Claims

1. Use of a water-insoluble controlled-release pattern recognition receptor agonist ("PRRA") or its pharmaceutically acceptable salt or a pharmaceutical composition comprising such water-insoluble controlled-release PRRA or its pharmaceutically acceptable salt for the manufacture of a medicament for the treatment of a cell-proliferation disorder, wherein the water-insoluble controlled-release PRRA is to be administered by intra-~~tissue~~ tumoral administration, and wherein the protein level of at least one cytokine selected from the group consisting of IL-6, CCL2 and IL-10 in plasma has a more than 10-fold lower maximum protein level within 24 hours compared to an equivalent molar dose of the corresponding free PRRA upon intra-tissue administration, wherein the water-insoluble controlled-release PRRA comprises a plurality of PRRA moieties covalently and reversibly conjugated to a carrier moiety, which carrier moiety is a PEG-based hydrogel and wherein the PRRA is resiquimod.

2. The use of claim 1, wherein the at least one cytokine is IL-6.

3. The use of claim 1, wherein the at least one cytokine is CCL2.

4. The use of claim 1, wherein the at least one cytokine is IL-10.

5. The use of any one of claims 1 to 4, wherein the maximum protein level of the at least one cytokine in plasma is more than 15-fold lower following intra-tissue administration of controlled-release PRRA compared to intra-tissue administration of an equivalent molar dose of the corresponding free PRRA.

6. Use of a water-insoluble controlled-release PRRA, its pharmaceutically acceptable salt or a pharmaceutical composition comprising such water-insoluble controlled-release PRRA or its pharmaceutically acceptable salt for the manufacture of a medicament for the treatment of a cell-proliferation disorder, wherein the water-insoluble controlled-release PRRA is to be administered by intra-tissue administration and wherein the maximum mRNA expression levels of at least 4 genes selected from the group consisting of *TNF, IL1A, IL1B, IL10, IL6, IL12B, CCL2, CCL8, CCL3, CCL4, CXCL2, CCL20, CSF2, pan-IFNA subtype members, IFNB1, IL18, CCL5, CXCL10 and*

CXCL1 in peripheral blood mononuclear cells within 24 hours after such intra-tissue administration are more than 1.5-fold lower than after intra-tissue administration of an equivalent molar dose of the corresponding free PRRA.

7. The use of claim 6, wherein at least 4 genes are selected from the group consisting of *TNF, IL1A, IL1B, IL10, IL6, CCL2, CCL3, CCL4, CXCL2, pan-IFNA subtype members, IL18, CCL5, CXCL10 and CXCL1*.

8. The use of claim 6 or 7, wherein at least 4 genes are selected from the group consisting of *TNF, IL1A, IL1B, IL10, CCL2, CCL3, CCL4, CXCL2, pan-IFNA subtype members, CXCL10 and CXCL1*.

9. The use of any one of claims 6 to 8, wherein the maximum expression levels of the at least 4 genes are more than 2-fold lower.

10. Use of a water-insoluble controlled-release PRRA or its pharmaceutically acceptable salt or a pharmaceutical composition comprising such water-insoluble controlled-release PRRA or its pharmaceutically acceptable salt for the manufacture of a medicament for the treatment of a cell-proliferation disorder, wherein the water-insoluble controlled-release PRRA is to be administered by intra-~~tissue~~ tumoral administration and wherein the maximum plasma level of free PRRA within 24 hours is at least 25-fold lower compared to the maximum plasma level within 24 hours after intra-tissue administration of an equivalent molar dose of the corresponding free PRRA, wherein the water-insoluble controlled-release PRRA comprises a plurality of PRRA moieties covalently and reversibly conjugated to a carrier moiety, which carrier moiety is a PEG-based hydrogel and wherein the PRRA is resiquimod.

11. The use of claim 10, wherein the maximum plasma level of free PRRA within 24 hours is at least 50-fold lower.

12. Use of a water-insoluble controlled-release PRRA or its pharmaceutically acceptable salt or a pharmaceutical composition comprising such water-insoluble controlled-release PRRA or its pharmaceutically acceptable salt for the manufacture of a medicament for the treatment of a cell-proliferation disorder, wherein after intra-~~tissue~~

tumoral administration of the water-insoluble controlled-release PRRA comprising 10 µg of free PRRA equivalents the maximum plasma concentration of free PRRA within 24 hours is less than 1.0 ng/ml, wherein the water-insoluble controlled-release PRRA comprises a plurality of PRRA moieties covalently and reversibly conjugated to a carrier moiety, which carrier moiety is a PEG-based hydrogel and wherein the PRRA is resiquimod.

13. The use of claim 12, wherein maximum plasma concentration of free PRRA within 24 hours is less than 0.25 ng/ml.

14. The use of any one of claims 1 to 13, wherein the cell-proliferation disorder is cancer.

15. The use of any one of claims 1 to 14, wherein the cancer is selected from the group consisting of liquid tumors, solid tumors and lymphomas.

16. The use of claim 14, wherein the cancer is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastasic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.

~~17. The use of any one of claims 1 to 16, wherein the intra-tissue administration is intra-tumoral administration.~~

~~18~~17. The use of any one of claims ~~17~~1 to 16, wherein the intra-tumoral administration is administration into a solid tumor or lymphoma.

~~19~~18. The use of claim ~~18~~17, wherein the solid tumor or lymphoma is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastasic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.

~~20. The use of any one of claims 1 to 19, wherein the one or more PRRA is selected from the group consisting of Toll-like receptor agonists, NOD-like receptors, RIG-I-like receptors, cytosolic DNA sensors, STING, and aryl hydrocarbon receptors.~~

~~21. The use of any one of claims 1 to 20, wherein the one or more PRRA is a Toll-like receptor agonist.~~

~~22. The use of any one of claims 1 to 21, wherein the one or more PRRA is a TLR7 agonist.~~

~~23. The use of any one of claims 1 to 22, wherein at least 10% of the PRRA of the water-insoluble controlled-release PRRA are imiquimod.~~

~~24. The use of any one of claims 1 to 21, wherein the one or more PRRA is a TLR7/8 agonist.~~

~~25. The use of any one of claims 1 to 21 or 24, wherein at least 10% of the PRRA of the water-insoluble controlled-release PRRA are resiquimod.~~

~~26~~19. The use of any one of claims 1 to ~~25~~18, wherein PRRA is released from the water-insoluble controlled-release PRRA with a release half-life under physiological conditions of at least 3 days.

~~27. The use of any one of claims 1 to 26, wherein the water-insoluble controlled-release PRRA comprises a plurality of PRRA moieties covalently and reversibly conjugated to a carrier moiety.~~

~~28. The use of claim 27, wherein the carrier comprises a polymer.~~

~~29. The use of claim 27 or 28, wherein the carrier is a hydrogel.~~

~~30. The use of any one of claims 27 to 29, wherein the carrier is a PEG-based hydrogel.~~

~~31~~20. The use of any one of claims 1 to ~~30~~19, wherein the treating of the cell-proliferation disorder in addition to the administration of the water-insoluble controlled-release PRRA includes the administration of at least one cancer therapeutic.

~~32~~21. The use of claim ~~31~~20, wherein the at least one cancer therapeutic is selected from the group consisting of cytotoxic/chemotherapeutic agents, immune checkpoint inhibitors or antagonists, immune checkpoint agonists, multi-specific drugs, antibody-drug conjugates (ADC), radionuclides or targeted radionuclide therapeutics, DNA damage repair inhibitors, tumor metabolism inhibitors, pattern recognition receptor agonists, protein kinase inhibitors, chemokine and chemoattractant receptor agonists, chemokine or chemokine receptor antagonists, cytokine receptor agonists, death

receptor agonists, CD47 or SIRPα antagonists, oncolytic drugs, signal converter proteins, epigenetic modifiers, tumor peptides or tumor vaccines, heat shock protein (HSP) inhibitors, proteolytic enzymes, ubiquitin and proteasome inhibitors, adhesion molecule antagonists, and hormones including hormone peptides and synthetic hormones.