[00150] 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-based inhibitors of MK2.

SUMMARY

[00151] According to one aspect, there is provided the use of a pharmaceutical composition in the manufacture of a medicament for treating asthma, wherein said pharmaceutical composition comprises a therapeutic amount of a polypeptide of the amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or a functional equivalent thereof made from a fusion between a first polypeptide that is a cell penetrating peptide (CPP) selected from the group consisting of a polypeptide of amino acid sequence WLRRIKAWLRRIKA (SEQ ID NO: 12), WLRRIKA (SEQ ID NO: 13), YGRKKRRQRRR (SEQ ID NO: 14), WLRRIKAWLRRI (SEQ ID NO: 15), FAKLAARLYR (SEQ ID NO: 16), KAFAKLAARLYR (SEQ ID NO: 17) and HRRIKAWLKKI (SEQ ID NO: 18), and a second polypeptide that is a therapeutic domain (TD) selected from the group consisting of a polypeptide of amino acid sequence KALARQLAVA (SEQ ID NO: 8), KALARQLGVA (SEQ ID NO: 9) and KALARQLGVAA (SEQ ID NO: 10), and a pharmaceutically acceptable carrier thereof, wherein the asthma is a disease, condition or pathologic process whose progression is characterized by one or more of aberrant fibroblast proliferation and extracellular matrix deposition producing constriction in an airway, airway remodeling, and airway obstruction, in lung tissue, and wherein the therapeutic amount of the polypeptide is effective to reduce the constriction of small airway dimensions and airway obstruction, treat airway remodeling, or a combination thereof. In an embodiment, the present disclosure provides a method for treating asthma comprising: administering to a subject in need thereof a pharmaceutical composition comprising a therapeutic amount of a polypeptide of the amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or a functional equivalent thereof made from a fusion between a first polypeptide that is a cell penetrating peptide (CPP) selected from the group consisting of a polypeptide of amino acid sequence WLRRIKAWLRRIKA (SEQ ID NO: 12), WLRRIKA (SEQ ID NO: 13), YGRKKRRQRRR (SEQ ID NO: 14), WLRRIKAWLRRI (SEQ ID NO: 15), FAKLAARLYR (SEQ ID NO: 16),

KAFAKLAARLYR (SEQ ID NO: 17) and HRRIKAWLKKI (SEQ ID NO: 18), and a second polypeptide that is a therapeutic domain (TD) selected from the group consisting of a polypeptide of amino acid sequence KALARQLAVA (SEQ ID NO: 8), KALARQLGVA (SEQ ID NO: 9) and KALARQLGVAA (SEQ ID NO: 10), and a pharmaceutically acceptable carrier thereof, the asthma being a disease, condition or pathologic process whose progression is characterized by one or more of aberrant fibroblast proliferation and extracellular matrix deposition producing constriction in an airway, airway remodeling, and airway obstruction in lung tissue, wherein the therapeutic amount of the polypeptide is effective to reduce the constriction of small airway dimensions and airway obstruction, treat airway remodeling, or a combination thereof. According to one embodiment of the method, the therapeutic amount of the polypeptide is effective to enhance isoproterenol-induced relaxation of human airway smooth muscle. According to another embodiment, the asthma is further characterized by an inflammation in the lung tissue. According to another embodiment, the inflammation is an acute or a chronic inflammation. According to another embodiment, 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). According to another embodiment, the aberrant fibroblast proliferation and extracellular matrix deposition in the lung tissue is characterized by

CLAIMS

What is claimed is:

1. Use of a pharmaceutical composition in the manufacture of a medicament for treating asthma, wherein said pharmaceutical composition comprises a therapeutic amount of a polypeptide of the amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or a functional equivalent thereof made from a fusion between a first polypeptide that is a cell penetrating peptide (CPP) selected from the group consisting of a polypeptide of amino acid sequence WLRRIKAWLRRIKA (SEQ ID NO: 12), WLRRIKA (SEQ ID NO: 13), YGRKKRRQRRR (SEQ ID NO: 14), WLRRIKAWLRRI (SEQ ID NO: 15), FAKLAARLYR (SEQ ID NO: 16), KAFAKLAARLYR (SEQ ID NO: 17) and HRRIKAWLKKI (SEQ ID NO: 18), and a second polypeptide that is a therapeutic domain (TD) selected from the group consisting of a polypeptide of amino acid sequence KALARQLAVA (SEQ ID NO: 8), KALARQLGVA (SEQ ID NO: 9) and KALARQLGVAA (SEQ ID NO: 10), and a pharmaceutically acceptable carrier thereof,

wherein the asthma is a disease, condition or pathologic process whose progression is characterized by one or more of aberrant fibroblast proliferation and extracellular matrix deposition producing constriction in an airway, airway remodeling, and airway obstruction, in lung tissue, and

wherein the therapeutic amount of the polypeptide is effective to reduce the constriction of small airway dimensions and airway obstruction, treat airway remodeling, or a combination thereof.

2. The use according to claim 1, wherein the therapeutic amount of the polypeptide is effective to enhance isoproterenol-induced relaxation of human airway smooth muscle.

3. The use according to claim 1, wherein the asthma is further characterized by an inflammation in the lung tissue.

4. The use according to claim 3, wherein the inflammation is an acute or a chronic inflammation.

5. The use according to claim 3, 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).

6. The use according to claim 1, wherein the aberrant fibroblast proliferation and extracellular matrix deposition in the lung 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.

7. The use according to claim 1, wherein the pharmaceutical composition is to be administered intratracheally, parenterally, intravenously, or intraperitoneally.

8. The use according to claim 1, wherein the pharmaceutical composition is to be administered intratracheally.

9. The use according to claim 1, wherein the pharmaceutical composition further comprises at least one additional therapeutic agent.

10. The use according to claim 9, wherein the additional therapeutic agent is selected from the group consisting of a purified bovine Type V collagen, an IL-13 receptor antagonist, a protein tyrosine kinase inhibitor, an endothelial receptor antagonist, a dual endothelin receptor antagonist, a prostacyclin analog, an anti-CTGF monoclonal antibody, an endothelin receptor antagonist (A-selective), AB0024, a lysyl oxidase-like 2 (LOXL2) monoclonal antibody, a c-Jun N-terminal kinase (JNK) inhibitor, pirfenidone, IFN-γ1b, a pan-neutralizing IgG4 human antibody against all three TGF-β isoforms, a TGF-β activation inhibitor, a recombinant human Pentraxin-2 protein (rhPTX-2), a bispecific IL-4/IL-13 antibody, a humanized monoclonal antibody targeting integrin αvβ6, N-acetylcysteine, sildenafil, a Tumor Necrosis Factor (TNF) antagonist (etanercept), and a combination thereof.

11. The use according to claim 9, wherein the additional therapeutic agent is a glucocorticoid selected from the group consisting of prednisone, budesonide, mometasone furoate, fluticasone propionate, fluticasone furoate, and a combination thereof.

12. The use according to claim 9, wherein the additional therapeutic agent is a bronchodilator selected from the group consisting of a leukotriene modifer, an anticholingertic bronchodilator, a short-acting β2-agonist, and long-acting β2-agonist, and a combination thereof.

13. The use according to claim 9, wherein the additional therapeutic agent is an analgesic agent.

14. The use according to claim 9, wherein the additional therapeutic agent is an anti-infective agent.

15. The use according to claim 1, wherein the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence FAKLAARLYRKALARQLGVAA (SEQ ID NO: 3).

16. The use according to claim 1, wherein the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence KAFAKLAARLYRKALARQLGVAA (SEQ ID NO: 4).

17. The use according to claim 1, wherein the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence YARAAARQARAKALARQLAVA (SEQ ID NO: 5).

18. The use according to claim 1, wherein the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence YARAAARQARAKALARQLGVA (SEQ ID NO: 6).

19. The use according to claim 1, wherein the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence HRRIKAWLKKIKALARQLGVAA (SEQ ID NO: 7).

20. The use according to claim 1, wherein the therapeutic domain (TD) of the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is made from the fusion of the first polypeptide that is the cell penetrating peptide (CPP) operatively linked to the second polypeptide that is the therapeutic domain (TD), is a polypeptide whose sequence has a substantial identity to amino acid sequence KALARQLGVAA (SEQ ID NO: 2).

21. The use according to claim 20, wherein the second polypeptide is a polypeptide of amino acid sequence KALARQLAVA (SEQ ID NO: 8).

22. The use according to claim 20, wherein the second polypeptide is a polypeptide of amino acid sequence KALARQLGVA (SEQ ID NO: 9).

23. The use according to claim 20, wherein the second polypeptide is a polypeptide of amino acid sequence KALARQLGVAA (SEQ ID NO: 10).

24. The use according to claim 1, wherein the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is a fusion protein comprising a first polypeptide operatively linked to a second polypeptide, wherein the first polypeptide is a cell penetrating peptide functionally equivalent to YARAAARQARA (SEQ ID NO: 11) selected from the group consisting of a polypeptide of amino acid sequence WLRRIKAWLRRIKA (SEQ ID NO: 12), WLRRIKA (SEQ ID NO: 13), YGRKKRRQRRR (SEQ ID NO: 14), WLRRIKAWLRRI (SEQ ID NO: 15), FAKLAARLYR (SEQ ID NO: 16), KAFAKLAARLYR (SEQ ID NO: 17) and HRRIKAWLKKI (SEQ ID NO: 18), and the second polypeptide is of amino acid sequence KALARQLGVAA (SEQ ID NO: 2).

25. The use according to claim 24, wherein the first polypeptide is a polypeptide of amino acid sequence WLRRIKAWLRRIKA (SEQ ID NO: 12).

26. The use according to claim 24, wherein the first polypeptide is a polypeptide of amino acid sequence WLRRIKA (SEQ ID NO: 13).

27. The use according to claim 24, wherein the first polypeptide is a polypeptide of amino acid sequence YGRKKRRQRRR (SEQ ID NO: 14).

28. The use according to claim 24, wherein the first polypeptide is a polypeptide of amino acid sequence WLRRIKAWLRRI (SEQ ID NO: 15).

29. The use according to claim 24, wherein the first polypeptide is a polypeptide of amino acid sequence FAKLAARLYR (SEQ ID NO: 16).

30. The use according to claim 24, wherein the first polypeptide is a polypeptide of amino acid sequence KAFAKLAARLYR (SEQ ID NO: 17).

31. The use according to claim 24, wherein the first polypeptide is a polypeptide of amino acid sequence HRRIKAWLKKI (SEQ ID NO: 18).

32. 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.

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

34. The use according to claim 33, wherein the dry powder comprises microparticles with Mass Median Aerodynamic Diameter (MMAD) of 1 to 5 microns.

35. The use according to claim 1, wherein the pharmaceutical composition is to be administered via an inhalation device.

36. The use according to claim 35, wherein the inhalation device is a nebulizer.

37. The use according to claim 35, wherein the inhalation device is a metered-dose inhaler (MDI).

38. The use according to claim 35, wherein the inhalation device is a dry powder inhaler (DPI).

39. The use according to claim 35, wherein the inhalation device is a dry powder nebulizer.

40. The use according to claim 1, wherein the asthma is further 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 induction of myofibroblast differentiation and an aberrant promotion of attachment of myofibroblasts to an extracellular matrix, compared to a normal healthy control subject.

41. The use according to claim 1, wherein the asthma is associated with an allergic reaction, inhalation of environmental particulates, smoking, a bacterial infection, a viral infection, mechanical damage to a lung of a subject, an autoimmune disorder, a genetic disorder, or a combination thereof.