[00136] Together, these data suggest that inhibition of MK2 may provide therapeutic benefits to patients with fibrotic disorders or conditions, for example, idiopathic pulmonary fibrosis (IPF), acute lung injury (ALI), and transplant rejection. In this respect, the described invention offers an approach to intervene in the process of inflammation and fibrosis using cell-penetrating, peptide base inhibitors of MK2.

SUMMARY OF THE INVENTION

[00137] According to one aspect, the disclosure provides use of a composition comprising a. a first amount of an anti-CD44 antibody; and b. a second amount of an MK2 inhibitor (MK2i) component containing a therapeutic amount of an MK2 inhibitor (MK2i) polypeptide of amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or at least one peptide functionally equivalent to YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) selected from a polypeptide of amino acid sequence FAKLAARLYRKALARQLGVAA (SEQ ID NO: 3), a polypeptide of amino acid sequence KAFAKLAARLYRKALARQLGVAA (SEQ ID NO: 4), a polypeptide of amino acid sequence YARAAARQARAKALARQLAVA (SEQ ID NO: 5), a polypeptide of amino acid sequence YARAAARQARAKALARQLGVA (SEQ ID NO: 6), and a polypeptide of amino acid sequence HRRIKAWLKKIKALARQLGVAA (SEQ ID NO: 7), and a pharmaceutically acceptable carrier; in the manufacture of a medicament, for attenuating lung allograft dysfunction after lung transplant, wherein the first amount and the second amount together comprise a therapeutic amount effective to reduce at least one pathobiology of the lung allograft dysfunction; wherein the therapeutic amount has a synergistic effect compared to an effect of the first amount alone or an effect of the second amount alone; and further wherein additional immunosuppressive medications are absent from the composition. In an embodiment, the disclosure relates to a method to attenuate lung allograft dysfunction after lung transplant comprising administering a composition comprising an antibody component containing a therapeutic amount of an anti-CD44 antibody; and an MK2 inhibitor (MK2i) component containing a therapeutic amount of an MK2 inhibitor (MK2i) polypeptide of amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or at least one peptide functionally equivalent to the therapeutic domain thereof selected from a polypeptide of amino acid sequence KALARQLAVA (SEQ ID NO: 8), a polypeptide of amino acid sequence KALARQLGVA (SEQ ID NO: 9) and a polypeptide of amino acid sequence

KALARQLGVAA (SEQ ID NO: 1), or a functional equivalent thereof, and a pharmaceutically acceptable carrier; wherein the composition is effective to synergistically reduce at least one pathobiology of the lung allograft dysfunction. According to one embodiment, the lung allograft dysfunction is characterized by an aberrant activity of Mitogen-Activated Protein Kinase-Activated Protein Kinase 2 (MK2) in the tissue compared to the activity of Mitogen-Activated Protein Kinase-Activated Protein Kinase 2 (MK2) in the tissue of a normal healthy control subject. According to another embodiment, the lung allograft dysfunction is a primary graft dysfunction. According to another embodiment, the lung allograft dysfunction is a chronic lung allograft dysfunction. According to another embodiment, the administering of the anti-CD44 antibody component of the composition is systemically. According to another embodiment, the administering of the MK2i component is systemically or by inhalation. According to another embodiment, the allograft dysfunction is characterized by inflammation. According to another embodiment, the composition is effective (i) to modulate at least one of TGFβ, CCL2, hyaluronic acid, and MMP9; (ii) to decrease plasma level of TNFα, IL6 or a combination thereof; (iii) to attenuate expression of α-smooth muscle actin; (iiv) to prevent TGFβ-induced myofibroblast activation, (v) to inhibit fibroblast invasion, or a combination thereof when compared to a control. According to another embodiment, the functional equivalent of the polypeptide

YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence FAKLAARLYRKALARQLGVAA (SEQ ID NO: 3). According to another embodiment, the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence KAFAKLAARLYRKALARQLGVAA (SEQ ID NO: 4). According to another embodiment, the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence YARAAARQARAKALARQLAVA (SEQ ID NO: 5). According to another embodiment, the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence YARAAARQARAKALARQLGVA (SEQ ID NO: 6). According to another embodiment, the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence HRRIKAWLKKIKALARQLGVAA (SEQ ID NO: 7). According to another embodiment, the carrier is selected from the group consisting of a controlled release carrier, a delayed release carrier, a sustained release carrier, and a long-term release carrier. According to another embodiment, the MK2i component of the pharmaceutical composition is in a form of a dry powder. According to another embodiment, the dry powder comprises microparticles with Mass Median Aerodynamic Diameter (MMAD) of 1 to 5 microns. According to another embodiment, the administering of the therapeutic amount of the MK2i component of the pharmaceutical composition is via an inhalation device. According to another embodiment, the inhalation device is a nebulizer. According to another embodiment, the inhalation device is a metered-dose inhaler (MDI). According to another embodiment, the inhalation device is a dry powder inhaler (DPI). According to another embodiment, the inhalation device is a dry powder nebulizer.

[00138] According to another aspect, the disclosure provides use a pharmaceutical composition comprising a. a first amount of an anti-CD44 antibody; and b. a second amount of an MK2 inhibitor (MK2i) component containing a therapeutic amount of an MK2 inhibitor (MK2i) polypeptide of amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or at least one peptide functionally equivalent to YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) selected from a polypeptide of amino acid sequence FAKLAARLYRKALARQLGVAA (SEQ ID NO: 3), a polypeptide of amino acid sequence KAFAKLAARLYRKALARQLGVAA (SEQ ID NO: 4), a

polypeptide of amino acid sequence YARAAARQARAKALARQLAVA (SEQ ID NO: 5), a polypeptide of amino acid sequence YARAAARQARAKALARQLGVA (SEQ ID NO: 6), and a polypeptide of amino acid sequence HRRIKAWLKKIKALARQLGVAA (SEQ ID NO: 7), and a pharmaceutically acceptable carrier; in the manufacture of a medicament, for treating a severe pulmonary fibrosis characterized by aberrant fibroblast proliferation and extracellular matrix deposition in a tissue of a subject, wherein the first amount and the second amount together comprise a therapeutic amount effective to reduce the fibroblast proliferation and extracellular matrix deposition in the tissue of the subject; wherein the therapeutic amount has a synergistic effect compared to an effect of the first amount alone or an effect of the second amount alone; and further wherein additional immunosuppressive medications are absent from the composition. In an embodiment, the disclosure relates to a method for treating a severe pulmonary fibrosis characterized by aberrant fibroblast proliferation and extracellular matrix deposition in a tissue of a subject comprising: administering to the subject a pharmaceutical composition comprising an antibody component containing a therapeutic amount of an anti-CD44 antibody; an MK2 inhibitor component containing a therapeutic amount of an MK2 inhibitor (MK2i) polypeptide of amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or at least one peptide functionally equivalent to the therapeutic domain thereof selected from a polypeptide of amino acid sequence KALARQLAVA (SEQ ID NO: 8), a polypeptide of amino acid sequence KALARQLGVA

CLAIMS

What is claimed is:

1. Use of a composition comprising

    a. a first amount of an anti-CD44 antibody; and

    b. a second amount of an MK2 inhibitor (MK2i) component containing a therapeutic amount of an MK2 inhibitor (MK2i) polypeptide of amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or at least one peptide functionally equivalent to YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) selected from a polypeptide of amino acid sequence FAKLAARLYRKALARQLGVAA (SEQ ID NO: 3), a polypeptide of amino acid sequence KAFAKLAARLYRKALARQLGVAA (SEQ ID NO: 4) , a polypeptide of amino acid sequence YARAAARQARAKALARQLAVA (SEQ ID NO: 5), a polypeptide of amino acid sequence YARAAARQARAKALARQLGVA (SEQ ID NO: 6), and a polypeptide of amino acid sequence HRRIKAWLKKIKALARQLGVAA (SEQ ID NO: 7), and a pharmaceutically acceptable carrier;

    in the manufacture of a medicament, for attenuating lung allograft dysfunction after lung transplant, wherein the first amount and the second amount together comprise a therapeutic amount effective to reduce at least one pathobiology of the lung allograft dysfunction;

    wherein the therapeutic amount has a synergistic effect compared to an effect of the first amount alone or an effect of the second amount alone; and

    further wherein additional immunosuppressive medications are absent from the composition.

2. The use according to claim 1, wherein the lung allograft dysfunction is characterized by an aberrant activity of Mitogen-Activated Protein Kinase-Activated Protein Kinase 2 (MK2) in the tissue as compared to the activity of Mitogen-Activated Protein Kinase-Activated Protein Kinase 2 (MK2) in the tissue of a normal healthy control subject.

3. The use according to claim 1, wherein the lung allograft dysfunction is a primary graft dysfunction.
4. The use according to claim 1, wherein the lung allograft dysfunction is a chronic lung allograft dysfunction.
5. The use according to claim 1, wherein the anti-CD44 antibody component of the composition is to be administered systemically.
6. The use according to claim 1, wherein the MK2i component is to be administered systemically or by inhalation.
7. The use according to claim 1, wherein the allograft dysfunction is characterized by inflammation.
8. The use according to claim 1, wherein the composition is effective (i) to modulate at least one of TGFβ, CCL2, hyaluronic acid, and MMP9; (ii) to decrease plasma level of TNFα, IL6 or a combination thereof; (iii) to attenuate expression of α-smooth muscle actin; (iv) to prevent TGFβ-induced myofibroblast activation, (v) to inhibit fibroblast invasion, or a combination thereof when compared to a control.

9. The use according to claim 1, wherein the carrier is selected from the group consisting of a controlled release carrier, a delayed release carrier, a sustained release carrier, and a long-term release carrier.

10. The use according to claim 1, wherein the MK2i component of the pharmaceutical composition is in a form of a dry powder.

11. The use according to claim 10, wherein the dry powder comprises microparticles with Mass Median Aerodynamic Diameter (MMAD) of 1 to 5 microns.

12. The use according to claim 1, wherein the therapeutic amount of the MK2i component of the pharmaceutical composition is to be administered via an inhalation device.

13. The use according to claim 12, wherein the inhalation device is a nebulizer.

14. The use according to claim 12, wherein the inhalation device is a metered-dose inhaler (MDI).

15. The use according to claim 12, wherein the inhalation device is a dry powder inhaler (DPI).

16. The use according to claim 12, wherein the inhalation device is a dry powder nebulizer.

17. Use of a pharmaceutical composition comprising

a. a first amount of an anti-CD44 antibody; and

b. A second amount of an MK2 inhibitor (MK2i) component containing a therapeutic amount of an MK2 inhibitor (MK2i) polypeptide of amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or at least one peptide functionally equivalent to YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) selected from a polypeptide of amino acid sequence FAKLAARLYRKALARQLGVAA (SEQ ID NO: 3), a polypeptide of amino acid sequence KAFAKLAARLYRKALARQLGVAA (SEQ ID NO: 4), a polypeptide of amino acid sequence YARAAARQARAKALARQLAVA (SEQ ID NO: 5), a polypeptide of amino acid sequence YARAAARQARAKALARQLGVA (SEQ ID NO: 6), and a polypeptide of amino acid sequence HRRIKAWLKKIKALARQLGVAA (SEQ ID NO: 7), and a pharmaceutically acceptable carrier;

in the manufacture of a medicament, for treating a severe pulmonary fibrosis characterized by aberrant fibroblast proliferation and extracellular matrix deposition in a tissue of a subject, wherein the first amount and the second amount together comprise a therapeutic amount effective to reduce the fibroblast proliferation and extracellular matrix deposition in the tissue of the subject; wherein the therapeutic amount has a synergistic effect compared to an effect of the first amount alone or an effect of the second amount alone; and

further wherein additional immunosuppressive medications are absent from the composition.

18. The use according to claim 17, wherein the severe pulmonary fibrosis is idiopathic pulmonary fibrosis.

19. The use according to claim 17, wherein the severe pulmonary fibrosis is caused by administration of bleomycin.

20. The use according to claim 17, wherein the severe pulmonary fibrosis is further characterized by an inflammation in the tissue.

21. The use according to claim 17, wherein the inflammation is mediated by at least one cytokine selected from the group consisting of Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and Interleukin-1β (IL-1β).

22. The use according to claim 17, wherein the aberrant fibroblast proliferation and extracellular matrix deposition in the tissue is characterized by an aberrant activity of Mitogen-Activated Protein Kinase-Activated Protein Kinase 2 (MK2) in the tissue compared to the activity of Mitogen-Activated Protein Kinase-Activated Protein Kinase 2 (MK2) in the tissue of a normal healthy control subject.

23. The use according to claim 17, wherein the severe pulmonary fibrosis is characterized by at least one pathology selected from the group consisting of an aberrant deposition of an extracellular matrix protein in a pulmonary interstitium, an aberrant promotion of fibroblast proliferation in the lung, an aberrant induction of myofibroblast differentiation, and an aberrant promotion of attachment of myofibroblasts to an extracellular matrix, compared to a normal healthy control subject.

24. The use according to claim 17, wherein the anti-CD44 antibody component of the composition is to be administered systemically.

25. The use according to claim 17, wherein the MK2i component is to be administered systemically or by inhalation.

26. The use according to claim 17, wherein the carrier is selected from the group consisting of a controlled release carrier, a delayed release carrier, a sustained release carrier, and a long-term release carrier.

27. The use according to claim 17, wherein the MK2i component of the pharmaceutical composition is in a form of a dry powder.

28. The use according to claim 27, wherein the dry powder comprises microparticles with Mass Median Aerodynamic Diameter (MMAD) of 1 to 5 microns.

29. The use according to claim 17, wherein the therapeutic amount of the MK2i component of the pharmaceutical composition is to be administered via an inhalation device.

30. The use according to claim 29, wherein the inhalation device is a nebulizer.

31. The use according to claim 29, wherein the inhalation device is a metered-dose inhaler (MDI).

32. The use according to claim 29, wherein the inhalation device is a dry powder inhaler (DPI).

33. The use according to claim 29, wherein the inhalation device is a dry powder nebulizer.