COMPOSITIONS AND METHODS FOR TREATING LUNG DISEASE AND INJURY

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 61/448,723, filed March 3, 2011, entitled "Combination Therapy for Treating Lung Disease And Injury" and which is incorporated herein by reference in its entirety and for all purposes.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing, which is entitled 228-PCT1_ST25.txt, created on February 6, 2012 and 2,280 kb in size, and is hereby incorporated by reference in its entirety.

[0003] Throughout this application various patents and publications are cited. The disclosures of these documents in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains.

FIELD OF THE INVENTION

[0004] Compositions, methods and kits for treating lung disease and injury are provided herein.

SUMMARY ~~OF THE INVENTION~~

[0005] Compositions, methods and kits for treating lung diseases are provided herein. In certain ~~aspects and~~ embodiments, provided are compositions and methods for therapy for treating lung disorders or injury in a mammal, including treatment of acute respiratory distress syndrome (ARDS), acute lung injury, pulmonary fibrosis (idiopathic), bleomycin induced pulmonary fibrosis, mechanical ventilator induced lung injury, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, lung transplantation-induced acute graft dysfunction and bronchiolitis obliterans after lung transplantation. In certain ~~aspects and~~ embodiments, provided are compositions and methods for combination therapy for treating or preventing inflammation and/or graft rejection associated with organ transplantation, in particular lung transplantation, including treatment, prevention or

attenuation of progression of ~~primary~~ graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, pulmonary reimplantation response, bronchiolitis obliterans after lung transplantation and/or primary graft dysfunction (PGD) after organ transplantation, in particular in lung transplantation. In certain ~~aspects and~~ embodiments, provided are compositions and methods for combination therapy for treating lung disorders or injury in a mammal. The compositions and methods involve inhibiting the gene Toll-like receptor 2 (TLR2) or the genes Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4).

[0006] In various ~~aspects and~~ embodiments, compositions, methods and kits provided herein may target, decrease, down-regulate or inhibit the expression/activity/function of the gene Toll-like receptor 2 (TLR2). In various ~~aspects and~~ embodiments, compositions, methods and kits provided herein may target, decrease, down-regulate or inhibit the expression/activity/function of the genes: (i) Toll-like receptor 2 (TLR2) and (ii) Toll-like receptor 4 (TLR4).

[0007] In one embodiment~~aspect~~, provided is a method for treating a lung disorder, disease or injury in a mammal in need thereof. The method may include administering to the mammal at least one therapeutic agent selected from a TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof, in an amount effective to treat the mammal.

[0007a] In one aspect, there is provided the use of at least one TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof, and at least one TLR4 inhibitor or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for treating a lung disorder, a lung disease or a lung injury; wherein the TLR2 inhibitor comprises a nucleic acid molecule targeting a TLR2 gene and the TLR4 inhibitor comprises a nucleic acid molecule targeting a TLR4 gene.

[0008] In one embodiment~~another aspect~~, provided is a method for treating a lung disorder, disease or injury in a mammal in need thereof. The method may include administering to the mammal at least two therapeutic agents selected from: (i) a TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof, and (ii) a TLR4 inhibitor or a pharmaceutically acceptable salt or prodrug thereof; in an amount effective to treat the mammal.

[0009] The methods may include preventing, treating, ameliorating, and/or slowing the progression of lung disorders or injury, such as, without being limited to, ARDS, acute lung injury, pulmonary fibrosis (idiopathic), bleomycin induced pulmonary fibrosis, mechanical ventilator induced lung injury, COPD and disease, disorder or injury associated with lung transplantation in a subject. The method may involve treating, ameliorating, and/or slowing the progression of the aforementioned diseases or conditions or associated symptoms or complications thereof by administering to said subject a therapeutically effective amount of a therapeutic agent directed to the gene TLR2. The method may involve treating, ameliorating, and/or slowing the progression of the aforementioned diseases or conditions or associated

for down-regulating the gene TLR2 and at least one therapeutic agent is for down-regulating the gene TLR4; and the therapeutic agents are selected from: (i) a TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof, and (ii) a TLR4 inhibitor or a pharmaceutically acceptable salt or prodrug thereof; or

[0014] C. Administration of a pharmaceutical composition comprising a combination of at least two therapeutic agents, wherein at least one therapeutic agent is for down-regulating the gene TLR2 and at least one therapeutic agent is for down-regulating the gene TLR4; and the therapeutic agents are selected from: (i) a TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof, and (ii) a TLR4 inhibitor or a pharmaceutically acceptable salt or prodrug thereof; and a pharmaceutically acceptable carrier; or

[0015] D. Administration of a pharmaceutical composition comprising a therapeutic agent which is capable of down-regulating the genes TLR2 and TLR4 and/or the gene products of the genes TLR2 and TLR4. Non-limiting examples of such single agents are tandem and multi-armed RNAi molecules disclosed in PCT Patent Publication No. WO 2007/091269.

[0016] In one embodiment~~aspect~~, provided is a medicament that includes a therapeutic agent which target, decrease, down-regulate or inhibit the expression/activity/function of the gene TLR2, or a pharmaceutically acceptable salt or prodrug thereof. Therapeutic agents useful in the combination as provided herein include, but are not limited to, small organic molecule chemical compounds; proteins, antibodies or fragments thereof, peptides, peptidomimetics and nucleic acid molecules.

[0017] In another embodiment~~aspect~~, provided is a medicament that includes at least two therapeutic agents which target, decrease, down-regulate or inhibit the expression/activity/function of the genes: (i) TLR2 and (ii) TLR4, wherein at least one therapeutic agent down-regulates the gene TLR2 and at least one therapeutic agent down-regulates the gene TLR4; and the therapeutic agents are selected from: (i) a TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof, and (ii) a TLR4 inhibitor or a pharmaceutically acceptable salt or prodrug thereof. Therapeutic agents useful in the combination as provided herein include, but are not limited to, small organic molecule; proteins, antibodies or fragments thereof, peptides, peptidomimetics and nucleic acid molecules.

[0018] In some embodiments the therapeutic agent comprises a nucleic acid molecule. In some embodiments each nucleic acid molecule is independently selected from the group

the second therapeutic agent and, optionally, instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

[0021] In one embodiment~~a first aspect~~, provided is a method of preventing or reducing the symptoms of primary graft dysfunction (PGD) in a recipient of a lung transplant, comprising administering to the recipient a therapeutically-effective amount of at least one TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof, and a therapeutically-effective amount of at least one TLR4 inhibitor or a pharmaceutically acceptable salt or prodrug thereof, thereby preventing or reducing the symptoms of PGD in the recipient. In various embodiments the symptoms of PGD include inflammation, acute graft rejection, graft rejection, ischemia-reperfusion injury, reperfusion injury, impaired pulmonary function, bronchiolitis obliterans, impaired blood oxygenation, increased inflammatory cytokine production, intra-graft and intra-airway accumulation of granulocytes, pulmonary edema and hypoxemia.

[0022] In some embodiments, the recipient of the lung transplant is a human that is at risk of developing or is being treated for primary graft dysfunction (PGD). In some embodiments the method as provided herein may, for example, be use for preventing or reducing the symptoms of cold ischemia-associated PGD. Alternatively, the method may, for example, be for preventing or reducing the symptoms of warm ischemia-associated PGD.

[0023] In various embodiments, the administration of the at least one TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof, and the at least one TLR4 inhibitor or a pharmaceutically acceptable salt or prodrug thereof results in one or more of the following: reduced pulmonary edema, increased blood oxygenation, preserved blood oxygenation, improved pulmonary function, preserved pulmonary function in the recipient of a lung transplant and improved pulmonary function of the transplanted lung.

[0024] In various embodiments, the at least one TLR2 inhibitor and the at least one TLR4 inhibitor are administered to the recipient of a lung transplant prior to, during or following the lung transplantation.

[0025] In some embodiments, the at least one TLR2 inhibitor and the at least one TLR4 inhibitor are co-administered to the recipient in the same formulation. Alternatively, the at least one TLR2 inhibitor and the at least one TLR4 inhibitor are co-administered to the recipient in different formulations.

wherein N1 is a moiety selected from the group consisting of uridine, modified uridine, ribothymidine, modified ribothymidine, deoxyribothymidine, modified deoxyribothymidine, riboadenine, deoxyriboadenine and modified deoxyriboadenine,

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of N2- (N')y; and

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides or unconventional moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present.

[0040] In various embodiments of structure (A2), the mRNA polynucleotide sequence of TLR2 is set forth in SEQ ID NO:1 and the mRNA polynucleotide sequence of TLR4 is set forth in any one of SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4.

[0041] In some preferred embodiments of structure (A2), x =y=18.

[0042] In some embodiments of structure (A2), the sequence of (N)x comprises an antisense strand oligonucleotide selected from the group consisting of oligonucleotides having SEQ ID NOs: 4153 – 5252, 5546 – 5838, 10319 – 12032, and 12085 – 12136 and the sequence of (N')y comprises a sense strand oligonucleotide selected from the group consisting of oligonucleotides having SEQ ID NOs: 3053 – 4152, 5253 – 5545, 8605 – 10318, and 12033 – 12084.

[0043] In one embodiment~~a second~~ aspect, provided is a method for treating a lung disorder, disease or injury in a patient in need thereof comprising administering to the patient a therapeutically-effective combination of at least one TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof, and at least one TLR4 inhibitor or a pharmaceutically acceptable salt or prodrug thereof, thereby treating the lung disorder, disease or injury in the patient. In various embodiments, the lung disorder, disease or injury is selected from acute respiratory distress syndrome (ARDS), acute lung injury, pulmonary fibrosis (idiopathic), bleomycin induced pulmonary fibrosis, mechanical ventilator induced lung injury, chronic obstructive pulmonary disease (COPD), chronic bronchitis, a disorder associated with lung transplantation and emphysema. In some embodiments, the lung disorder, disease or injury is a disorder associated with lung transplantation. In various embodiments, the lung disorder associated with lung transplantation is selected from the group consisting of inflammation, graft rejection, primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, acute graft dysfunction, pulmonary reimplantation

wherein N1 is a moiety selected from the group consisting of uridine, modified uridine, ribothymidine, modified ribothymidine, deoxyribothymidine, modified deoxyribothymidine, riboadenine, deoxyriboadenine and modified deoxyriboadenine,

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of N2- (N')y; and

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides or unconventional moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present.

[0057] In various embodiments of structure (A2), the mRNA polynucleotide sequence of TLR2 is set forth in SEQ ID NO:1 and the mRNA polynucleotide sequence of TLR4 is set forth in any one of SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4.

[0058] In some preferred embodiments of structure (A2), x =y=18.

[0059] In some embodiments of structure (A2), the sequence of (N)x comprises an antisense oligonucleotide selected from the group consisting of oligonucleotides having SEQ ID NOs: 4153 – 5252, 5546 – 5838, 10319 – 12032, and 12085 – 12136 and the sequence of (N')y comprises a sense oligonucleotide selected from the group consisting of oligonucleotides having SEQ ID NOs: 3053 – 4152, 5253 – 5545, 8605 – 10318, and 12033 – 12084.

[0060] In another embodiment~~aspect~~, provided is a composition comprising at least one TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof and at least one TLR4 inhibitor or a pharmaceutically acceptable salt or prodrug thereof; and a pharmaceutically acceptable carrier. In various embodiments, each inhibitor is independently selected from the group consisting of a small organic molecule; a protein, an antibody or fragments thereof, a peptide, a peptidomimetic and a nucleic acid molecule. In some embodiments, each inhibitor is independently selected from the group consisting of a small organic molecule; a protein; an antibody or fragment thereof; and a nucleic acid molecule.

[0061] In some embodiments of the provided composition, each inhibitor comprises a nucleic acid molecule. In some embodiments a first nucleic acid molecule is a double-stranded oligonucleotide that binds a nucleotide sequence encoding a TLR2 gene and a second nucleic acid molecule is a double-stranded oligonucleotide that binds a nucleotide sequence encoding a TLR4 gene. In some embodiments of the composition the nucleic acid molecules are linked in tandem or annealed in RNAistar formation.

wherein z'' may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of N2- (N')y; and

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides or unconventional moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present.

[0069] In various embodiments of the provided composition, in structure (A2), the mRNA polynucleotide sequence of TLR2 is set forth in SEQ ID NO:1 and the mRNA polynucleotide sequence of TLR4 is set forth in any one of SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4.

[0070] In some preferred embodiments of the provided composition, in structure (A2), x=y=18.

[0071] In some embodiments, the provided composition is formulated for administering to the recipient once. In other embodiments, the provided composition is formulated for administering to the recipient at least once-a-day. In yet other embodiments, the provided composition is formulated for multiple administrations to the recipient.

[0072] In another embodiment~~aspect~~, provided is a kit comprising at least two therapeutic agents, wherein at least one agent comprises a TLR2 inhibitor and a second agent comprises a TLR4 inhibitor; optionally with instructions for use.

[0073] In some embodiments of the provided kit, each therapeutic agent is independently selected from the group consisting of a small organic molecule, a protein, an antibody or fragment thereof, a peptide, a peptidomimetic and nucleic acid molecule. In some embodiments of the kit, at least one therapeutic agent comprises a nucleic acid molecule. In other embodiments of the provided kit, each therapeutic agent comprises a nucleic acid molecule.

[0074] In some embodiments of the provided kit, a first nucleic acid molecule is a double-stranded oligonucleotide that binds a nucleotide sequence encoding a TLR2 gene and a second nucleic acid molecule is a double-stranded oligonucleotide that binds a nucleotide sequence encoding a TLR4 gene. In some embodiments of the, the double stranded oligonucleotides are linked one to the other in tandem or annealed in RNAistar formation.

[0075] In some embodiments of the provided kit, the first double-stranded oligonucleotide comprises:

wherein each of (N)x and (N')y is an oligonucleotide in which each consecutive N or N' is joined to the adjacent N or N' by a covalent bond;

wherein each of x and y is independently an integer between 17 and 39;

wherein the sequence of (N')y is complementary to the sequence of (N)x and (N)x is complementary to a consecutive sequence in an mRNA selected from an mRNA encoding TLR2 and an mRNA encoding TLR4;

wherein N1 is covalently bound to (N)x and is mismatched to an mRNA selected from an mRNA encoding TLR2 and an mRNA encoding TLR4;

wherein N1 is a moiety selected from the group consisting of uridine, modified uridine, ribothymidine, modified ribothymidine, deoxyribothymidine, modified deoxyribothymidine, riboadenine, deoxyriboadenine and modified deoxyriboadenine,

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of N2- (N')y; and

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides or unconventional moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present.

[0083] In various embodiments of the provided kit, in structure (A2), the mRNA polynucleotide sequence of TLR2 is set forth in SEQ ID NO:1 and the mRNA polynucleotide sequence of TLR4 is set forth in any one of SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4.

[0084] In some preferred embodiments of the provided kit, in structure (A2), x =y=18.

[0085] In another embodiment~~aspect~~, provided is a package comprising A) at least two separate dosage units selected from (i) at least one dosage unit comprising a TLR2 inhibitor and (ii) at least one dosage unit comprising a TLR4 inhibitor; and optionally B) a package insert comprising instructions for use of the dosage units.

[0086] In various embodiments of the provided package, the TLR2 inhibitor is a double-stranded oligonucleotide that binds a nucleotide sequence encoding a TLR2 gene and the TLR4 inhibitor is a double-stranded oligonucleotide that binds a nucleotide sequence encoding a TLR4 gene.

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of N2- (N')y; and

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides or unconventional moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present.

[0092] In various embodiments of the provided kit or the provided package, the instructions or package insert indicates that the therapeutic agents or dosage units are suitable for use in treating a patient suffering from a lung disease, injury or disorder selected from the group consisting of acute respiratory distress syndrome (ARDS), acute lung injury, pulmonary fibrosis (idiopathic), bleomycin induced pulmonary fibrosis, mechanical ventilation induced lung injury, chronic obstructive pulmonary disease (COPD), chronic bronchitis, a disorder associated with lung transplantation and emphysema. In some embodiments of the provided kit or the provided package, the instructions or package insert indicate that the therapeutic agents or dosage units are suitable for use in treating a patient suffering from a disorder associated with lung transplantation.

[0093] In some embodiments of the provided kit or the provided package, the lung disorder associated with lung transplantation is selected from the group consisting of inflammation, graft rejection, primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, acute graft dysfunction, pulmonary reimplantation response, bronchiolitis obliterans and primary graft dysfunction (PGD).

[0093a] In one aspect, there is provided the use of at least one TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for preventing or reducing the symptoms of primary graft dysfunction (PGD) in a recipient of lung transplant; wherein the TLR2 inhibitor comprises a nucleic acid molecule targeting a TLR2 gene.

In another embodiment~~aspect~~, provided is a method of preventing or reducing the symptoms of primary graft dysfunction (PGD) in a recipient of a lung transplant, comprising administering to the recipient a therapeutically-effective amount of at least one TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof, thereby preventing or reducing the symptoms of PGD in the recipient.

[0094] In some embodiments of the provided method, the recipient of a lung transplant is a human that is being treated for primary graft dysfunction (PGD). In some embodiments, the method is for preventing or reducing the symptoms of cold ischemia-associated PGD. In other embodiments the method is for preventing or reducing the symptoms of warm ischemia-associated PGD. In various embodiments of the provided method, the symptoms are selected from the group consisting of inflammation, acute graft rejection, graft rejection, ischemia-reperfusion injury, reperfusion injury, impaired pulmonary function, bronchiolitis

wherein N1 is a moiety selected from the group consisting of uridine, modified uridine, ribothymidine, modified ribothymidine, deoxyribothymidine, modified deoxyribothymidine, riboadenine, deoxyriboadenine and modified deoxyriboadenine,

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of N2- (N')y; and

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides or unconventional moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present.

[00109] In various embodiments of the provided method, in structure (A2), the mRNA polynucleotide sequence of TLR2 is set forth in SEQ ID NO:1

[00110] In some preferred embodiments of the provided method, in structure (A2), x=y=18.

[00111] In various embodiments of the provided method, in structure (A2), the sequence of (N)x is selected from anyone of SEQ ID NOs: 4153 – 5252 and 5546 – 5838 and the sequence of (N')y is selected from anyone of SEQ ID NOs: 3053 – 4152 and 5253 – 5545.

[00112] In various embodiments of the provided method, administration of the at least one double-stranded oligonucleotide that binds a nucleotide sequence encoding a TLR2 gene results in down-regulation of TLR2 expression.

[00113] In another embodiment~~aspect~~ provided is a kit or package comprising at least one dosage unit comprising a TLR2 inhibitor; optionally with instructions for use, wherein the instructions indicate that the dosage unit is suitable for use in treating a patient suffering from a lung disease, injury or disorder selected from the group consisting of respiratory distress syndrome (ARDS), acute lung injury, pulmonary fibrosis (idiopathic), bleomycin induced pulmonary fibrosis, mechanical ventilator induced lung injury, chronic obstructive pulmonary disease (COPD), chronic bronchitis, a disorder associated with lung transplantation and emphysema.

[00114] In some embodiments the provided kit or package are for use in treating a patient suffering from a disorder associated with lung transplantation.

[00120] In some embodiments, the provided kit or package is for use in treating a patient suffering from a disorder associated with lung transplantation. In various embodiments the disorder associated with lung transplantation is selected from the group consisting of inflammation, graft rejection, primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, acute graft dysfunction, pulmonary reimplantation response, bronchiolitis obliterans and primary graft dysfunction (PGD).

[00121] In another embodiment~~aspect~~ provided is a use of a composition comprising at least one TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof and at least one TLR4 inhibitor or a pharmaceutically acceptable salt or prodrug thereof; and a pharmaceutically acceptable carrier, for the preparation of a medicament for treating or preventing or reducing the symptoms of primary graft dysfunction (PGD) in a recipient of a lung transplant.

[00122] In another embodiment~~aspect~~ provided is a use of a composition comprising at least one TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof and at least one TLR4 inhibitor or a pharmaceutically acceptable salt or prodrug thereof; and a pharmaceutically acceptable carrier, for treating or preventing or reducing the symptoms of primary graft dysfunction (PGD) in a recipient of a lung transplant.

[00123] In various embodiments of the provided use, the recipient of a lung transplant is a human that is being treated for primary graft dysfunction (PGD). In some embodiments, the use is for preventing or reducing the symptoms of cold ischemia-associated PGD. In other embodiments, the use is for preventing or reducing the symptoms of warm ischemia-associated PGD.

[00124] In various embodiments of the use, the symptoms are selected from the group consisting of inflammation, acute graft rejection, graft rejection, ischemia-reperfusion injury, reperfusion injury, impaired pulmonary function, bronchiolitis obliterans, impaired blood oxygenation, increased inflammatory cytokine production, intra-graft and intra-airway accumulation of granulocytes, pulmonary edema and hypoxemia.

[00125] In another embodiment~~aspect~~ provided is a use of a composition comprising at least one TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof and at least one TLR4 inhibitor or a pharmaceutically acceptable salt or prodrug thereof; and a pharmaceutically acceptable carrier, for the preparation of a medicament for treating or

preventing a lung disease, disorder or injury selected from acute respiratory distress syndrome (ARDS), acute lung injury, pulmonary fibrosis (idiopathic), bleomycin induced pulmonary fibrosis, mechanical ventilator induced lung injury, chronic obstructive pulmonary disease (COPD), chronic bronchitis, and emphysema.

[00126] In another embodiment~~aspect~~ provided is a use of a composition comprising at least one TLR2 inhibitor or a pharmaceutically acceptable salt or prodrug thereof and at least one TLR4 inhibitor or a pharmaceutically acceptable salt or prodrug thereof; and a pharmaceutically acceptable carrier, for treating or preventing a lung disease, disorder or injury selected from acute respiratory distress syndrome (ARDS), acute lung injury, pulmonary fibrosis (idiopathic), bleomycin induced pulmonary fibrosis, mechanical ventilator induced lung injury, chronic obstructive pulmonary disease (COPD), chronic bronchitis, and emphysema.

BRIEF DESCRIPTION OF THE FIGURES

[00127] Fig. 1 shows that combined administration of a double-stranded RNA (dsRNA) specific for TLR2, at a dose of 25 μg/mouse and a double-stranded RNA (dsRNA) specific for TLR4, at a dose of 25 μg/mouse efficiently reduced post-transplantation lung edema and hemorrhages in the transplanted mouse lung. Photographs of the recipient's lung were taken at 24 hours after orthotopic lung transplantation. Left: dsRNA combination (combination of dsRNA specific for TLR2 and dsRNA specific for TLR4, each at 25 μg/mouse (identified in the figure as "siRNA cocktail, 25μg")) was administered at the end of lung transplantation surgery (immediately after anastomosis opening), by intratracheal instillation to the recipient. Right: vehicle. Arrows: prominent hemorrhages.

[00128] Fig. 2 shows that dual target dsRNA combination, targeting TLR2 and TLR4 genes z93rd and 4th columns), restored pulmonary function in the recipient's lung. Oxygenation of the arterial blood in mice was measured at 24 h after lung transplantation and dsRNA administration. Administration of a single dsRNA targeting TLR2 (5th and 6th columns), was also significantly effective in preserving pulmonary function. While administration of a single dsRNA targeting TLR4 (8th and 9th columns), was not effective in preserving pulmonary function. Control groups were composed of (i) mice that were administered with vehicle (general negative control, 2nd column), and (ii) mice that