherein the secondary drug or agent is a composition comprising conditioned natural killer (NK) Cells.
86. The method of claim 65, wherein the secondary drug or agent is a composition comprising conditioned mesenchymal stem cells (MSCs).
87. The method of claim 65, wherein the secondary drug or agent is a recombinant Interferon.
88. The method of claim 65, wherein the ARDS is caused by a sudden acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus, and wherein the secondary drug or agent is an intravenous formulated immunoglobulin.
89. The method of claim 65, wherein the ARDS is caused by a sudden acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus, and wherein the secondary drug or agent comprises a SARS-CoV-2-specific neutralizing antibody, Fab fragment or antibody binding domain.
90. The method of claim 65, wherein the secondary drug or agent comprises a C5a-specific antibody, Fab fragment or antibody binding domain.
91. The method of claim 65, wherein the secondary drug or agent is selected from Thalidomide, Fingolimod, anti-angiogenic drugs, hydroxychloroquine and glucocorticoids.
92. The method of claim 65, wherein the ARDS is caused by a sudden acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus, and wherein anti-ARDS TPA compound and secondary drug or agent are combinatorially effective to mediate one or more significant clinical benefits relating to prevention and/or treatment of SARS-CoV-2 viral infection and COVID-19 disease selected from: 1) preventing or reducing viral infection or titer in the upper respiratory tract; 2) preventing or reducing viral infection or titer the lower respiratory tract; 3) preventing or reducing viral infection or titer in non-respiratory, ACE-2 positive cell and tissues; 4) preventing or reducing viral attachment and entry into lung and other ACE-2 positive cells and tissues; 5) preventing or reducing viral replication in lung and other ACE-2 positive cell and tissues; and/or 7) preventing or reducing viral shedding from an upper respiratory tract of infected subjects.

93. A method for treating an immune dysfunction or hyper-inflammatory condition in a mammalian subject suffering from a Cytokine Storm Syndrome (CSS), Pediatric Inflammatory Multisystem Syndrome (PIMS), Extrapulmonary Systemic Hyperinflammation Syndrome (ESHS) generally, or a vascular congestive or thrombotic condition caused by hyperinflammation, including Disseminated Intravascular Coagulation (DIC), thrombosis, stroke, thrombocytopenia, and/or gangrene, comprising: administering an anti-inflammatory effective amount of a TPA compound to the subject.

94. The method of claim 93, wherein the subject is at elevated risk for or is infected with sudden acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus, and wherein the anti-inflammatory TPA compound is effective to mediate an anti-CSS response in the subject.

95. The method of claim 94, wherein the anti-CSS response includes prevention or reduction of one or more CSS-associated condition(s) or symptom(s) selected from: 1) hyper-elevated level(s) of one or more pro-inflammatory cytokine(s) in the lung or another tissue or organ site of hyper-inflammation; 2) hyper-elevated level(s) of monocyte/macrophage cells and/or neutrophils in a lung parenchyma, pulmonary alveolar compartment or other tissue or organ site of hyper-inflammation; 3) degradation or disruption of endothelial and/or epithelial barrier(s) in the lung or other tissue or organ site of hyper-inflammation; 4) elevated indicia of oxidative stress in the lung or other tissue or organ site of hyper-inflammation, determinable by elevated levels of reactive oxygen species (ROS); and/or 5) one or more pathogenic symptom(s) of tissue or organ injury selected from hyper-inflammation, fibrosis, diffuse alveolar damage (DAD), macrophage and/or neutrophil infiltration into the lung parenchyma or other tissue or organ site of hyper-inflammation, macrophage and/or neutrophil infiltration into capillaries of the lung or another tissue or organ site of hyper-inflammation, deposition of extensive neutrophil extracellular traps (NETs) in a lung interstitium or parenchyma or other tissue or organ site of hyper-inflammation, pulmonary and/or coronary vessel thromboses, and/or vasculitis in treated subjects.

96. The method of claim 93, wherein the subject presents with CSS and the TPA compound is an anti-CSS effective TPA compound that elicits at least a 25% reduction in one or more condition(s), symptom(s) or diagnostic index(ices) associated with CSS selected from 1) hyper-elevated pro-inflammatory cytokine activation, expression and/or levels in CSS-affected cells or tissues; 2) increased infiltration and/or elevated numbers of macrophages and/or neutrophils in

the lung parenchyma, pulmonary alveolar airspaces, or another CSS-affected tissue or organ; 3) lymphocytopenia marked by numerical decline of lymphocytes; 4) elevated oxidative stress markers; 5) inflammatory injury to endothelial and/or epithelial barriers in the lungs or another CSS-affected tissue or organ; 6) pathogenic fibrosis or other pathologic inflammatory injury to the lungs or another CSS-affected tissue or organ/organ; 7) inflammatory injury, loss or atrophy of lymph nodes; 8) splenic inflammatory injury or atrophy; 9) Sepsis; 10) Toxic Shock Syndrome (TSS); 11) oxidative stress symptoms; and/or 12) one or more pathogenic symptom(s) of tissue or organ injury selected from hyper-inflammation, fibrosis, diffuse alveolar damage (DAD), macrophage and/or neutrophil infiltration into the lung parenchyma or other tissue or organ site of hyper-inflammation, macrophage and/or neutrophil infiltration into capillaries of the lung or another tissue or organ site of hyper-inflammation, deposition of extensive neutrophil extracellular traps (NETs) in a lung interstitium or parenchyma or other tissue or organ site of hyper-inflammation, pulmonary and/or coronary vessel thromboses, and/or vasculitis in treated subjects (wherein each indicator/value is measured and determined in treated subjects, in comparison to the same indicator/value measured and determined in similar, placebo-treated control subjects).

97. The method of claim 96, wherein the anti-CSS TPA compound is effective to prevent or reduce dysregulation and hyper-elevation of pro-inflammatory cytokines associated with CSS, wherein treated subjects show at least a 25% reduction in hyper-elevated level(s) of one or more pro-inflammatory cytokine(s).

98. The method of claim 94, wherein the anti-inflammatory TPA compound is effective to prevent or reduce a hyper-elevated level and/or activity of one or more pro-inflammatory cytokine(s) in the lung, plasma or other cell, tissue or compartment linked to ARDS-associated hyper-inflammation.

99. The method of claim 98, wherein the one or more pro-inflammatory cytokine(s) is/are selected from: (IL)-1B; IL-2; IL-6; IL-7; IL-8; IL-9; IL-10; fibroblast growth factor (FGF); granulocyte-macrophage colony stimulating factor (GM-CSF); IFN γ ; granulocyte-colony stimulating factor (G-CSF); interferon- γ -inducible protein (IP10); monocyte chemoattractant protein (MCP1); macrophage inflammatory protein 1 alpha (MIP1A); platelet derived growth factor (PDGF); tumor necrosis factor (TNF α); and vascular endothelial growth factor (VEGF), and combinations thereof.

100. The method of claim 94, wherein the anti-inflammatory TPA compound is effective to prevent or reduce hyper-elevated level(s) of monocyte/macrophage cells and/or neutrophils in a lung parenchyma, pulmonary alveolar compartment or other tissue or organ site of hyper-inflammation in CSS-affected subjects.

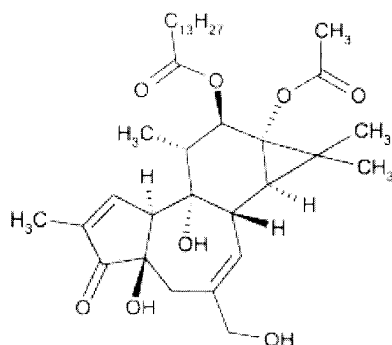
101. The method of claim 94, wherein the anti-inflammatory TPA compound is effective to prevent or reduce hyper-elevated levels of neutrophils and deposition of associated neutrophil extracellular traps (NETs) in a lung parenchyma, pulmonary alveolar compartment, pulmonary blood vessels or other tissue or organ site of hyper-inflammation in CSS-affected subjects.

102. The method of claim 94, wherein the anti-inflammatory TPA compound is effective to prevent or reduce degradation or disruption of endothelial and/or epithelial barrier(s) in the lungs or other tissue or organ site of hyper-inflammation in CSS-affected subjects.

103. The method of claim 94, wherein the anti-inflammatory TPA compound is effective to prevent or reduce oxidative stress in a lung or other tissue or organ site of hyper-inflammation in CSS-affected subjects.

104. The method of claim 94, wherein the anti-inflammatory TPA compound is effective to prevent or reduce the extent of a hyper-inflammatory tissue or organ injury selected from hyper-inflammation, fibrosis, diffuse alveolar damage (DAD), macrophage and/or neutrophil infiltration into the lung parenchyma or other tissue or organ site of hyper-inflammation, macrophage and/or neutrophil infiltration into capillaries of the lung or other tissue or organ site of hyper-inflammation, deposition of extensive neutrophil extracellular traps (NETs) in a lung interstitium or parenchyma or other tissue or organ site of hyper-inflammation, pulmonary and/or coronary vessel thromboses, and vasculitis in CSS-affected subjects.

105. The method of claim 94, wherein the anti-inflammatory TPA compound is selected from Formula I below and anti-inflammatory active analogs, derivatives, complexes, conjugates, salts, enantiomers and mixtures thereof.



Formula II

106. The method of claim 94, wherein the anti-inflammatory TPA compound is a phorbol ester selected from: phorbol 13-butyrate; phorbol 12-decanoate; phorbol 13-decanoate; phorbol 12,13-diacetate; phorbol 13,20-diacetate; phorbol 12,13-dibenzoate; phorbol 12,13-dibutyrate; phorbol 12,13-didecanoate; phorbol 12,13-dihexanoate; phorbol 12,13-dipropionate; phorbol 12-myristate; phorbol 13-myristate; phorbol 12,13,20-triacetate; 12-deoxyphorbol 13-angelate; 12-deoxyphorbol 13-angelate 20-acetate; 12-deoxyphorbol 13-isobutyrate; 12-deoxyphorbol 13-isobutyrate-20-acetate; 12-deoxyphorbol 13-phenylacetate; 12-deoxyphorbol 13-phenylacetate 20-acetate; 12-deoxyphorbol 13-tetradecanoate; phorbol 12-tiglate 13-decanoate; 12-deoxyphorbol 13-acetate; phorbol 12-acetate; phorbol 13-acetate; and anti-inflammatory active analogs, derivatives, complexes, conjugates, salts, enantiomers and mixtures thereof.

107. The method of claim 94, wherein the anti-inflammatory TPA compound is 12-O-tetradecanoylphorbol-13-acetate.

108. The method of claim 94, wherein the wherein the anti-inflammatory TPA compound is first administered within 2 weeks of a subject being initially diagnosed with SARS-CoV-2 infection.

109. The method of claim 94, wherein the anti-inflammatory TPA compound is first administered 7-10 days after the subject is initially diagnosed with SARS-CoV-2 infection.

110. The method of claim 94, wherein the anti-inflammatory TPA compound is 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.

111. The method of claim 94, wherein the anti-inflammatory TPA compound is effective to treat one or more disease condition(s) or symptom(s) associated with acute respiratory distress syndrome (ARDS) selected from 1) lower respiratory symptoms of pulmonary congestion, tightness, shortness of breath and/or hypoxemia; 2) Extrapulmonary Systemic Hyperinflammation Syndrome (ESHS), and/or 3) another 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.

112. The method of claim 94, wherein the anti-inflammatory TPA compound is formulated and administered simultaneously with, or coordinately administered simultaneously or sequentially in a coordinate, multi-drug prophylactic or treatment protocol with, a secondary therapeutic or prophylactic drug or agent selected from: 1) a conventional anti-viral drug or agent; 2) a secondary anti-CSS drug or agent; 3) an anti-ARDS drug or agent, 4) an anti-PIMS drug or agent; 5) an anti-ESHS drug or agent; 6) an anti-DAD drug or agent; and/or 7) an anti-inflammatory, pro-immune, anti-cytopathic and/or pro-apoptotic drug or agent, and combinations thereof.

113. The method of claim 94, wherein the anti-inflammatory TPA compound is formulated and administered simultaneously with, or coordinately administered simultaneously or sequentially in a coordinate, multi-drug prophylactic or treatment protocol with, a secondary anti-viral drug or agent.

114. The method of claim 113, wherein the secondary anti-viral drug or agent is selected from: Abacavir, Acyclovir, Adefovir, Amantadine, Ampligen, Amprenavir (Agenerase), Arbidol, Atazanavir, Atripla, Balavir, Baloxavir marboxil (Xofluza), Biktarvy, Boceprevir (VICTRELIS), Cidofovir, Cobicistat (Tybost), Combivir, Daclatasvir (Daklinza), Darunavir, Delavirdine, Descovy, Didanosine, Docosanol, Dolutegravir, Doravirine (Pifeltro), Ecoliever, Edoxudine,

Efavirenz, Elvitegravir, Emtricitabine, Enfuvirtide, Entecavir, Etravirine (Intelence), Famciclovir, Fomivirsen, Fosamprenavir, Foscarnet, Fosfonet, Fusion inhibitor, Ganciclovir (Cytovene), Ibacitabine, Ibalizumab (Trogarzo), Idoxuridine, Imiquimod, Imunovir, Indinavir, Inosine, Integrase inhibitor, Interferon type I, Interferon type II, Interferon type III, Lamivudine, Letemovir (Prevymis), Lopinavir, Loviride, Maraviroc, Methisazone, Moroxydine, Nelfinavir, Nevirapine, Nexavir, Nitazoxanide, Norvir, Nucleoside analogues, Oseltamivir (Tamiflu), Peginterferon alfa-2a, Peginterferon alfa-2b, Penciclovir, Peramivir (Rapivab), Pleconaril, Podophyllotoxin, Pyrimidine, Raltegravir, Remdesivir, Reverse transcriptase inhibitor, Ribavirin, Rilpivirine (Edurant), Rimantadine, Ritonavir, Saquinavir, Simeprevir (Olysio), Sofosbuvir, Stavudine, Telaprevir, Telbivudine (Tyzeka), Tenofovir alafenamide, Tenofovir disoproxil, Tenofovir, Tipranavir, Trifluridine, Trizivir, Tromantadine, Truvada, Valaciclovir (Valtrex), Valganciclovir, Vicriviroc, Vidarabine, Viramidine, Zalcitabine, Zanamivir (Relenza), and Zidovudine, and combinations thereof.

115. The method of claim 112, wherein the secondary drug or agent is an anti-ACE2 drug or agent.

116. The method of claim 112, wherein the secondary drug or agent is an anti-inflammatory drug or agent.

117. The method of claim 116, wherein the anti-inflammatory drug or agent is selected from non-steroidal anti-inflammatory drugs (NSAIDs).

118. The method of claim 117, wherein the NSAIDs include: aspirin, celecoxib (Celebrex), diclofenac (Cambia, Cataflam, Voltaren-XR, Zipsor, Zorvolex), diflunisal, etodolac, ibuprofen (Motrin, Advil), indomethacin (Indocin), celecoxib (Celebrex), piroxicam (Feldene), indomethacin (Indocin), meloxicam (Mobic Vivlodex), ketoprofen (Orudis, Ketoprofen ER, Oruvail, Actron), sulindac (Clinoril), diflunisal (Dolobid), nabumetone (Relafen), oxaprozin (Daypro), tolmetin (Tolmetin Sodium, Tolectin), salsalate (Disalcid), fenoprofen (Nalfon), flurbiprofen (Ansaid), ketorolac (Toradol), meclofenamate, mefenamic acid (Ponstel), and combinations thereof.

119. The method of claim 112, wherein the secondary drug or agent is a cytokine inhibitor drug or agent.

120. The method of claim 119, wherein the cytokine inhibitor drug or agent is effective to inhibit or lower induction, synthesis, activation and/or circulating level(s) of one or more pro-

inflammatory cytokine targets selected from: (IL)-1B; IL-2; IL-6, IL-7; IL-8; IL-9; IL-10; fibroblast growth factor (FGF); granulocyte-macrophage colony stimulating factor (GM-CSF); IFN γ ; granulocyte-colony stimulating factor (G-CSF); interferon- γ -inducible protein (IP10); monocyte chemoattractant protein (MCP1); macrophage inflammatory protein 1 alpha (MIP1A); platelet derived growth factor (PDGF); tumor necrosis factor (TNF α); and vascular endothelial growth factor (VEGF), and combinations thereof.

121. The method of claim 112, wherein coordinate multi-drug therapy with the TPA compound and cytokine inhibitor drug is combinatorially effective to yield improved, additive, synergistic and/or potentiating therapeutic benefits (compared to benefits yielded by either drug/agent alone in a same dosage) for reducing induction, synthesis, activation and/or circulating level(s) of one or more pro-inflammatory cytokine targets that are hyper-elevated in association with SARS-CoV-2 infection, COVID-19 disease, ARDS, SARS, CSS, PIMS, ESHS, DAD or another hyper-inflammatory condition mediated or exacerbated by SARS-CoV-2 infection.

122. The method of claim 112, wherein the secondary drug or agent is an anti-IL-6 drug or biologic agent.

123. The method of claim 122, 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.

124. The method of claim 122, wherein the anti-IL-6 drug or biologic is selected from siltuximab, sarilumab (Kevzara), and tocilizumab (TCZ).

125. The method of claim 122, 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.

126. The method of claim 125, wherein the anti-IL-6 drug is andrographolide.

127. The method of claim 112, wherein the secondary drug or agent is a kinase modulating drug or agent.

128. The method of claim 127, 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.

129. The method of claim 127, wherein the kinase modulator drug or agent modulates a mitogen activated protein kinase (MAPK), janus kinase (JAK) and/or protein kinase C (PKC).

130. The method of claim 127, wherein coordinate treatment of COVID-19 disease subjects with the TPA compound and kinase modulator drug clinically reduces one or more disease condition(s) or symptom(s) associated with severe SARS-CoV-2 infection, including one or more condition(s) or symptom(s) associated with ARDS, SARS, CSS, PIMS, ESHS, and DAD.

131. The method of claim 112, wherein the secondary drug or agent is an anti-SARS-CoV-2 vaccine agent.

132. The method of claim 112, wherein the secondary drug or agent is a composition comprising conditioned natural killer (NK) Cells.

133. The method of claim 112, wherein the secondary drug or agent is a composition comprising conditioned mesenchymal stem cells (MSCs).

134. The method of claim 112, wherein the secondary drug or agent is a recombinant Interferon.

135. The method of claim 112, wherein the secondary drug or agent is an intravenous formulated immunoglobulin.

136. The method of claim 112, wherein the secondary drug or agent comprises a SARS-CoV-2-specific neutralizing antibody, Fab fragment or antibody binding domain.

137. The method of claim 112, wherein the secondary drug or agent comprises a C5a-specific antibody, Fab fragment or antibody binding domain.

138. The method of claim 112, wherein the secondary drug or agent is selected from Thalidomide, Fingolimod, anti-angiogenic drugs, hydroxychloroquine and glucocorticoids.

139. The method of claim 112, wherein the anti-inflammatory TPA compound and secondary drug or agent are combinatorially effective to mediate one or more significant clinical benefits relating to prevention and/or treatment of SARS-CoV-2 viral infection and COVID-19 disease selected from: 1) preventing or reducing viral infection or titer in the upper respiratory tract; 2) preventing or reducing viral infection or titer the lower respiratory tract; 3) preventing or reducing viral infection or titer in non-respiratory, ACE-2 positive cell and tissues; 4) preventing or reducing viral attachment and entry into lung and other ACE-2 positive cells and tissues; 5)

preventing or reducing viral replication in lung and other ACE-2 positive cell and tissues; and/or
7) preventing or reducing viral shedding from an upper respiratory tract of infected subjects.

140. An anti-viral composition or kit for use in human subjects presenting with medical risk factors for COVID-19 disease mediated by a SARS-CoV-2 virus, or in patients presenting with a positive diagnosis for infection by the SARS-CoV-2 virus, comprising an anti-viral effective TPA compound formulated or packaged with a secondary anti-viral drug or agent.

141. The anti-viral pharmaceutical composition or kit of claim 140, wherein the secondary anti-viral drug or agent is selected from: Abacavir, Acyclovir, Adefovir, Amantadine, Ampligen, Amprenavir (Agenerase), Arbidol, Atazanavir, Atripla, Balavir, Baloxavir marboxil (Xofluza), Biktarvy, Boceprevir (Victrelis), Cidofovir, Cobicistat (Tybost), Combivir, Daclatasvir (Daklinza), Darunavir, Delavirdine, Descovy, Didanosine, Docosanol, Dolutegravir, Doravirine (Pifeltro), Ecoliever, Edoxudine, Efavirenz, Elvitegravir, Emtricitabine, Enfuvirtide, Entecavir, Etravirine (Intelence), Fanciclovir, Fomivirsen, Fosamprenavir, Foscarnet, Fosfonet, Fusion inhibitor, Ganciclovir (Cytovene), Ibacitabine, Ibalizumab (Trogarzo), Idoxuridine, Imiquimod, Immunovir, Indinavir, Inosine, Integrase inhibitor, Interferon type I, Interferon type II, Interferon type III, Lamivudine, Letermovir (Prevymis), Lopinavir, Loviride, Maraviroc, Methisazone, Moroxydine, Nelfinavir, Nevirapine, Nexavir, Nitazoxanide, Norvir, Nucleoside analogues, Oseltamivir (Tamiflu), Peginterferon alfa-2a, Peginterferon alfa-2b, Penciclovir, Peramivir (Rapivab), Pleconaril, Podophyllotoxin, Pyrimidine, Raltegravir, Remdesivir, Reverse transcriptase inhibitor, Ribavirin, Rilpivirine (Edurant), Rimantadine, Ritonavir, Saquinavir, Simeprevir (Olysio), Sofosbuvir, Stavudine, Telaprevir, Telbivudine (Tyzeka), Tenofovir alafenamide, Tenofovir disoproxil, Tenofovir, Tipranavir, Trifluridine, Trizivir, Tromantadine, Truvada, Valaciclovir (Valtrex), Valganciclovir, Vicriviroc, Vidarabine, Viramidine, Zalcitabine, Zanamivir (Relenza), and Zidovudine, and combinations thereof.

142. A pharmaceutical composition or kit for use in prevention or treatment of acute respiratory syndrome (ARDS) in a mammalian subject comprising an anti-ARDS effective TPA compound formulated or packaged with a secondary therapeutic or prophylactic drug or agent selected from: 1) a conventional anti-viral drug or agent; 2) a secondary anti-ARDS drug or agent; 3) an anti-CSS drug or agent; 4) an anti-PIMS drug or agent; 5) an anti-ESHS drug or agent; 6) an anti-DAD drug or agent; and/or 7) an anti-inflammatory, pro-immune, anti-cytopathic and/or pro-apoptotic drug or agent; and combinations thereof.

143. A pharmaceutical composition or kit for use in prevention or treatment of acute respiratory syndrome (ARDS) in a mammalian subject comprising an anti-ARDS effective TPA compound formulated or packaged with a secondary therapeutic or prophylactic drug or agent selected from non-steroidal anti-inflammatory drugs (NSAIDs).

144. The pharmaceutical composition of claim 143, wherein the NSAIDs include: aspirin, celecoxib (Celebrex), diclofenac (Cambia, Cataflam, Voltaren-XR, Zipsor, Zorvolex), diflunisal, etodolac, ibuprofen (Motrin, Advil), indomethacin (Indocin), celecoxib (Celebrex), piroxicam (Feldene), indomethacin (Indocin), meloxicam (Mobic Vivlodex), ketoprofen (Orudis, Ketoprofen ER, Oruvail, Actron), sulindac (Clinoril), diflunisal (Dolobid), nabumetone (Relafen), oxaprozin (Daypro), tolmetin (Tolmetin Sodium, Tolectin), salsalate (Disalcid), fenoprofen (Nalfon), flurbiprofen (Ansaid), ketorolac (Toradol), meclofenamate, mefenamic acid (Ponstel), and combinations thereof.

145. A pharmaceutical composition or kit for use in prevention or treatment of acute respiratory syndrome (ARDS) in a mammalian subject comprising an anti-ARDS effective TPA compound formulated or packaged with a secondary therapeutic or prophylactic drug or agent selected from cytokine inhibitor drugs and agents.

146. The pharmaceutical composition or kit of claim 145, wherein the cytokine inhibitor drug or agent is effective to inhibit or lower induction, synthesis, activation and/or circulating level(s) of one or more pro-inflammatory cytokine targets selected from: (IL)-1B; IL-2; IL-6, IL-7; IL-8; IL-9; IL-10; fibroblast growth factor (FGF); granulocyte-macrophage colony stimulating factor (GM-CSF); IFN γ ; granulocyte-colony stimulating factor (G-CSF); interferon- γ -inducible protein (IP10); monocyte chemoattractant protein (MCP1); macrophage inflammatory protein 1 alpha (MIP1A); platelet derived growth factor (PDGF); tumor necrosis factor (TNF α); and vascular endothelial growth factor (VEGF), and combinations thereof.

147. A pharmaceutical composition or kit for use in prevention or treatment of acute respiratory syndrome (ARDS) in a mammalian subject comprising an anti-ARDS effective TPA compound formulated or packaged with a secondary therapeutic or prophylactic drug or agent selected from anti-IL-6 drugs and biologic agents.

148. The pharmaceutical composition or kit of claim 147, 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.

149. The pharmaceutical composition or kit of claim 147, wherein the anti-IL-6 drug or biologic is selected from siltuximab, sarilumab (Kevzara), and tocilizumab (TCZ).
150. The pharmaceutical composition or kit of claim 147, 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.
151. The pharmaceutical composition or kit of claim 150, wherein the anti-IL-6 drug is andrographolide.
152. A pharmaceutical composition or kit for use in prevention or treatment of acute respiratory syndrome (ARDS) in a mammalian subject comprising an anti-ARDS effective TPA compound formulated or packaged with a secondary therapeutic or prophylactic drug or agent selected from kinase modulating drugs and agents.
153. The pharmaceutical composition or kit of claim 152, 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.
154. The pharmaceutical composition or kit of claim 152, wherein the kinase modulator drug or agent modulates a mitogen activated protein kinase (MAPK), janus kinase (JAK) and/or protein kinase C (PKC).
155. A pharmaceutical composition or kit for use in prevention or treatment of acute respiratory syndrome (ARDS) in a mammalian subject comprising an anti-ARDS effective TPA compound formulated or packaged with a secondary therapeutic or prophylactic drug or agent selected from sudden acute respiratory syndrome (SARS)-2 (SARS-CoV-2 or COVID-19) coronavirus vaccine agents.
156. A pharmaceutical composition or kit for use in prevention or treatment of acute respiratory syndrome (ARDS) in a mammalian subject comprising 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.