cutaneous scar formation by utilizing a cell-penetrating, peptide-based inhibitor of MK2.

SUMMARY OF THE INVENTION

In one embodiment, there is provided a use of a pharmaceutical composition comprising a therapeutic amount of a Mitogen-Activated Protein Kinase-Activated Protein Kinase 2 (MK2) inhibitor comprising an MK2 polypeptide inhibitor of amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or a functional equivalent thereof selected from the group consisting of YARAAARQARAKALNRQLGVA (SEQ ID NO: 19), FAKLAARLYRKALARQLGVAA (SEQ ID NO: 3), KAFAKLAARLYRKALARQLGVAA (SEQ ID NO: 4) or HRRIKAWLKKIKALARQLGVAA (SEQ ID NO: 7), whose therapeutic domain has an amino acid sequence KALARQLGVAA (SEQ ID NO: 2), and a pharmaceutically acceptable carrier in the manufacture of a medicament for treating a dermal fibrous replacement tissue, which results from a wound that had healed by resolution rather than regeneration, in a subject in need thereof, wherein the subject in need thereof has suffered a wound, wherein the medicament is to be administered to the subject, and wherein

the therapeutic amount is effective (a) to reduce incidence, severity, or both, of the dermal fibrous replacement tissue without impairing one or more of an inflammatory phase, a proliferative phase or a remodeling phase of normal wound healing and (b) to reduce at least one of the wound size, scar area, and collagen whorl formation in the wound compared to an untreated dermal wound control.

In one embodiment, there is provided a pharmaceutical composition for use in treating a cutaneous scar in a subject in need thereof, comprising a therapeutic amount of a Mitogen-Activated Protein Kinase-Activated Protein Kinase 2 (MK2) inhibitor comprising an MK2 polypeptide inhibitor of amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or a functional equivalent thereof whose therapeutic domain has an amino acid sequence KALARQLGVAA (SEQ ID NO: 2), and a pharmaceutically acceptable carrier, wherein

the subject in need thereof has suffered a wound, and

the therapeutic amount is effective (a) to reduce incidence, severity, or both, of the cutaneous scar without impairing normal wound healing and (b) to treat the cutaneous scar in the

subject, such that at least one of the wound size, scar area, and collagen whorl formation in the wound is reduced compared to the control.

In one embodiment, there is provided a use of pharmaceutical composition comprising a therapeutic amount of a Mitogen-Activated Protein Kinase-Activated Protein Kinase 2 (MK2) inhibitor comprising an MK2 polypeptide inhibitor of amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or a functional equivalent thereof whose therapeutic domain has an amino acid sequence KALARQLGVAA (SEQ ID NO: 2), and a pharmaceutically acceptable carrier in the manufacture of a medicament for treating a cutaneous scar in a subject in need thereof, wherein the subject in need thereof has suffered a wound, wherein the need is to be administered to the subject, and wherein

the therapeutic amount is effective (a) to reduce incidence, severity, or both, of the cutaneous scar without impairing normal wound healing and (b) to treat the cutaneous scar in the subject, such that at least one of the wound size, scar area, and collagen whorl formation in the wound is reduced compared to the control.

In one embodiment, there is provided a dressing for use in treating a cutaneous scar in a

What is claimed is:

1. Use of a pharmaceutical composition comprising a therapeutic amount of a Mitogen-Activated Protein Kinase-Activated Protein Kinase 2 (MK2) inhibitor comprising an MK2 polypeptide inhibitor of amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or a functional equivalent thereof selected from the group consisting of YARAAARQARAKALNRQLGVA (SEQ ID NO: 19), FAKLAARLYRKALARQLGVAA (SEQ ID NO: 3), KAFAKLAARLYRKALARQLGVAA (SEQ ID NO: 4) or HRRIKAWLKKIKALARQLGVAA (SEQ ID NO: 7), whose therapeutic domain has an amino acid sequence KALARQLGVAA (SEQ ID NO: 2), and a pharmaceutically acceptable carrier in the manufacture of a medicament for treating a dermal fibrous replacement tissue, which results from a wound that had healed by resolution rather than regeneration, in a subject in need thereof, wherein the subject in need thereof has suffered a wound, wherein the medicament is to be administered to the subject, and wherein

the therapeutic amount is effective (a) to reduce incidence, severity, or both, of the dermal fibrous replacement tissue without impairing one or more of an inflammatory phase, a proliferative phase or a remodeling phase of normal wound healing and (b) to reduce at least one of the wound size, scar area, and collagen whorl formation in the wound compared to an untreated dermal wound control.

2. The use according to claim 1, wherein the wound is an abrasion, a laceration, a crush, a contusion, a puncture, an avulsion, a burn, an ulcer, an incisional wound, a high-tension wound, or a combination thereof.

3. The use according to claim 1, wherein the dermal fibrous replacement tissue, which results from a wound that had healed by resolution rather than regeneration is a pathological scar, an incisional scar, or a combination thereof.

4. The use according to claim 3, wherein the pathological scar is selected from the group consisting of a hypertrophic scar, a keloid, an atrophic scar, a scar contracture, or a combination thereof.

5. The use according to claim 3, wherein the pathological scar results from a high-tension wound located in close proximity to a joint comprising a knee, an elbow, a wrist, a shoulder, a hip, a spine, or a combination thereof.

6. The use according to claim 3, wherein the pathological scar results from an abrasion, a laceration, an incision, a crush, a contusion, a puncture, an avulsion, a burn, an ulcer, an autoimmune skin disorder, or a combination thereof.

7. The use according to claim 6, wherein the autoimmune skin disorder is selected from the group consisting of systemic lupus erythematosus (SLE), systemic sclerosis (scleroderma), pemphigus, vitiligo, dermatitis herpetiformis, psoriasis, or a combination thereof.

8. The use according to claim 1, wherein the medicament is to be administered topically.

9. The use according to claim 8, wherein the medicament is to be administered by means of a dressing comprising the pharmaceutical composition.

10. The use according to claim 9, wherein at least one surface of the dressing is impregnated with the medical composition.

11. The use according to claim 9, wherein the dressing is selected from the group consisting of a gauze dressing, a tulle dressing, an alginate dressing, a polyurethane dressing, a silicone foam dressing, a synthetic polymer scaffold dressing, or a combination thereof.

12. The use according to claim 9, wherein the dressing is an occlusive dressing selected from the group consisting of a film dressing, a semi-permeable film dressing, a hydrogel dressing, a hydrocolloid dressing, and a combination thereof.

13. The use according to claim 9, wherein the dressing further comprises a dermal substitute embedded in or on a surface of the dressing with the pharmaceutical composition.

14. The use according to claim 13, wherein the dermal substitute provides a three-dimensional extracellular scaffold.

15. The use according to claim 13, wherein the dermal substitute is made of a natural biological material, a constructive biological material, or a synthetic material.

16. The use according to claim 15, wherein the natural biological material comprises human cadaver skin, porcine cadaver skin, or porcine small intestine submucosa.

17. The use according to claim 15, wherein the natural biological material comprises a matrix.

18. The use according to claim 15, wherein the natural biological material consists essentially of a matrix that is sufficiently devoid of cell remnants.

19. The use according to claim 15, wherein the constructive biological material comprises collagen, glycosaminoglycan, fibronectin, hyaluronic acid, elastine, or a combination thereof.

20. The use according to claim 15, wherein the constructive biological material is a bilayer, non-cellularized dermal regeneration template or a single layer, cellularized dermal regeneration template.

21. The use according to claim 15, wherein the synthetic dermal substitute comprises a hydrogel.

22. The use according to claim 15, wherein the synthetic dermal substitute further comprises an RGD peptide with amino acid sequence Arginine-Glycine-Aspartate.

23. The use according to claim 1, wherein the medicament is to be administered intraperitoneally, intravenously, intradermally, intramuscularly, or a combination thereof.

24. The use according to claim 23, wherein the medicament is to be administered via an injection device, wherein the injection device is soaked with the pharmaceutical composition prior to administration.

25. The use according to claim 24, wherein the injection device is selected from the group consisting of a needle, a cannula, a catheter, a suture, or a combination thereof.

26. The use according to claim 23, wherein the therapeutic amount of the MK2 polypeptide inhibitor of the amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or a functional equivalent thereof for intradermal injection ranges from 50 ng/100 µl/linear centimeter of wound margin to 500 ng/100 µl/linear centimeter of wound margin.

27. The use according to claim 23, wherein the therapeutic amount of the MK2 polypeptide inhibitor of the amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or a functional equivalent thereof for intraperitoneal administration ranges from 70 µg/kg to 80 µg/kg.

28. The use according to claim 1, wherein

(a) the medicament is formulated for delivery in a single dose at one time; or

(b) the medicament is formulated for delivery in a plurality of doses for a period of at least one day, at least one week, at least one month, at least one year, or a combination thereof; or

(c) the medicament is formulated for delivery at least once daily, at least once weekly, or at least once monthly; or

(d) the medicament is formulated for delivery before, during, or after closing of the wound.

29. The use according to claim 1, wherein the pharmaceutical composition further comprises at least one additional therapeutic agent selected from the group consisting of an anti-inflammatory agent, an analgesic agent, an anti-infective agent, or a combination thereof.

30. The use according to claim 29, wherein

(a) the additional therapeutic agent comprises EXC001 (an anti-sense RNA against connective tissue growth factor (CTGF)), AZX100 (a phosphopeptide analog of Heat Shock Protein 20 (HSP20)), PRM-151 (recombinant human serum amyloid P/Pentaxin 2), PXL01 (a synthetic peptide derived from human lactoferrin), DSC127 (an angiotensin analog), RXI-109 (a self-delivering RNAi compound that targets connective tissue growth factor (CTGF)), TCA (trichloroacetic acid), Botulium toxin type A, or a combination thereof; or

(b) the additional therapeutic agent is selected from the group consisting of rose hip oil, vitamin E, 5-fluorouracil, bleomycin, onion extract, pentoxifylline, prolyl-4-hydroxylase, verapamil, tacrolimus, tamoxifen, tretinoin, colchicine, tranilst, zinc, an antibiotic, and a combination thereof; or

(c) the additional therapeutic agent is a small molecule MK2 inhibitor, wherein the small molecule MK2 inhibitor is a pyrrolopyridone analogue or a multicyclic lactam analogue.

31. The use according to claim 28, wherein the closing of the wound is by means of at least one subcutaneous suture, at least one staple, at least one adhesive tape, a surgical adhesive, or a combination thereof.

32. The use according to claim 31, wherein the surgical adhesive comprises octyl-2-cyanoacrylate or fibrin tissue adhesive.

33. The use according to claim 1, wherein

(a) the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is a fusion peptide comprising a first polypeptide operatively linked to a second polypeptide, wherein the first polypeptide comprises a protein transduction domain functionally equivalent to YARAAARQARA (SEQ ID NO: 11) and is a polypeptide of amino acid sequence selected from the group consisting of 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); or

(b) is selected from the group consisting of FAKLAARLYRKALARQLGVAA (SEQ ID NO: 3), KAFAKLAARLYRKALARQLGVAA (SEQ ID NO: 4) and HRRIKAWLKKIKALARQLGVAA (SEQ ID NO: 7).

34. The use according to claim 1, wherein the therapeutic amount

(a) is effective to inhibit at least 65% of a kinase activity of at least one kinase selected from the group consisting of Mitogen-Activated Protein Kinase-Activated Protein Kinase 2 (MK2), Mitogen-Activated Protein Kinase-Activated Protein Kinase 3 (MK3), calcium/calmodulin-dependent protein kinase I (CaMKI), BDNF/NT-3 growth factors receptor (TrkB), or a combination thereof without substantially inhibiting an off-target protein; or

(b) is effective to modulate an expression level of at least one scar-related gene or scar-related protein in a wound selected from the group consisting of Transforming Growth Factor-β1 (TGF-β1), Tumor Necrosis Factor-α (TNF-α), a collagen, Interleukin-6 (IL-6), chemokine (C-C motif) ligand 2 (CCL2) (or monocyte chemotactic protein-1 (MCP-1)), chemokine (C-C motif) receptor 2 (CCR2), EGF-like module-containing mucin-like hormone receptor-like 1 (EMR1), or a sma/mad-related protein (SMAD); or

(c) is effective to reduce either a level of transforming growth factor-β (TGF-β) expression in the wound; or number of at least one immunomodulatory cell or a progenitor cell infiltrating into the wound, or both.

35. The use according to claim 34, wherein the immunomodulatory cell is selected from the group consisting of a monocyte, a mast cell, a dendritic cell, a macrophage, a T-lymphocyte, a fibrocyte, or a combination thereof.

36. The use according to claim 34, wherein the progenitor cell is selected from the group consisting of a hematopoietic stem cell, a mesenchymal stem cell, or a combination thereof.

37. The use according to claim 9, wherein the dressing is a mechano-active dressing further comprising an anti-infective agent, a growth factor, a vitamin, a clotting agent, or a combination thereof.

38. The use according to claim 9, wherein

(a) the pharmaceutically acceptable carrier is a controlled release carrier; or

(b) the pharmaceutically acceptable carrier comprises particles.