[0093] Proline-rich tyrosine kinase 2 (Pyk2) is an extensively expressed non-receptor tyrosine kinase that integrates signals from receptor tyrosine kinases and intracellular signaling molecules in such essential cellular processes as cell differentiation, proliferation and migration. Id. Pyk2 is rapidly tyrosine phosphorylated in response to various extracellular signals, and activated Pyk2 signaling promotes cell survival and migration in an anchorage-independent manner. Id. The tyrosine 402 (Tyr402) of Pyk2 serves as the primary autophosphorylation site essential for Pyk2 activity and function. Id. High activity of Tyr402 is found in tumor cells with a more invasive and metastatic phenotype. Id.

[0094] High expression of TrkB has been reported in NSCLC, particularly correlated with lymph node metastasis and TNM stage. Id. TrkB-siRNA interrupted BDNF-promoted Pyk2 and extracellular regulating kinase (ERK) activation and invasion of lung adenocarcinoma A549 cells. Id. Moreover, Pyk2-siRNA inhibited BDNF-associated ERK phosphorylation and cell invastion. Id. The investigators considered these data as evidence that TrkB/Pyk2/ERK signaling mediates BDNF-induced invasion of A549 cells, and suggested that suppression of TrkB may provide a helpful target for inhibitory therapies of metastasis in NSCLC. Id.

[0095] The described invention offers an approach to treat non-small cell lung carcinoma using cell-penetrating, peptide-based inhibitors of MK2, that may be effective to overcome tumor chemoresistance, to enhance tumor chemosensitivity and to slow progression of the non-small cell lung cancer solid tumor comprising the population of tumor cells.

SUMMARY OF THE INVENTION

[0096] According to one aspect, the present disclosure provides a pharmaceutical composition for use in treating a non-small cell lung cancer (NSCLC) solid tumor comprising a population of tumor cells, wherein the pharmaceutical composition comprises a therapeutic amount of a polypeptide of the amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or a functional equivalent thereof, and a pharmaceutically acceptable carrier thereof, and wherein the therapeutic amount is effective to inhibit a kinase activity of a kinase selected from the group listed in Table 1 in the population of tumor cells and to reduce cancer cell proliferation, to reduce tumor size, to reduce tumor burden, to induce tumor cell death, to overcome tumor chemoresistance, to enhance tumor chemosensitivity, to slow progression of the population of tumor cells, or a combination thereof.

[0097] The present disclosure also provides a method for treating non-small cell lung cancer solid tumor comprising a population of tumor cells, the method 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, and a pharmaceutically acceptable carrier thereof, wherein therapeutic amount of the polypeptide is effective to inhibit kinase activity of the population of tumor cells, to reduce cancer cell proliferation, to reduce tumor size, to reduce tumor burden, to induce cancer cell death, to overcome tumor chemoresistance, to enhance tumor chemosensitivity,to slow progression of the population of tumor cells, or a combination thereof.

In another aspect, the present disclosure provides 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, and a pharmaceutically acceptable carrier thereof in the manufacture of a medicament, for treating non-small cell lung cancer solid tumor comprising a population of tumor cells, wherein the therapeutic amount of the polypeptide is effective to inhibit kinase activity of the population of tumor cells, to reduce cancer cell proliferation, to reduce tumor size, to reduce tumor burden, to induce cancer cell death, to overcome tumor chemoresistance, to enhance tumor chemosensitivity, to slow progression of the population of tumor cells, or a combination thereof.

[0098] According to another aspect, the present disclosure provides a system for the treatment of a non-small cell lung cancer (NSCLC) tumor comprising a population of tumor cells comprising: (a) a pharmaceutical composition, wherein the pharmaceutical composition comprises a therapeutic amount of a polypeptide of the amino acid sequence YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) or a functional equivalent thereof, and a pharmaceutically acceptable carrier thereof, and wherein therapeutic amount may be effective to inhibit a kinase activity of a kinase selected from the group listed in **Table 1** in the population of tumor cells and to reduce proliferation of the population of tumor cells, to reduce tumor size, to reduce tumor burden, to induce tumor cell death, to overcome tumor chemoresistance, to enhance tumor chemosensitivity, to slow progression of the population of tumor cells, or a combination thereof; and (b) an inhalation device for pulmonary delivery.

[0099] According to one embodiment, the tumor is selected from the group consisting of a primary tumor, a secondary tumor, a recurrent tumor, a refractory tumor and a combination thereof. According to another embodiment, the primary tumor is selected from the group consisting of a squamous cell carcinoma, an adenocarcinoma, a large cell carcinoma and a combination thereof. According to another embodiment, the secondary tumor is a metastatic tumor. According to another embodiment, the metastatic tumor is a selected from the group consisting of an adrenal metastatic tumor, a bone metastatic tumor, a liver metastatic tumor, a brain metastatic tumor and a combination thereof.

[00100] According to some embodiments, the step of administering occurs intratracheally, (e.g., by inhalation), parenterally, intravenously, or intraperitoneally.

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

33. The pharmaceutical composition according to claim 32, wherein the inhalation device is a nebulizer.

34. The pharmaceutical composition according to claim 32, wherein the inhalation device is a metered-dose inhaler (MDI).

35. The pharmaceutical composition according to claim 32, wherein the inhalation device is a dry powder inhaler (DPI).

36. The pharmaceutical composition according to claim 32, wherein the inhalation device is a dry powder nebulizer.

37. 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, and a pharmaceutically acceptable carrier thereof in the manufacture of a medicament, for treating non-small cell lung cancer solid tumor comprising a population of tumor cells,

wherein the therapeutic amount of the polypeptide is effective to inhibit kinase activity of the population of tumor cells, to reduce cancer cell proliferation, to reduce tumor size, to reduce tumor burden, to induce cancer cell death, to overcome tumor chemoresistance, to enhance tumor chemosensitivity, to slow progression of the population of tumor cells, or a combination thereof.

38. The use according to claim 37, wherein the tumor is selected from the group consisting of a primary tumor, a secondary tumor, a recurrent tumor, a refractory tumor and a combination thereof.

39. The use according to claim 38, wherein the primary tumor is selected from the group consisting of a squamous cell carcinoma, an adenocarcinoma, a large cell carcinoma and a combination thereof.

40. The use according to claim 38, wherein the secondary tumor is a metastatic tumor.

41. The use according to claim 40, wherein the metastatic tumor is a selected from the group consisting of an adrenal metastatic tumor, a bone metastatic tumor, a liver metastatic tumor, a brain metastatic tumor and a combination thereof.

42. The use according to claim 37, wherein the medicament is to be administered intratracheally, parenterally, intravenously, intraperitoneally or by pulmonary administration.

43. The use according to claim 42, wherein the medicament is to be administered by pulmonary administration.

44. The use according to claim 43, wherein the pulmonary administration is inhalation.

45. The use according to claim 37, wherein the pharmaceutical composition further comprises at least one additional therapeutic agent.

46. The use according to claim 45, wherein the additional therapeutic agent is a chemotherapeutic agent selected from the group consisting of Abitrexate (Methotrexate), Abraxane (Paclitaxel Albumin-stabilized Nanoparticle Formulation), Afatinib Dimaleate, Alimta (Pemetrexed Disodium), Avastin (Bevacizumab), Bvacizumab, Carboplatin, Ceritinib, Cisplatin, Crizotinib, Cyramza (Ramucirumab), Docetaxel, Erlotinib Hydrochloride, Folex PFS (Methotrexate), Gefitinib, Gilotrif (Afatinib Dmaleate), Gemcitabine Hydrochloride, Gemzar (Gemcitabine Hydrochloride), Iressa (Gefitinib), Mechlorethamine Hydrochloride, Methotrexate, Methotrexate LPF (Methotrexate), Mexate (Methotrexate), Mexate-AQ (Methotrexate), Mustargen (mechlorethamine Hydrochloride), Navelbine (Vinorelbine Tartrate), Paclitaxel, Paclitaxel Albumin-stabilized nanoparticle Formulation, Paraplat (Carboplatin), Paraplatin (Carboplatin), Pemetrexed Disodium, Platinol (Cisplatin), Platinol-AQ (Cisplatin), Ramucirumab, Tarceva (Erlotinib Hydrochloride), Taxol (Paclitaxel), Taxotere (Docetaxel), Vinorelbine Tartrate, Xalkori (Crizotinib), Zykadia (Ceritinib), Carboplatin-Taxol, Gemcitabine-Cisplatin and a combination thereof.

47. The use according to claim 45, 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.

48. The use according to claim 45, 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.

49. The use according to claim 45, wherein the additional therapeutic agent is an analgesic agent.

50. The use according to claim 45, wherein the additional therapeutic agent is an anti-infective agent.

51. The use according to claim 37, wherein the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence FAKLAARLYRKALARQLGVAA (SEQ ID NO: 3).

52. The use according to claim 37, wherein the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence KAFAKLAARLYRKALARQLGVAA (SEQ ID NO: 4).

53. The use according to claim 37, wherein the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence YARAAARQARAKALARQLAVA (SEQ ID NO: 5).

54. The use according to claim 37, wherein the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence YARAAARQARAKALARQLGVA (SEQ ID NO: 6).

55. The use according to claim 37, wherein the functional equivalent of the polypeptide YARAAARQARAKALARQLGVAA (SEQ ID NO: 1) is of amino acid sequence HRRIKAWLKKIKALARQLGVAA (SEQ ID NO: 7).

56. The use according to claim 37, wherein 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 therapeutic domain (TD), is a polypeptide whose sequence has a substantial identity to amino acid sequence KALARQLGVAA (SEQ ID NO: 2).

57. The use according to claim 56, wherein the second polypeptide is a polypeptide of amino acid sequence KALARQLAVA (SEQ ID NO: 8).

58. The use according to claim 56, wherein the second polypeptide is a polypeptide of amino acid sequence KALARQLGVA (SEQ ID NO: 9).

59. The use according to claim 56, wherein the second polypeptide is a polypeptide of amino acid sequence KALARQLGVAA (SEQ ID NO: 10).

60. The use according to claim 37, 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).

61. The use according to claim 60, wherein the first polypeptide is a polypeptide of amino acid sequence WLRRIKAWLRRIKA (SEQ ID NO: 12).

62. The use according to claim 60, wherein the first polypeptide is a polypeptide of amino acid sequence WLRRIKA (SEQ ID NO: 13).

63. The use according to claim 60, wherein the first polypeptide is a polypeptide of amino acid sequence YGRKKRRQRRR (SEQ ID NO: 14).

64. The use according to claim 60, wherein the first polypeptide is a polypeptide of amino acid sequence WLRRIKAWLRRI (SEQ ID NO: 15).

65. The use according to claim 60, wherein the first polypeptide is a polypeptide of amino acid sequence FAKLAARLYR (SEQ ID NO: 16).

66. The use according to claim 60, wherein the first polypeptide is a polypeptide of amino acid sequence KAFAKLAARLYR (SEQ ID NO: 17).

67. The use according to claim 60, wherein the first polypeptide is a polypeptide of amino acid sequence HRRIKAWLKKI (SEQ ID NO: 18).

68. The use according to claim 37, 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.

69. The use according to claim 37, wherein the pharmaceutical composition is in a form of a dry powder.

70. The use according to claim 69, wherein the dry powder comprises microparticles with Mass Median Aerodynamic Diameter (MMAD) of 1 to 5 microns.

71. The use according to claim 37, wherein the pharmaceutical composition is to be administered via an inhalation device.

72. The use according to claim 71, wherein the inhalation device is a nebulizer.

73. The use according to claim 71, wherein the inhalation device is a metered-dose inhaler (MDI).

74. The use according to claim 71, wherein the inhalation device is a dry powder inhaler (DPI).

75. The use according to claim 71, wherein the inhalation device is a dry powder nebulizer.

76. A system for the treatment of a non-small cell lung cancer (NSCLC) tumor comprising a population of tumor cells comprising:

(a) a pharmaceutical composition, wherein the pharmaceutical composition comprises a therapeutic amount of a polypeptide of the amino acid sequence