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] The present disclosure relates to 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] In one 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 a polypeptide of amino acid sequence FAKLAARLYRKALARQLGVAA (SEQ ID NO: 3); or a polypeptide of amino acid sequence KAFAKLAARLYRKALARQLGVAA (SEQ ID NO: 4); or a polypeptide of amino acid sequence HRRIKAWLKKIKALARQLGVAA (SEQ ID NO: 7), 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, for treating fibrotic remodeling of the liver tissue, kidney tissue or vascular tissue, or both, 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 reduces progression of the fibrosis, treats remodeling of the liver tissue, kidney tissue, or vascular tissue due to the fibrosis, or both reduces progression of the fibrosis in liver, kidney or vascular tissue and treats remodeling of the liver tissue, kidney tissue, or vascular tissue due to the fibrosis.

[00198] According to one embodiment, the described disclosure 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

[00787] Tumor necrosis factor (TNF, also referred as TNF-α) is a cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction. Studies have shown that TNF-α induces expression of IL-6 via three distinct signaling pathways inside the cell, i.e., 1) NF-κB pathway 2) MAPK pathway, and 3) death signaling pathway.

[00788] As shown in **Figure 20**, administration of either intraperitoneal (BLEO+MMI-0100 (IP)) or nebulized (BLEO+MMI-0100 (NEB)) MMI-0100 (YARAAARQARAKALARQLGVAA; SEQ ID NO: 1) significantly reduced the plasma level of both TNF-α (A, upper panel) and IL-6 (B, lower panel) in the bleomycin mouse model of idiopathic pulmonary fibrosis.

Example 11. Either Systemic or Local Administration of MMI-0100 (YARAAARQARAKALARQLGVAA; SEQ ID NO: 1) Effectively Blocks Myofibroblast Activation Accumulation in Murine Lung That Is Significantly Scarred Due to Bleomycin-Injury.

[00789] The hallmark of idiopathic pulmonary fibrosis (IPF) is the accumulation of myofibroblasts at fibrotic lesions and expression of abundant alpha-smooth muscle actin (α-SMA), a marker for myofibroblast activation. Furthermore, activated myofibroblasts are in part responsible for rigidity of the lung parenchyma and aggravation of lung function.

[00790] Therefore, the expression level of α-SMA in bleomycin-injured lungs was assessed in the lungs of bleomycin-injured mice treated with MMI-0100 (YARAAARQARAKALARQLGVAA; SEQ ID NO: 1), either systemically (via intraperitoneal administration) or locally (via nebulization). As shown in **Figure 21**, the level of α-SMA was significantly attenuated in MMI-0100 (YARAAARQARAKALARQLGVAA; SEQ ID NO: 1)-treated lungs compared to the level of α-SMA in untreated bleomycin-injured lungs.

Example 12a. Dose Response Studies of MMI-0100 (YARAAARQARAKALARQLGVAA; SEQ ID NO: 1) in Modulating TGF-β1-Induced Myofibroblast Activation In Vitro

[00791] The major hallmarks of idiopathic pulmonary fibrosis (IPF) are the presence of atypical and apoptotic epithelial cells, along with activated myofibroblasts that secrete exuberant amounts of matrix proteins including collagens, fibronectin and matrix metalloproteinases

[00794] In addition, the MK2 inhibitory peptides of the described invention were derived from the substrate binding site of MK2 downstream target HSPB1. Therefore, they can competitively inhibit the kinase activity of MK2 toward HSPB1. Without being limited by theory, the differential effects of MMI-0200 (SEQ ID NO: 19) on fibrosis may be attributed to its sequence differences, its homology to the HSPB1 biding sites, and its differential inhibition of MK2 kinase activity toward a distinct target protein binding site.

Example 12b. Efficacy of MMI-0100 (YARAAARQARAKALARQLGVAA; SEQ ID NO: 1) and MMI-0100 in Combination with an antiviral, agent, e.g., Sofosbuvir (Sovaldi®), on Liver Fibrosis in a Murine Liver Fibrosis Model

[00795] The most commonly used approach to induce experimental liver inflammation and fibrinogenesis is the periodic administration of carbon tetrachloride (CCl_4) in mice (Liedtke C, et al., Fibrogenesis & Tissue Repair, 2013; 6:19). The CCl_4 model resembles all the important properties of human liver fibrosis, including inflammation, regeneration, fiber formation and potentially fibrosis regression (Liedtke C, et al., Fibrogenesis & Tissue Repair, 2013; 6:19; Heindryckx F, et al., Int. J. Exp. Pathol., 2009; 90: 367-386; Iredale J P, et al., J. Clin. Invest., 1998; 102: 538-549; Kisseleva T, et al., PNAS, 2012; 109: 9448-9453). Most studies still rely on the CCl_4-model to induce toxic liver fibrosis in mice due to its good comparability with the abundance of previous publications, excellent reproducibility and moderate burden for the animals (Liedtke C, et al., Fibrogenesis & Tissue Repair, 2013; 6:19).

[00796] Pathogen free 8-10 week old female BALB/c mice can be obtained from Charles River Laboratories (Wilmington, MA). The mice can be divided into three groups: Group 1 to receive MMI-0100 (YARAAARQARAKALARQLGVAA; SEQ ID NO: 1) or a functional equivalent; Group 2 to receive MMI-0100 (YARAAARQARAKALARQLGVAA; SEQ ID NO: 1) or a functional equivalent + one 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, ribavirin, or a combination. Group 3 to receive phosphate buffer saline (PBS) (Control Group). Mice can be injected intraperitoneally two to three times per week with CCl_4 (Sigma-Aldrich, St. Louis, MO) (0.5 to 2 mL/kg body weight diluted in corn oil) for 4 to 6 weeks. At the time of CCl_4 injection, Group 1

CLAIMS

What is claimed is:

1. 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 a polypeptide of amino acid sequence FAKLAARLYRKALARQLGVAA (SEQ ID NO: 3); or a polypeptide of amino acid sequence KAFAKLAARLYRKALARQLGVAA (SEQ ID NO: 4); or a polypeptide of amino acid sequence HRRIKAWLKKIKALARQLGVAA (SEQ ID NO: 7), 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, for treating fibrotic remodeling of the liver tissue, kidney tissue or vascular tissue, or both, 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 reduces progression of the fibrosis, treats remodeling of the liver tissue, kidney tissue, or vascular tissue due to the fibrosis, or both reduces progression of the fibrosis in liver, kidney or vascular tissue and treats remodeling of the liver tissue, kidney tissue or vascular tissue due to fibrosis.

2. The use according to claim 1, wherein the tissue fibrosis is further characterized by an inflammation in the tissue.

3. The use according to claim 2, wherein the inflammation is an acute or a chronic inflammation.

4. The use according to claim 2, 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).

5. The use according to claim 1, 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.

6. The use according to claim 1, wherein the medicament is to be administered orally, intratracheally, parenterally, intravenously, or intraperitoneally.

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

8. The use according to claim 7, wherein the additional therapeutic agent is an anti-infective agent.

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

10. The use according to claim 9, wherein the antiviral agent is one or more of sofosbuvir , 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.

11. The use according to claim 7, 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 7, wherein the additional therapeutic agent is an analgesic agent.

13. The use according to claim 7, 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.

14. 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.