

WHAT IS CLAIMED:

1. A method of treating cancer in a subject, comprising administering a surface functionalized particle alone or in combination with a cancer therapeutic, wherein the subject has one or more immune evasive tumors.
- 5 2. A method for treating an immune-evasive tumor in a subject, comprising
(i) diagnosing the subject as having an immune-evasive tumor, and (ii) administering surface functionalized particles to the subject alone or in combination with a cancer therapeutic.
- 10 3. The method of claim 2, wherein the diagnosing comprises assaying biomarkers/characteristics associated with an immune-evasive tumor, microsatellite stability/instability, tumor mutational burden, resistance to therapy, tumor heterogeneity, or combinations thereof.
- 15 4. The method of claim 2 or 3, further comprising (iii) determining if the subject's tumor becomes immune responsive, and then (iv) administering surface functionalized particles in combination with an immunotherapy.
- 20 5. A method for treating a subject having cancer and who had previously received immunotherapy or in which the cancer is refractory to immunotherapy, comprising administering to the subject a surface functionalized particle alone or in combination with a cancer therapeutic.
- 25 6. The method of any one of the preceding claims wherein the particle comprises are polyglycolic acid (PGA) polymers, polylactic acid (PLA), poly (lactic-co-glycolic acid) (PLGA), polystyrene, chitosan, polysaccharide, one or more lipids, diamond, or iron, zinc, cadmium, gold, or silver.
- 30 7. The method of any one of the preceding claims, wherein the surface functionalized particles are poly (lactic-co-glycolic acid) (PLGA) particles.
8. The method of claim 7, wherein the particle comprises polylactic acid: poly glycolic acid ratio from about 1:99 to about 99:1.
9. The method of claim 8, wherein the particle comprises about 50:50, about 80:20 to about 100:0 poly lactic acid: poly glycolic acid or from about 50:50, about 80:20 to about 100:0 poly glycolic acid: poly lactic acid.
10. The method of any one of the preceding claims, wherein the particle comprises 50:50 poly lactic acid: poly glycolic acid.

11. The method of any one of the preceding claims, wherein the particle is surface functionalized by the addition of one or more carboxyl groups.
12. The method of any one of the preceding claims, wherein the particle is a negatively charged particle.
- 5 13. The method of claim 12, wherein the particle is free from therapeutic agents.
14. The method of claim 12 or 13, wherein the particle is free from attached peptide or antigenic moieties or other bioactive agents.
15. The method of any one of the preceding claims, wherein the particle has a zeta potential between -100 mV and -1 mV.
- 10 16. The method of any one of the preceding claims, wherein the particle has a zeta potential between -80 mV and -30 mV.
17. The method of any one of the preceding claims, wherein the diameter of the surface functionalized surface is between 0.1 μm to 10 μm .
18. The method of any one of the preceding claims, wherein the diameter of the surface functionalized particle is between 400 nm to 800 nm.
- 15 19. The method of any one of claims 1-18 wherein the surface functionalized particle and/or cancer therapeutic are administered in a composition.
20. The method of claim 19 wherein the composition comprises a pharmaceutically acceptable excipient, diluent or carrier.
- 20 21. The method of any one of the preceding claims, wherein the subject has one or more immunologically cold tumors.
22. The method of any one of the preceding claims, wherein the subject has one or more tumors with a low tumor mutational burden.
23. The method of any one of the preceding claims, wherein the subject has one or more microsatellite stable tumors.
- 25 24. The method of any one of the preceding claims, wherein the subject has one or more tumors with low microsatellite instability.
25. The method of any one of the preceding claims wherein the subject has one or more tumors with a low tumor immune infiltrate.
- 30 26. The method of any one of the preceding claims, wherein the administering alters the tumor immune infiltrate.

27. The method of claim 25 or 26, wherein the tumor immune infiltrate comprises antigen-presenting cells, myeloid cells, and lymphoid cells.
28. The method of claim 27, wherein the antigen presenting cells comprise macrophages and/or dendritic cells.
- 5 29. The method of claim 27, wherein myeloid cells comprise monocytes, neutrophils, myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs).
30. The method of claim 29, wherein the tumor-associated macrophages comprise M1 macrophages, M2 macrophages, and/or MARCO+ macrophages.
- 10 31. The method of claim 27, wherein lymphoid cells comprise T-cells, B-cells, NK T-cells, and NK cells.
32. The method of any one of the preceding claims, wherein the administering alters the anti-tumor immune response.
33. The method of any one of the preceding claims, wherein the administering
15 alters the tumor microenvironment.
34. The method of claim 33, wherein the tumor microenvironment comprises tumor cells, cancer stem cells, immune cells, and stroma.
35. The method of claim 34, wherein the stroma comprises fibroblasts, adipocytes, endothelium, vasculature, mesenchymal stromal cells, and/or extracellular
20 matrix.
36. The method of any one of the preceding claims, wherein the administering transforms an immunologically cold tumor into an immunologically hot tumor.
37. The method of any one of the preceding claims, wherein the administering reduces tumor size and/or inhibits tumor growth.
- 25 38. The method of any one of the preceding claims, wherein the subject has a cancer selected from the group consisting of brain cancer, skin cancer, eye cancer, breast cancer, prostate cancer, pancreatic cancer, lung cancer, esophageal cancer, head and neck cancer, cervical cancer, liver cancer, colorectal cancer, bone cancer, uterine cancer, ovarian cancer, bladder cancer, endometrial cancer, stomach cancer, gastric cancer, oral cancer,
30 thyroid cancer, kidney cancer, testicular cancer, leukemia, lymphoma, and mesothelioma.
39. The method of any one of the preceding claims, wherein the cancer therapeutic administered in combination with the particle is a chemotherapeutic selected from the group consisting of growth inhibitors, DNA-replication inhibitors, kinase inhibitors,

receptor tyrosine kinase inhibitors, signaling cascade inhibitors, angiogenesis inhibitors, metabolic inhibitors, amino acid synthesis inhibitors, selective inhibitors of oncogenic proteins, inhibitors of metastasis, inhibitors of anti-apoptosis factors, apoptosis inducers, enzyme inhibitors, nucleoside signaling inhibitors, antibody-drug conjugates, and DNA-damaging agents.

40. The method of any one of claims 1-38, wherein the cancer therapeutic administered in combination with the particle comprises one or more biologic agents selected from the group consisting of cytokines, angiogenesis inhibitors, receptor tyrosine kinase inhibitors, immune checkpoint modulators enzymes, and, monoclonal antibodies.

41. The method of claim 40, wherein the cytokines are selected from the group consisting of transforming growth factors, tumor necrosis factor, interferons and interleukins.

42. The method of claim 40, wherein the immune checkpoint modulators target Programmed cell death protein 1 (PD1), Programmed cell death protein ligand-1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), T cell Immunoglobulin and Mucin-domain containing-3 (TIM-3), Lymphocyte-activation Gene-3 (LAG-3) and/or TIGIT (T cell immunoreceptor with Ig and ITIM domains).

43. The method of claim 42, wherein the immune checkpoint modulator is an antibody selected from the group consisting of ipilimumab, Tremelimumab, Pembrolizumab, Nivolumab, Atezolizumab, Avelumab, Cemiplimab and Durvalumab.

44. The method of claim 40, wherein the monoclonal antibody comprises a mono-specific, bi-specific, or tri-specific antibody.

45. The method of claim 40, wherein the monoclonal antibody comprises a bi-specific T-cell engager (BiTE).

46. The method of claim 40, wherein the monoclonal antibody is selected from the group comprising Alemtuzumab, Bevacizumab, Brentuximab, Cetuximab, Denosumab, Ibritumomab, Trastuzumab, Panitumumab, Pertuzumab, and Rituximab.

47. The method of claims 1-38, wherein the cancer therapeutic administered in combination with the particle comprises one or more cell-based therapies selected from the group consisting of adoptive cell transfer, tumor-infiltrating leukocyte therapy, chimeric antigen receptor T-cell therapy (CAR-T), NK-cell therapy and stem cell therapy.

48. The method of any one of claims 1-38, wherein the cancer therapeutic administered in combination with the particle is a hormone therapy.

49. The method of any one of claims 1-38, wherein the cancer therapeutic administered in combination with the particle comprises one or more cancer vaccines.

50. The method of any one of claims 1-38, wherein the cancer therapeutic administered in combination with the particle is one or more immunotherapies comprising
5 oncolytic virus, oncolytic bacteria or other bacterial compositions, Bacillus Calmette-Guerin (BCG), microbiome modulator, STING pathway modulator, and/or toll-like receptor (TLR) modulator.

51. A method of treating cancer in a subject comprising the steps of:

- a. determining the immunologic status of the tumor and/or the tumor mutational
10 burden and/or microsatellite instability status of the tumor;
- b. diagnosing the tumor to be immunologically protected and/or immunologically cold and/or having a low tumor immune infiltrate and/or having a low tumor mutational burden and/or as microsatellite stable and/or refractory; and
- c. administering surface functionalized particles alone or in combination with a
15 cancer therapeutic.

52. The method of any one of the preceding claims wherein the particle and/or the cancer therapeutic is administered once daily, twice daily, three times per day, seven times per week, six times per week, five times per week, four times per week, three times per week, twice weekly, once weekly, once every two weeks, once every three weeks, once
20 every 4 weeks, once every two months, once every three months, once every 6 months or once per year.

53. The method of any one of the preceding claims, wherein the particles are administered intravenously, orally, nasally, intramuscularly, ocularly, transdermally, or subcutaneously.

25 54. The method of any one of the preceding claims, wherein the subject is human.

55. The method of any one of the preceding claims wherein the administration improves one or more symptoms of the cancer.

56. The method of any one of the preceding claims, wherein the surface
30 functionalized particle is a negatively charged particle free from attached peptide or antigenic moieties or other bioactive agents.

57. The method of claim 56, wherein the particle is a PLGA particle having a zeta potential between -80 to -30 mV and a diameter between 200 and 2000 nm.