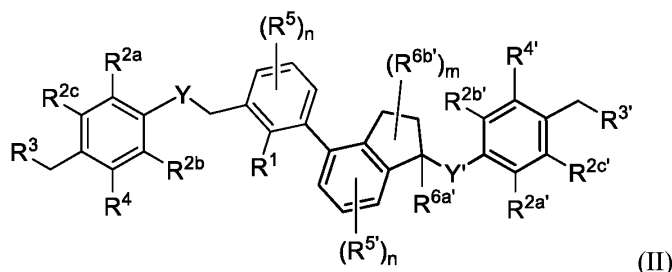
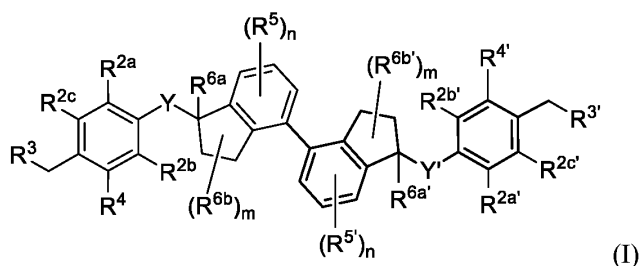


WHAT IS CLAIMED IS:

1. A compound represented by Formula (I) or Formula (II):



or a pharmaceutically acceptable salt, solvate, or hydrate thereof, wherein

Y and Y' are each independently selected from the group consisting of O, NH and N(C₁₋₄ alkyl);

R¹ is independently selected from the group consisting of H, halogen, CN, C₁₋₄ alkyl, C₁₋₄

haloalkyl, -O-C₁₋₄ alkyl and -O-C₁₋₄ haloalkyl;

each R^{2a}, R^{2b}, R^{2c}, R^{2a'}, R^{2b'} and R^{2c'} is independently selected from the group consisting of H,

halogen, -CN, -R^a, -CO₂R^b, -CONR^bR^c, -OC(O)NR^bR^c, -NR^cC(O)R^b, -NR^cC(O)₂R^a,

-NR^b-C(O)NR^bR^c, -NR^bR^c, -OR^b, -X¹-OR^b, -X¹-NR^bR^c, -X¹-CO₂R^b, -SF₅,

and -S(O)₂NR^bR^c, wherein each X¹ is a C₁₋₄ alkylene; each R^b and R^c is independently

selected from hydrogen, C₁₋₈ alkyl, and C₁₋₈ haloalkyl, or when attached to the same

nitrogen atom can be combined with the nitrogen atom to form a five or six-membered

ring having from 0 to 2 additional heteroatoms as ring members selected from N, O and

S, and optionally substituted with oxo; each R^a is independently selected from the group

consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, and C₁₋₈ haloalkyl;

17 R^3 and $R^{3'}$ are each independently selected from the group consisting of $-NR^dR^e$ and 4- to 12-
 18 membered monocyclic, bicyclic or spirocyclic non-aromatic heterocyclic ring, optionally
 19 substituted with 1 to 6 R^{3a} , wherein
 20 R^d is selected from the group consisting of H, C_{1-8} haloalkyl and C_{1-8} alkyl;
 21 R^e is selected from H, $-C_{1-8}$ alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-X^2-CO_2R^g$, $-X^2-$
 22 $CONR^gR^h$, and $-X^2-CONHSO_2R^g$, $-X^2-SO_2NR^gR^h$, $-X^2-SO_3R^g$, $-X^2-B(OH)_2$, $-X^2-$
 23 PO_3H_2 , $-X^2-C(O)NHOH$, $-X^2-NR^gR^h$, $-C(O)R^g$, C_{3-10} cycloalkyl, $-C_{3-10}$ cycloalkyl-
 24 $COOR^g$, $-C_{3-10}$ cycloalkyl- OR^g , C_{4-8} heterocyclyl, $-C_{4-8}$ heterocyclyl- $COOR^g$, $-C_{4-8}$
 25 heterocyclyl- OR^g , $-X^2-C_{4-8}$ heterocyclyl, $-C(=O)O-X^2-C_{4-8}$ heterocyclyl, $-X^2-C_{3-10}$
 26 cycloalkyl, C_{5-10} heteroaryl, $-X^2-C_{5-10}$ heteroaryl, $-X^2-C_{6-10}$ aryl, $-X^2-(C=O)-C_{6-10}$
 27 aryl, $-CO_2-X^2-O_2C-C_{1-8}$ alkyl, $-X^2-NH(C=O)-C_{2-8}$ alkenyl, $-X^2-NH(C=O)-C_{1-8}$
 28 alkyl, $-X^2-NH(C=O)-C_{2-8}$ alkynyl, $-X^2-(C=O)-NH-X^2-COOR^g$, and $-X^2-(C=O)-$
 29 $NH-X^2-OR^g$ optionally substituted with CO_2H ; wherein the alkyl or alkylene portions
 30 of R^e are optionally further substituted with from 1 to 3 substituents independently
 31 selected from OH, $COOH$, SO_2NH_2 , $CONH_2$, $C(O)NHOH$, $COO-C_{1-8}$ alkyl, and
 32 PO_3H_2 ; the C_{5-10} heteroaryl and the C_{6-10} aryl portions of R^e are optionally substituted
 33 with 1 to 3 substituents independently selected from OH, $B(OH)_2$, $COOH$, NH_2 ,
 34 SO_2NH_2 , $CONH_2$, $C(O)NHOH$, PO_3H_2 , $COO-C_{1-8}$ alkyl, C_{1-4} alkyl, C_{1-4} alkylene-OH,
 35 C_{1-4} alkylene- SO_2NH_2 , C_{1-4} alkylene $CONH_2$, C_{1-4} alkylene- $C(O)NHOH$, C_{1-4} alkylene-
 36 PO_3H_2 , and C_{1-4} alkylene- $COOH$; and the C_{4-8} heterocyclyl and C_{3-10} cycloalkyl
 37 portions of R^e are optionally substituted with 1 to 4 R^w substituents;
 38 or
 39 R^e combined with the N to which it is attached is a mono-amino acid, di- or tri-peptide
 40 comprising natural amino acids and non-natural amino acids, wherein the non-natural
 41 amino acids have an alpha carbon substituent selected from the group consisting of
 42 C_{2-4} hydroxyalkyl, C_{1-3} alkyl-guanidiny, and C_{1-4} alkyl-heteroaryl, and wherein the
 43 alpha carbon of each natural or non-natural amino acid is optionally further
 44 substituted with a methyl group, and the terminal moiety of the mono-, di-, or tri-
 45 peptide is selected from the group consisting of $C(O)OH$, $C(O)O-C_{1-6}$ alkyl, $C(O)NH_2$
 46 and PO_3H_2 ;

47 each R^{3a} is independently selected from the group consisting of halogen, -CN, oxo, $-R^f$,
 48 $-CO_2R^g$, $-CONR^gR^h$, $-CONHC_{1-6}$ alkyl-OH, $-C(O)R^g$, $-OC(O)R^g$, $-OC(O)NR^gR^h$,
 49 $-NR^gC(O)R^h$, $-NR^gC(O)_2R^h$, $-CONHOH$, $-PO_3H_2$, $-NR^g-X^2-C(O)_2R^h$,
 50 $-NR^gC(O)NR^gR^h$, $-NR^gR^h$, $-OR^g$, $-S(O)_2NR^gR^h$, $-O-X^2-OR^g$, $-O-X^2-NR^gR^h$,
 51 $-O-X^2-CO_2R^g$, $-O-X^2-CONR^gR^h$, $-X^2-OR^g$, $-X^2-NR^gR^h$, $-X^2-CO_2R^g$, $-X^2-CONR^gR^h$,
 52 $-X^2-CONHSO_2R^g$ and SF_5 ; wherein X^2 is C_{1-6} alkylene and is optionally further
 53 substituted with OH, NH_2 , SO_2NH_2 , $CONH_2$, $C(O)NHOH$, PO_3H_2 , $COO-C_{1-8}$ alkyl or
 54 CO_2H , wherein each R^g and R^h is independently selected from hydrogen, C_{1-8} alkyl
 55 optionally substituted with 1 to 2 substituents selected from OH, NH_2 , SO_2NH_2 ,
 56 $CONH_2$, $C(O)NHOH$, PO_3H_2 , $COO-C_{1-8}$ alkyl and CO_2H , and C_{1-8} haloalkyl
 57 optionally substituted with 1 to 2 substituents selected from OH, NH_2 , SO_2NH_2 ,
 58 $CONH_2$, $C(O)NHOH$, PO_3H_2 , $COO-C_{1-8}$ alkyl and CO_2H , or when attached to the
 59 same nitrogen atom R^g and R^h can be combined with the nitrogen atom to form a five
 60 or six-membered ring having from 0 to 2 additional heteroatoms as ring members
 61 selected from N, O or S, and optionally substituted with oxo; each R^f is independently
 62 selected from the group consisting of $-OH$, C_{1-8} alkyl, C_{2-8} alkenyl, and C_{1-8} haloalkyl
 63 each of which may be optionally substituted with OH, NH_2 , SO_2NH_2 , $CONH_2$,
 64 $C(O)NHOH$, PO_3H_2 , $COO-C_{1-8}$ alkyl or CO_2H ;
 65 each R^w substituent is independently selected from C_{1-4} alkyl, C_{1-4} alkylene-OH, C_{1-4}
 66 alkylene-COOH, C_{1-4} alkylene- SO_2NH_2 , C_{1-4} alkylene- $CONH_2$, C_{1-4} alkylene-
 67 $C(O)NHOH$, C_{1-4} alkylene- PO_3H_2 , OH, $COO-C_{1-8}$ alkyl, COOH, SO_2NH_2 , $CONH_2$,
 68 $C(O)NHOH$, PO_3H_2 and oxo;
 69 R^4 and $R^{4'}$ are each independently selected from the group consisting of $O-C_{1-8}$ alkyl, $O-C_{1-8}$
 70 haloalkyl, C_{6-10} aryl, C_{5-10} heteroaryl, $-O-C_{1-4}$ alkyl- C_{4-7} heterocycloalkyl, $-O-C_{1-4}$ alkyl- C_{6-}
 71 $_{10}$ aryl and $-O-C_{1-4}$ alkyl- C_{5-10} heteroaryl, each of which is optionally substituted with 1 to
 72 5 R^{4a} ,
 73 each R^{4a} is independently selected from the group consisting of halogen, -CN, $-R^i$,
 74 $-CO_2R^j$, $-CONR^jR^k$, $-C(O)R^j$, $-OC(O)NR^jR^k$, $-NR^jC(O)R^k$, $-NR^jC(O)_2R^i$,
 75 $-NR^j-C(O)NR^jR^k$, $-NR^jR^k$, and $-OR^j$; wherein
 76 each R^i is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, and C_{1-}
 77 $_8$ haloalkyl; and optionally when two R^{4a} substituents are on adjacent atoms, they are

78 combined to form a fused five or six-membered carbocyclic or heterocyclic ring
79 optionally substituted with oxo;
80 each R^j and R^k is independently selected from hydrogen, C₁₋₈ alkyl, and C₁₋₈ haloalkyl, or
81 when attached to the same nitrogen atom can be combined with the nitrogen atom to
82 form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring
83 members selected from N, O or S, and optionally substituted with oxo;
84 each n is independently 0, 1, 2 or 3;
85 each R⁵ and R^{5'} is independently selected from the group consisting of halogen, -CN, -R^q,
86 -CO₂R^r, -CONR^rR^s, -C(O)R^r, -NR^rR^s, and -OR^r, wherein
87 each R^r and R^s is independently selected from hydrogen, C₁₋₄ alkyl, and C₁₋₄ haloalkyl, or
88 when attached to the same nitrogen atom can be combined with the nitrogen atom to
89 form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring
90 members selected from N, O or S, and optionally substituted with oxo; each R^q is
91 independently selected from the group consisting of C₁₋₈ alkyl, and C₁₋₈ haloalkyl;
92 R^{6a} and R^{6a'} are each independently selected from the group consisting of H, C₁₋₄ alkyl and C₁₋₄
93 haloalkyl;
94 each m is independently 0, 1, 2, 3 or 4;
95 each R^{6b} and R^{6b'} is independently selected from the group consisting of F, C₁₋₄ alkyl, and C₁₋₄
96 haloalkyl.

1 2. A compound of claim 1, wherein said compound is represented by
2 Formula (I).

1 3. A compound of claim 1, wherein said compound is represented by
2 Formula (II).

1 4. A compound of claim 1, wherein Y and Y' are each independently
2 selected from the group consisting of O and NH.

1 5. A compound of claim 1, wherein Y and Y' are each O.

- 1 **6.** A compound of any one of claims **2** or **3**, wherein each subscript n is
2 independently 0 or 1.
- 1 **7.** A compound of any one of claims **2** or **3**, wherein each subscript m is
2 independently 0 or 1.
- 1 **8.** A compound of any one of claims **2** or **3**, wherein each subscript m is
2 independently 0 or 1 and each subscript n is independently 0 or 1.
- 1 **9.** A compound of any one of claims **2** or **3**, wherein each R³ and R^{3'} is
2 independently a 4- to 9-membered monocyclic or spirocyclic non-aromatic heterocyclic ring,
3 optionally substituted with 1 to 4 R^{3a}.
- 1 **10.** A compound of any one of claims **2** or **3**, wherein each R³ and R^{3'} is
2 independently -NR^dR^e.
- 1 **11.** A compound of any one of claims **2** or **3**, wherein R³ and R^{3'} are each
2 -NR^dR^e and R^e combined with the N to which it is attached is a natural or non-natural amino
3 acid, wherein the non-natural amino acids have an alpha carbon substituent selected from the
4 group consisting of C₂₋₄ hydroxyalkyl and C₁₋₃ alkyl-guanidiny, and wherein the alpha carbon of
5 each natural or non-natural amino acid is optionally further substituted with a methyl group, and
6 the terminal moiety is selected from the group consisting of C(O)OH, C(O)O-C₁₋₆ alkyl, and
7 C(O)NH₂.
- 1 **12.** A compound of any one of claims **2** or **3**, wherein R³ and R^{3'} are each
2 -NR^dR^e and R^e combined with the N to which it is attached is a natural or non-natural amino
3 acid, wherein the non-natural amino acids have a C₂₋₄ hydroxyalkyl alpha carbon wherein the
4 alpha carbon of each natural or non-natural amino acid is further substituted with a methyl group,
5 and the terminal moiety is selected from the group consisting of C(O)OH, C(O)O-C₁₋₄ alkyl, and
6 C(O)NH₂.
- 1 **13.** A compound of any one of claims **2** or **3**, wherein each R^{2a}, R^{2b}, R^{2c}, R^{2a'},
2 R^{2b'} and R^{2c'} is independently selected from the group consisting of H, halogen, -CN, -R^a,

3 -CO₂R^b, -CONR^bR^c, -NR^bR^c, and -OR^b; wherein each R^b and R^c is independently selected from
4 hydrogen, C₁₋₈ alkyl, and C₁₋₈ haloalkyl, or when attached to the same nitrogen atom can be
5 combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2
6 additional heteroatoms as ring members selected from N, O and S, and optionally substituted
7 with oxo; each R^a is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl,
8 and C₁₋₈ haloalkyl.

1 14. A compound of claim 3, wherein R¹ is H, halogen, CN or C₁₋₄ alkyl.

1 15. A compound of any one of claims 2 or 3, wherein each R⁴ and R^{4'} is
2 independently selected from the group consisting of O-C₁₋₈ alkyl, O-C₁₋₈ haloalkyl, -O-C₁₋₄ alkyl-
3 C₆₋₁₀aryl and -O-C₁₋₄ alkyl-C₅₋₁₀ heteroaryl, each of which is optionally substituted with 1 to 5
4 R^{4a}.

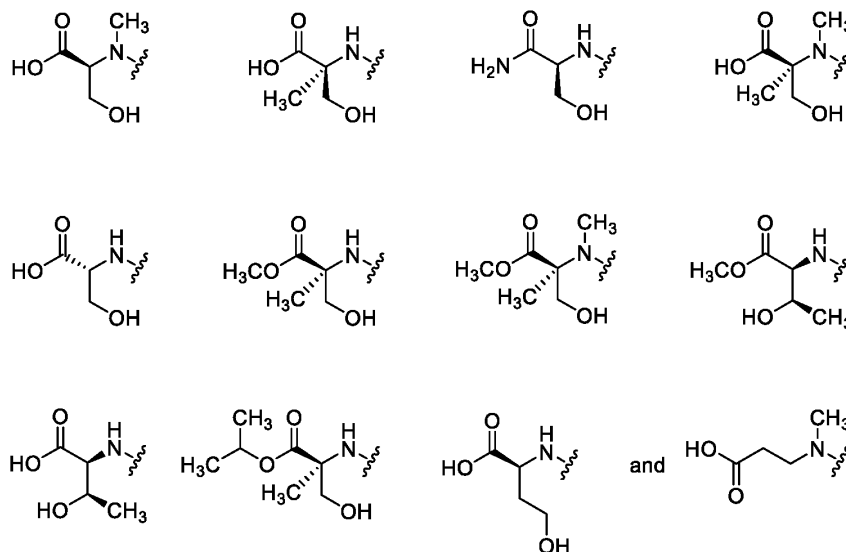
1 16. A compound of any one of claims 2 or 3, wherein each R⁴ and R^{4'} is
2 independently selected from the group consisting of O-C₁₋₈ alkyl, -O-C₁₋₄ alkyl-phenyl and -O-
3 C₁₋₄ alkyl-pyridyl, each of which is optionally substituted with 1 to 3 R^{4a}.

1 17. A compound of any one of claims 2 or 3, wherein each R^{2a}, R^{2b}, R^{2c}, R^{2a'},
2 R^{2b'} and R^{2c'} is independently selected from the group consisting of H, halogen, -CN, -R^a,
3 -CO₂R^b, -CONR^bR^c, -NR^bR^c, and -OR^b; wherein each R^b and R^c is independently selected from
4 hydrogen, C₁₋₈ alkyl, and C₁₋₈ haloalkyl, or when attached to the same nitrogen atom can be
5 combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2
6 additional heteroatoms as ring members selected from N, O and S, and optionally substituted
7 with oxo; each R^a is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl,
8 and C₁₋₈ haloalkyl; each R³ is a 4- to 9-membered monocyclic or spirocyclic non-aromatic
9 heterocyclic ring, optionally substituted with 1 to 4 R^{3a}; and each R⁴ is selected from the group
10 consisting of O-C₁₋₈ alkyl, -O-C₁₋₄ alkyl-phenyl and -O-C₁₋₄ alkyl-pyridyl, each of which is
11 optionally substituted with 1 to 3 R^{4a}.

1 18. A compound of any one of claims 2 or 3, wherein each R^{2a}, R^{2b}, R^{2c}, R^{2a'},
2 R^{2b'} and R^{2c'} is independently selected from the group consisting of H, halogen, -CN, -R^a,
3 -CO₂R^b, -CONR^bR^c, -NR^bR^c, and -OR^b; wherein each R^b and R^c is independently selected from

hydrogen, C₁₋₈ alkyl, and C₁₋₈ haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O and S, and optionally substituted with oxo; each R^a is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, and C₁₋₈ haloalkyl; each R³ is -NR^dR^e and R^e combined with the N to which it is attached is a natural or non-natural amino acid, wherein the non-natural amino acids have an alpha carbon substituent selected from the group consisting of C₂₋₄ hydroxyalkyl and C₁₋₃ alkyl-guanidiny, and wherein the alpha carbon of each natural or non-natural amino acid is optionally further substituted with a methyl group, and the terminal moiety is selected from the group consisting of C(O)OH, C(O)O-C₁₋₆ alkyl, and C(O)NH₂; and each R⁴ is selected from the group consisting of O-C₁₋₈ alkyl, -O-C₁₋₄ alkyl-phenyl and -O-C₁₋₄ alkyl-pyridyl, each of which is optionally substituted with 1 to 3 R^{4a}.

19. A compound of claim 1 or claim 18, wherein each R³ and R^{3'} is independently selected from the group consisting of



3

20. A compound of claim 1, selected from the compounds of Table 1 having ++ or +++ activity.

- 1 **21.** A compound of any one of claims **1** to **20**, or a pharmaceutically
2 acceptable salt thereof, wherein the compound is an optically pure or enriched isomer.
- 1 **22.** A pharmaceutical composition comprising a compound of any one of
2 claims **1** to **21**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable
3 excipient.
- 1 **23.** The pharmaceutical composition of claim **22**, further comprising one or
2 more additional therapeutic agents.
- 1 **24.** The pharmaceutical composition of claim **23**, wherein the one or more
2 additional therapeutic agent is selected from the group consisting of an antimicrobial agent, an
3 antiviral agent, a cytotoxic agent, a gene expression modulatory agent, a chemotherapeutic agent,
4 an anti-cancer agent, an anti-angiogenic agent, an immunotherapeutic agent, an anti-hormonal
5 agent, an anti-fibrotic agent, radiotherapy, a radiotherapeutic agent, an anti-neoplastic agent, and
6 an anti-proliferation agent.
- 1 **25.** A method of modulating an immune response mediated by the PD-1
2 signaling pathway in a subject, comprising administering to the subject a therapeutically
3 effective amount of a compound of any one of claims **1** to **21**, or a pharmaceutically acceptable
4 salt thereof or a composition of any one of claims **22** to **24**.
- 1 **26.** A method of enhancing, stimulating, modulating and/or increasing the
2 immune response in a subject in need thereof, comprising administering to the subject a
3 therapeutically effective amount of a compound of any one of claims **1** to **21**, or a
4 pharmaceutically acceptable salt thereof or a composition of any one of claims **22** to **24**.
- 1 **27.** A method of inhibiting growth, proliferation, or metastasis of cancer cells
2 in a subject in need thereof, comprising administering to the subject a therapeutically effective
3 amount of a compound of any one of claims **1** to **21**, or a pharmaceutically acceptable salt
4 thereof or a composition of any one of claims **22** to **24**.

1 **28.** A method of treating a subject suffering from or susceptible to a disease or
2 disorder mediated by the PD-1 signaling pathway, comprising administering to the subject a
3 therapeutically effective amount of a compound of any one of claims **1** to **21**, or a
4 pharmaceutically acceptable salt thereof or a composition of any one of claims **22** to **24**.

1 **29.** The method of any one of claims **25** to **28**, wherein the subject suffers
2 from a disease or disorder selected from the group consisting of an infectious disease, a bacterial
3 infectious disease, a viral infectious disease a fungal infectious disease, a solid tumor, a
4 hematological malignancy, an immune disorder, an inflammatory disease, and cancer.

1 **30.** The method of claim **28**, wherein the disease or disorder is selected from
2 the group consisting of melanoma, glioblastoma, esophagus tumor, nasopharyngeal carcinoma,
3 uveal melanoma, lymphoma, lymphocytic lymphoma, primary CNS lymphoma, T-cell
4 lymphoma, diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, prostate
5 cancer, castration-resistant prostate cancer, chronic myelocytic leukemia, Kaposi's sarcoma
6 fibrosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma,
7 lymphangiosarcoma, synovioma, , meningioma, leiomyosarcoma, rhabdomyosarcoma, sarcoma
8 of soft tissue, sarcoma, sepsis, biliary tumor, basal cell carcinoma, thymus neoplasm, cancer of
9 the thyroid gland, cancer of the parathyroid gland, uterine cancer, cancer of the adrenal gland,
10 liver infection, Merkel cell carcinoma, nerve tumor, follicle center lymphoma, colon cancer,
11 Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, chronic or acute leukemias including
12 acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic
13 lymphocytic leukemia, multiple myeloma, ovary tumor, myelodysplastic syndrome, cutaneous or
14 intraocular malignant melanoma, renal cell carcinoma, small-cell lung cancer, lung cancer,
15 mesothelioma, breast cancer, squamous non-small cell lung cancer (SCLC), non-squamous
16 NSCLC, colorectal cancer, ovarian cancer, gastric cancer, hepatocellular carcinoma, pancreatic
17 carcinoma, pancreatic cancer, Pancreatic ductal adenocarcinoma, squamous cell carcinoma of the
18 head and neck, cancer of the head or neck, gastrointestinal tract, stomach cancer, HIV, Hepatitis
19 A, Hepatitis B, Hepatitis C, Hepatitis D, herpes viruses, papillomaviruses, influenza, bone
20 cancer, skin cancer, rectal cancer, cancer of the anal region, testicular cancer, carcinoma of the
21 fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the

22 vagina, carcinoma of the vulva, cancer of the esophagus, cancer of the small intestine, cancer of
23 the endocrine system, cancer of the urethra, cancer of the penis, cancer of the bladder, cancer of
24 the kidney, cancer of the ureter, carcinoma of the renal pelvis, neoplasm of the central nervous
25 system (CNS), tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma,
26 epidermoid cancer, abestosis, carcinoma, adenocarcinoma, papillary carcinoma,
27 cystadenocarcinoma, bronchogenic carcinoma, renal cell carcinoma, transitional cell carcinoma,
28 choriocarcinoma, seminoma, embryonal carcinoma, wilm's tumor, pleomorphic adenoma, liver
29 cell papilloma, renal tubular adenoma, cystadenoma, papilloma, adenoma, leiomyoma,
30 rhabdomyoma, hemangioma, lymphangioma, osteoma, chondroma, lipoma and fibroma.

1 **31.** The method of any one of claims **25** to **30**, further comprising
2 administering to the subject a therapeutically effective amount of one or more additional
3 therapeutic agents.

1 **32.** The method of claim **31**, wherein the one or more additional therapeutic
2 agents is selected from the group consisting of an antimicrobial agent, an antiviral agent, a
3 cytotoxic agent, a gene expression modulatory agent, a chemotherapeutic agent, an anti-cancer
4 agent, an anti-angiogenic agent, an immunotherapeutic agent, an anti-hormonal agent, an anti-
5 fibrotic agent, radiotherapy, a radiotherapeutic agent, an anti-neoplastic agent, and an anti-
6 proliferation agent.