

WLRRIKAWLRRI (SEQ ID NO: 15); FAKLAARLYR (SEQ ID NO: 16); KAFAKLAARLYR (SEQ ID NO: 17); and HRRIKAWLKKI (SEQ ID NO: 18).

Compositions Comprising PTDs Fused to MK2 Inhibitor Peptide Therapeutic Domains (TD)

[0064] Several MK2 inhibitor peptides (TD) have been synthesized, fused to synthetic PTDs and the use of compositions comprising these fused polypeptides has been studied. These polypeptides include, but are not limited to, YARAAARQARAKALARQLGVAA (SEQ ID NO: 1; MMI-0100), YARAAARQARAKALNRQLGVA (SEQ ID NO: 19; MMI-0200), FAKLAARLYRKALARQLGVAA (SEQ ID NO: 3; MMI-0300), KAFAKLAARLYRKALARQLGVAA (SEQ ID NO: 4; MMI-0400), HRRIKAWLKKIKALARQLGVAA (SEQ ID NO: 7; MMI-0500), YARAAARQARAKALNRQLAVAA (SEQ ID NO: 23; MMI-0600), and YARAAARQARAKALNRQLAVA (SEQ ID NO: 24; MMI-0600-2). Both in vitro and in vivo studies have shown that these polypeptides can be useful in the treatment of various diseases, disorders and conditions. These include, without limitation, hyperplasia and neoplasm (U.S. Patent No. 8,536,303 and 8,741,849) inflammatory disorders (U.S. Application No. 12/634,476 and U.S. Application No. 13/934,933), adhesions (U.S. Application No. 12/582516), failure of a vascular graft due to neospasm (U.S. Application No. 13/114,872), improving neurite outgrowth (U.S. Application No. 12, 844,815), a cutaneous scar (U.S. Application No. 13/829,876), failure of a coronary artery bypass vascular graft (U.S. Application No. 13/700,087) and interstitial lung disease and pulmonary fibrosis (U.S. Application No. 13/445,759).

[0065] Peptide compositions present a number of particular challenges to formulation scientists (R. W. Payne and M.C. Manning, "Peptide formulation: challenges and strategies," *Innovations in Pharmaceutical Technology*, 64-68 (2009)). First, since peptides do not have a globular structure that can sequester reactive groups, the side chains of nearly all residues in a peptide are fully solvent exposed, and can exhibit chemical degradation through hydrolytic reactions, for example, oxidation and deamidation. Second, the conformation in aqueous solution may have little similarity to the structure found when bound to a receptor. Third, many peptides tend to be monomeric at very low concentration, but may self-assemble as the concentration is increased and behave as if in a highly associated state, but these structures are too transient or fluxional to provide any increase in long-term stability. Fourth, the

formulation is delivered to a subject via an implantation device. According to another embodiment, the pharmaceutical formulation is delivered to a subject topically. According to another embodiment, the pharmaceutical formulation is delivered to a subject parenterally.

[0073] According to one embodiment, the functional equivalent is made from a fusion between a first polypeptide that is a protein transduction domain (PTD) and a second polypeptide that is a therapeutic domain (TD). According to another embodiment, the protein transduction domain (PTD) is selected from the group consisting of a polypeptide of amino acid sequence YARAAARQARA (SEQ ID NO: 11), FAKLAARLYR (SEQ ID NO: 16), and KAFAKLAARLYR (SEQ ID NO: 17), and a second polypeptide that is a therapeutic domain (TD) of amino acid sequence KALARQLGVAA (SEQ ID NO: 2).

[0073a] According to another aspect, the described invention provides use of the pharmaceutical formulation as described herein comprising a therapeutic amount of a polypeptide of amino sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or a functional equivalent thereof, and a nano-polyplex polymer, in the manufacture of a medicament for treating a vascular graft-induced intimal hyperplasia in a subject,

wherein the medicament

inhibits MK2; and

treats a vascular graft-induced intimal hyperplasia; and wherein the medicament is to be administered to the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0074] **FIGURE 1** shows the technical characteristics of the blister lidding –push through.

[0075] **FIGURE 2** shows the technical characteristics of the Formpack® - 4PLY.

[0076] **FIGURE 3** shows a dynamic vapor sorption isotherm for a MMI-0100 5% solids formulation.

[0077] **FIGURE 4** shows a chromatogram of an MMI-0100 working standard.

[0078] **FIGURE 5** shows an EPIC inhaler device. On the left is an assembled device (base unit with attached flow channel). The inhaler is tethered to an external drive box (pictured on the right) which contains the electronics.

[0079] **FIGURE 6** shows a particle size distribution plot of initial aerosol performance results for a MMI-0100 5% formulation at 1 mg and 2 mg.

[0080] **FIGURE 7** shows a particle size distribution plot of fill weights up to 10 mg for MMI-0100 1% solids formulation (after optimization).

[0081] **FIGURE 8** shows a linearity plot of fine particle dose (FPD) from 5 to 10 mg of MMI-0100 1% solids formulation.

[0082] **FIGURE 9** shows a particle size distribution plot of MMI-0100/Trehalose variant formulations.

[00193] The terms "formulation" as used herein refers to a mixture prepared according to a specific procedure, formula or rule.

[00194] The terms "functional equivalent" or "functionally equivalent" are used interchangeably herein to refer to substances, molecules, polynucleotides, proteins, peptides, or polypeptides having similar or identical effects or use. A polypeptide functionally equivalent to polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1), for example, may have a biologic activity, e.g., an inhibitory activity, kinetic parameters, salt inhibition, a cofactor-dependent activity, and/or a functional unit size that is substantially similar or identical to the expressed polypeptide of SEQ ID NO: 1.

[00195] Examples of polypeptides functionally equivalent to YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) include, but are not limited to, 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), a polypeptide of amino acid sequence HRRIKAWLKKIKALARQLGVAA (SEQ ID NO: 7), a polypeptide of amino acid sequence YARAAARQARAKALNRQLGVA (SEQ ID NO: 19), a polypeptide of amino acid sequence YARAAARQARAKALNRQLAVAA (SEQ ID NO: 23) and a polypeptide of amino acid sequence YARAAARQARAKALNRQLAVA (SEQ ID NO: 24).

[00196] The MMI-0100 peptide of amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) described in the present invention comprises a fusion protein in which a protein transduction domain (PTD; YARAAARQARA; SEQ ID NO: 11) is operatively linked to a therapeutic domain (KALARQLGVAA; SEQ ID NO: 2) in order to enhance therapeutic efficacy.

[00197] Examples of polypeptides functionally equivalent to the therapeutic domain (TD; KALARQLGVAA; SEQ ID NO: 2) of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) include, but are not limited to, a polypeptide of amino acid sequence KALARQLAVA (SEQ ID NO: 8), a polypeptide of amino acid sequence KALARQLGVA (SEQ ID NO: 9), a polypeptide of amino acid sequence KALARQLGVAA (SEQ ID NO: 10), a polypeptide of amino acid sequence

22. The pharmaceutical formulation according to claim 21, wherein the nano-polyplex polymer is poly(propylacrylic acid) (PPAA).
23. The pharmaceutical formulation according to claim 20, wherein the pharmaceutical formulation comprises a charge ratio (CR) of the polypeptide of amino acid sequence YARAAARQARAKALARQLGVAA; SEQ ID NO: 1 or a functional equivalent thereof to PPAA selected from the group consisting of 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, 1:1.5, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9 and 1:10.
24. The pharmaceutical formulation according to claim 23, wherein the charge ratio (CR) is 1:3.
25. The pharmaceutical formulation according to claim 21, wherein the nano-polyplex polymer is poly(acrylic acid) (PAA).
26. The pharmaceutical formulation according to claim 20, wherein the functional equivalent is made from a fusion between a first polypeptide that is a protein transduction domain (PTD) and a second polypeptide that is a therapeutic domain (TD).
27. The pharmaceutical formulation according to claim 26, wherein the protein transduction domain (PTD) is selected from the group consisting of a polypeptide of amino acid sequence YARAAARQARA (SEQ ID NO: 11), FAKLAARLYR (SEQ ID NO: 16), and KAFAKLAARLYR (SEQ ID NO: 17), and a second polypeptide that is a therapeutic domain (TD) of amino acid sequence KALARQLGVAA (SEQ ID NO: 2).
28. The pharmaceutical formulation according to claim 20, wherein the pharmaceutical formulation is delivered to a subject via an implantation device.
29. The pharmaceutical formulation according to claim 20, wherein the pharmaceutical formulation is delivered to a subject topically.
30. The pharmaceutical formulation according to claim 20, wherein the pharmaceutical formulation is delivered to a subject parenterally.

31. Use of the pharmaceutical formulation of claim 20 comprising a therapeutic amount of a polypeptide of amino sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or a functional equivalent thereof, and a nano-polyplex polymer, in the manufacture of a medicament for treating a vascular graft-induced intimal hyperplasia in a subject,

wherein the medicament

inhibits MK2; and

treats a vascular graft-induced intimal hyperplasia; and wherein the medicament is to be administered to the subject.

32. The use according to claim 31, wherein the nano-polyplex polymer is anionic and endosomolytic.

33. The use according to claim 32, wherein the nano-polyplex polymer is poly(propylacrylic acid) (PPAA).

34. The use according to claim 31, wherein the pharmaceutical formulation comprises a charge ratio (CR) of the polypeptide of amino acid sequence YARAAARQARAKALARQLGVAA; SEQ ID NO: 1 or a functional equivalent thereof to PPAA selected from the group consisting of 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, 1:1.5, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9 and 1:10.

35. The use according to claim 34, wherein the charge ratio (CR) is 1:3.

36. The use according to claim 32, wherein the nano-polyplex polymer is poly(acrylic acid) (PAA).

37. The use according to claim 31, wherein the functional equivalent is made from a fusion between a first polypeptide that is a protein transduction domain (PTD) and a second polypeptide that is a therapeutic domain (TD).

38. The use according to claim 37, wherein the protein transduction domain (PTD) is selected from the group consisting of a polypeptide of amino acid sequence YARAAARQARA (SEQ ID NO: 11), FAKLAARLYR (SEQ ID NO: 16), and KAFKLAARLYR (SEQ ID NO: 17), and a second polypeptide that is a therapeutic domain (TD) of amino acid sequence KALARQLGVAA (SEQ ID NO: 2).

39. The use according to claim 31, wherein the administration is by an implantation

device.

40. The use according to claim 31, wherein the administration is by topical administration.

41. The use according to claim 31, wherein the administration is by parenteral administration.