CLAIMS

What is claimed is:

~~1. A method of treating a subject having an infectious disease, wherein the infectious disease is characterized by a pathology that involves hemorrhaging or pathological vascular leakage in the subject, the method comprising administering to the subject a mast cell modulator.~~

~~2. A method of inhibiting or preventing hemorrhaging or vascular leakage induced by infectious disease in a subject, the method comprising administering to the subject a mast cell modulator.~~

~~3.~~ 1. Use of a mast cell modulator for the manufacture of a medicament for treating an infectious disease ~~A method of diagnosing and treating a subject having an infectious disease, wherein the infectious disease is~~ characterized by a pathology that involves hemorrhaging or pathological vascular leakage, wherein the infectious disease is characterized by the presence of ~~in the subject, the method comprising~~:

~~(a) obtaining a biological sample from the subject;~~

~~(b) determining the level of at least one biomarker in the biological sample from the subject;~~

~~(c) comparing the level of the at least one biomarker in the biological sample to a reference level of the at least one biomarker;~~

~~(d) identifying the subject as having the infectious disease or having an increased risk of developing the infectious disease if the level of the~~ at least one biomarker in a sample from a subject having the infectious disease at a level ~~is~~ greater than ~~the~~ a reference level of the at least one biomarker; wherein the mast cell modulator is selected from the group consisting of a leukotriene antagonist, a platelet activating factor inhibitor, a protease inhibitor, a VEGF inhibitor, a prostaglandin inhibitor, a heparin inhibitor, and a mast cell stabilizer; and wherein the infectious disease is a viral hemorrhagic fever.

~~(e) administering an infectious disease treatment regimen to the subject identified as having the infectious disease or having an increased risk of developing the infectious disease~~.

~~4. The method of claim 3, wherein the infectious disease treatment~~

~~regimen comprises a mast cell modulator.~~

~~5.~~ 2. The ~~method~~ use of claim 1 ~~3 or 4~~, wherein the reference level of the at least one biomarker is the level of the at least one biomarker in a control sample.

~~6.~~ 3. The ~~method~~ use of claim 2 ~~5~~, wherein the control sample is a sample from a healthy patient, a patient having the mild form of the infectious disease, or a patient having the severe form of the infectious disease.

~~7.~~ 4. The ~~method~~ use of claim 3 ~~6~~, wherein the control sample is a sample from a healthy patient.

~~8.~~ 5. The ~~method~~ use of claim 4 ~~7~~, wherein the reference level is about 0.18 ng/mL to about 0.5 ng/mL.

~~9.~~ 6. The ~~method~~ use of claim 3 ~~6~~, wherein the control sample is a sample from a patient having the mild form of the infectious disease.

~~10.~~ 7. The ~~method~~ use of claim 6 ~~9~~, wherein the reference level is about 0.8 ng/mL to about 6.0 ng/mL.

~~11.~~ 8. The ~~method~~ use of claim 3 ~~6~~, wherein the control sample is a sample from a patient having the severe form of the infectious disease.

~~12.~~ 9. The ~~method~~ use of claim 8 ~~11~~, wherein the reference level is greater than about 6.0 ng/mL.

~~13.~~ 10. The ~~method~~ use of claim 3 ~~6~~, wherein the level of the at least one biomarker ~~in the biological sample~~ is at least two times greater than the level of the at least one biomarker in the control sample, wherein the control sample is from a healthy patient.

~~14.~~ 11. Use of a mast cell modulator for the manufacture of a medicament for treating an infectious disease ~~A method of diagnosing and treating a subject having a mild or severe form of an infectious disease, wherein the infectious disease is~~ characterized by a pathology that involves hemorrhaging or pathological vascular leakage~~, in the subject, the method comprising:~~ wherein the mild form of the infectious disease is characterized by the presence of at least one biomarker in a sample from a subject having the infectious disease at a level greater a first reference level of the at least one biomarker and at a level less than a second reference level of the at least one biomarker; wherein the severe form of the infectious disease is characterized by the presence of the at least one biomarker at a level greater than the first reference level and the second reference level of the at least one biomarker; wherein the mast cell modulator is selected from the group consisting of a leukotriene antagonist, a platelet activating factor

inhibitor, a protease inhibitor, a VEGF inhibitor, a prostaglandin inhibitor, a heparin inhibitor, and a mast cell stabilizer; and wherein the infectious disease is a viral hemorrhagic fever.

~~(a) obtaining a biological sample from the subject;~~

~~(b) determining the level of at least one biomarker in the biological sample from the subject;~~

~~(c) comparing the level of the at least one biomarker in the biological sample to a first reference level of the at least one biomarker and a second reference level of the at least one biomarker;~~

~~(d) correlating the level of the at least one biomarker in the biological sample with the mild or severe form of the infectious disease in the subject, where if the level of the at least one biomarker is greater than the first reference level of the at least one biomarker and the second reference level of the at least one biomarker, thesubject is diagnosed as having the severe form of the infectious disease, and wherein if the level of the at least one biomarker is greater than the first reference level of the at least one biomarker but less than the second reference level of the at least one biomarker, the subject is diagnosed as having the mild form of the infectious disease; and~~

~~(e) administering an aggressive treatment regimen to the subject identified as having the severe form of the infectious disease or an infectious disease treatment regimen to the subject identified as having the mild form of the infectious disease.~~

~~15. The method of claim 14, wherein the infectious disease treatment regimen comprises a mast cell modulator.~~

~~16.~~ 12. The ~~method~~ use of claim 11 ~~13 or 14~~, wherein the first reference level of the at least one biomarker is the level of the at least one biomarker in a first control sample and the second reference level of the at least one biomarker is the level of the at least one biomarker in a second control sample.

~~17.~~ 13. The ~~method~~ use of claim 12 ~~16~~, wherein the first control sample is a sample from a healthy patient and the second control sample is a sample from a patient having the severe form of the infectious disease.

~~18.~~ 14. The ~~method~~ use of claim 13 ~~17~~, wherein the first reference level is about 0.18 ng/mL to about 0.5 ng/mL.

~~19.~~ 15. The ~~method~~ use of claim 13 or 14 ~~17 or 18~~, wherein the second reference level is greater than about 6.0 ng/mL.

~~20. The method of claim 14-19, wherein the aggressive treatment regimen comprises a mast cell modulator.~~

~~21.~~ 16. The ~~method~~ use of any one of claims 1-15 ~~3-20~~, wherein the at least one biomarker comprises a mast cell-derived product.

~~22.~~ 17. The ~~method~~ use of claim 16 ~~21~~, wherein the mast cell-derived product comprises at least one of chymase, tryptase, leukotrienes, prostaglandins, tumor necrosis factor (TNF), vascular endothelial growth factor (VEGF), histamine, serotonin, carboxypeptidase A, -hexosaminidase, metalloproteinases, endorphins, somatostatin (SRIF), kinins, urocortin, substance P, vasoactive intestinal peptide, granulocyte-macrophage colony-stimulating factor (GM-CSF), β-fibroblast growth factor, nerve growth factor, histones, chondroitin sulfate, heparin, hyaluronic acid, nitric oxide, angiotensin-1, heptatocyte growth factor, thrombin, stem cell factor, a2-macroglobulin, neurotensin, connective tissue-activating peptide III (CTAP-III), ApoA, ApoB, ApoE, porforin, granzymes, cathepsin, elastase, calreticulin, cathelicidins, serum trypsin inhibitors, chymotrypsin inhibitor, serpins, metabolic byproducts thereof, or combinations thereof.

~~23.~~ 18. The ~~method~~ use of claim 17 ~~22~~, wherein the mast cell-derived product comprises chymase.

~~24.~~ 19. The ~~method~~ use of ~~any one of claims 3-23~~ claim 1 or claim 11, wherein the ~~biological~~ sample ~~of a~~ from the subject is selected from the group consisting of tissue sample, bodily fluid, whole blood, plasma, serum, urine, bronchoalveolar lavage fluid, saliva, tissue biopsy, and a cell culture suspension or fraction thereof.

~~25.~~ 20. The ~~method~~ use of claim 19 ~~24~~, wherein the biological sample of a subject is blood plasma or blood serum.

~~26.~~ 21. The ~~method~~ use of claim 19 ~~24~~, wherein the tissue sample comprises a somatic cell.

~~27. The method of any one of claims 1, 2, 4 or 15, wherein the mast cell modulator stabilizes mast cell activity in the subject.~~

~~28.~~ 22. The ~~method~~ use of claim 1 or claim 11 ~~27~~, wherein the mast cell modulator comprises a mast cell stabilizer, wherein the mast cell stabilizer comprises a

calcium channel blocker, a cytochrome P450 inhibitor or a histamine antagonist.

~~29.~~ 23. The ~~method~~ use of claim 22 ~~28~~, wherein the mast cell modulator comprises at least one cromolyn, nedocromil, pemirolast, lodoxamide, tranilast, glucosamine, N-acetylglucosamine, FPL 52694, aloe vera, quercetin, chondroitin sulfate, dehydroleucodine, mast cell stabilizer TF002, rupatadine, loratadine, cetirizine, clemastime, fexofenadine, diphenhydramine, chlorpheniramine, azelastine, olopatadine, naphazoline, ketotifen, emedastine, and ebrotidine, combinations thereof and pharmaceutical compositions thereof.

~~30.~~ 24. The ~~method~~ use of claim 23 ~~29~~, wherein the mast cell modulator comprises cromolyn.

~~31. The method of any one of claims 1, 2, 4 or 15, wherein the mast cell modulator inhibits mast cell derived products in the subject~~.

~~32. The method of claim 31, wherein the mast cell modulator comprises a leukotriene antagonist, a platelet activating factor inhibitor, a protease inhibitor, a VEGF inhibitor, a prostaglandin inhibitor, or a heparin inhibitor~~.

~~33.~~ 25. The ~~method~~ use of ~~claim 32~~ claim 1 or claim 11, wherein the mast cell modulator comprises at least one of zafirlukast, montelukast, pranlukast, zileuton, SM-12502, rupatadine, PAP-targeting antibodies, tumor necrosis factor immunomodulators, infliximab, adalimumab, certolizumab pegol, golimumab, etanercept, xanthine derivatives, methylxanthines like theophylline oxtriphylline, dyphylline, aminophylline, bupropion, curcumin, catechins, aprotinin, serpin, a chymase inhibitor, chymostatin, leupeptin, APC-336, SUN-C8257, NK3201, R0566852, BCEAB, NK3201, TEI-E548, APC-2095, RWJ-355871, bevacizumab, ranibizumab, lapatinib, sunitinib sorafenib, axitinib, pazopanib, thiazolidinediones, benzoxazole, benzthiazole, benzinidzole, CP105,696, laropiprant, acetylsalicylic acid (ASA), indomethacin, sodium meclofenamate (FEN), phenylbutazone (PB), phloretin phosphates (PP), SC-19220, diethylcarbamazine citrate (DECC), protamine and polybrene, combinations thereof and pharmaceutical compositions thereof.

~~34.~~ 26. The ~~method~~ use of claim 25 ~~33~~, wherein the mast cell modulator comprises a chymase inhibitor or montelukast.

~~35. The method of any of the preceding claims, wherein the infectious disease is a viral hemorrhagic fever.~~

~~36.~~ 27. The ~~method~~ use of ~~claim 34~~ claim 1 or claim 11, wherein the viral

hemorrhagic fever is caused by a virus, wherein the virus is a member of at least one of the Arenaviridae, Filoviridae, Bunyaviridae, Flaviviridae, and Rhabdoviridae.

~~37.~~ 28. The ~~method~~ use of ~~claim 35~~ claim 27, wherein the viral hemorrhagic fever is caused by at least one of Dengue Virus, Ebola virus, Marburg virus, Ranta virus, West Nile virus, St. Louis, Kunjin, Lassa Virus, Crimean-Congo hemorrhagic fever virus, Rift Valley fever virus, yellow fever, Japanese encephalitis virus, Lujo virus, Junin virus, Argentine hemorrhagic fever, Brazilian hemorrhagic fever, Bolivian hemorrhagic fever, argentine hemorrhagic fever, Garissa virus, SFTS virus, Hantan virus, omsk hemorrhagic fever virus, kyasanur forest disease virus, Langat virus, alkhurma virus, and Henipaviruses.

~~38.~~ 29. The ~~method~~ use of claim 27 ~~36~~, wherein the viral infection is caused by Dengue virus.

~~39. The method of any one of claims 1, 2, 4 or 15, wherein the mast cell modulator is administered at the onset of the infectious disease.~~

~~40. The method of any one of claims 1, 2, 4 or 15, wherein the mast cell modulator is administered after the onset of the infectious disease.~~

~~41. The method of any one of claims 1, 2, 4 or 15, wherein the mast cell modulator is administered prior to the onset of the infectious disease.~~

~~42. The method of any one of claims 1, 2, 4 or 15, wherein the mast cell modulator is administered prior to vascular leakage.~~

~~43. The method of any one of claims 1, 2, 4 or 15, wherein the mast cell modulator is administered after to vascular leakage.~~