Biochem Biophys Res Commun., 382(3):535-9, 2009). These include, but are not limited to, cancer, intimal hyperplasia, organ fibrosis, abdominal adhesions, inflammatory bowel disease, and rheumatoid arthritis. In addition to idiopathic pulmonary fibrosis (IPF), other disorders that involve inflammation and fibrosis and impact the lung include acute lung injury (ALI), organ transplant rejection (with lung transplant also a later-stage treatment for IPF), organ failure secondary to sepsis, acute lung failture, auto-immune diseases such as scleroderma, and chronic pulmonary obstructive disease (COPD).

[00196] The development of fibrosis is known to require inflammation, proliferation and recruitment of fibroblast that results in cells of myofibroblastic phenotype (Horowitz J. et al., *Semin Respir Crit Care Med.*, 27(6):600-612, 2006). MK2 has been shown to control gene expression at transcriptional and post-transcriptional levels (Neininger A. et al., *J Biol Chem.* 2002;277(5):3065-8, Thomas T. et al., *J Neurochem.*, 105(5): 2039-52, 2008; Johansen C. et al., *J Immunol.*, 176(3):1431-8, 2006; Rousseau S. et al., *EMBO J.* 21(23):6505-14, 2002) as well as cytoskeletal architecture (Lopes, L. et al., *Biochem Biophys Res Commun.*, 382(3):535-9, 2009). In addition, it was shown that activated MK2 increases translation and stability of inflammatory cytokine mRNAs and causes actin reorganization; and that inhibition of MK2 is associated with reduced inflammation (Ward, B. et al., *J Surg Res.*, 169(1):e27-36, 2011) and myofibroblast differentiation (Lopes, L. et al., *Biochem Biophys Res Commun.*, 382(3):535-9, 2009).

[00197] 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), hepatic fibrosis, renal fibrosis, vascular fibrosis, 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 DISCLOSURE

[00197a] According to one aspect, there is provided 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, for use in therapy.

[00197b] According to another aspect, there is provided a use of 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, in the manufacture of a medicament for reducing progression of a fibrosis in liver tissue, kidney tissue or vascular tissue, wherein the medicament is to be administered to a subject in need thereof, wherein progression of the fibrosis being characterized by one or more of aberrant fibroblast proliferation and extracellular matrix deposition producing remodeling in liver tissue, kidney tissue or vascular tissue, wherein the therapeutic amount of the polypeptide is effective to reduce progression of the fibrosis, to treat remodeling of the tissue, or a combination thereof.

[00198] According to one embodiment, the described disclsoure provides a method for reducing progression of a fibrosis in a tissue selected from a liver tissue, a kidney tissue or a vascular tissue, 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

CLAIMS

What is claimed is:

1. 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, for use in therapy.

2. Use of 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, in the manufacture of a medicament for reducing progression of a fibrosis in liver tissue, kidney tissue or vascular tissue, wherein the medicament is to be administered to a subject in need thereof, wherein

progression of the fibrosis being characterized by one or more of aberrant fibroblast proliferation and extracellular matrix deposition producing remodeling in liver tissue, kidney tissue or vascular tissue,

wherein the therapeutic amount of the polypeptide is effective to reduce progression of the fibrosis, to treat remodeling of the tissue, or a combination thereof.

3. The use according to claim 2, wherein the tissue fibrosis is further characterized by an inflammation in the 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 2, wherein the aberrant fibroblast proliferation and extracellular matrix deposition in the tissue 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 2, wherein the medicament is to be administered orally, intratracheally, parenterally, intravenously, or intraperitoneally.

8. The use according to claim 2, wherein the pharmaceutical composition further comprises at least one additional therapeutic agent.

9. The use according to claim 8, wherein the additional therapeutic agent is an anti-infective agent.

10. The use according to claim 9, wherein the anti-infective agent is an antiviral agent.

11. The use according to claim 10, wherein the antiviral agent is one or more of sofosbuvir (Sovaldi®), an HCV boosted protease inhibitor (ABT-450, AbbVie), a nonnucleoside NS5B inhibitor (dasabuvir, ABT-333, AbbVie), an NS5a inhibitor (ombitasvir, ABT-267, AbbVie), ABT-450 /r (ABT-450 with ritonavir), ABT-450 co-formulated with ABT-267, ABT-450 formulated with sofosbuvir, and ribavirin.

12. The use according to claim 8, 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.

13. The use according to claim 8, wherein the additional therapeutic agent is an analgesic agent.

14. The use according to claim 8, 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) antibody, a c-Jun N-terminal kinase (JNK) inhibitor, pirfenidone, IFN-γ1b, a 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, an antibody targeting integrin αvβ6, N-acetylcysteine, sildenafil, a Tumor Necrosis Factor (TNF) antagonist (etanercept), and a combination thereof.

15. The use according to claim 2, 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 2, 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 2, 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 2, 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 2, 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 2, wherein the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence YARAAARQARAKALNRQLAVAA (SEQ ID NO: 26).

21. The use according to claim 2, wherein the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence YARAAARQARAKALNRQLAVA (SEQ ID NO: 27).

22. The use according to claim 2, 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).

23. The use according to claim 22, wherein the second polypeptide is a polypeptide of amino acid sequence KALARQLAVA (SEQ ID NO: 8).

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

25. The use according to claim 22, wherein the second polypeptide is a polypeptide of amino acid sequence KALARQLGVAA (SEQ ID NO: 10).

26. The use according to claim 22, wherein the second polypeptide is a polypeptide of amino acid sequence KALNRQLAVAA (SEQ ID NO: 28).

27. The use according to claim 22, wherein the second polypeptide is a polypeptide of amino acid sequence KALNRQLAVA (SEQ ID NO: 29).

28. The use according to claim 2, 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).

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

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

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

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

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

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

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

36. The use according to claim 2, 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.