and/or combination chemotherapy) and second-line (e.g., anti-PD-1/L1) treatment or are unresponsive altogether. Common features of such tumors are that they are immunologically ‘cold’, immunologically protected, contain anti-inflammatory and immune suppressive mediators in the TME, harbor a low TMB, or are microsatellite stable (MSS)/MSI-low. Tumor heterogeneity further complicates treatment as therapeutically unresponsive tumors are often composed of heterogeneous populations of tumor cells that exhibit varying degrees of factors (e.g., immune infiltrate, TMB, and MSI) that play a role in determining response to therapy (28,29).

SUMMARY

[0006a] In an aspect of the present disclosure, there is provided a use of a surface functionalized particle alone or in combination with a cancer therapeutic in the manufacture of a medicament for treating cancer in a subject, wherein the subject has one or more immune evasive tumors.

[0006b] In another aspect of the present disclosure, there is provided a use of surface functionalized particles alone or in combination with a cancer therapeutic in the manufacture of a medicament for a method for treating an immune-evasive tumor in a subject, the method comprising

(i) diagnosing the subject as having an immune-evasive tumor, and subsequently (ii) surface functionalized particles are to be administered to the subject alone or in combination with a cancer therapeutic.

[0006c] In a further aspect of the present disclosure, there is provided a use of a surface functionalized particle alone or in combination with a cancer therapeutic in the manufacture of a medicament for treating a subject having cancer and who had previously received immunotherapy or in which the cancer is refractory to immunotherapy.

[0006d] In another aspect of the present disclosure, there is provided a use of surface functionalized particles alone or in combination with a cancer therapeutic in the manufacture of a medicament for amethod of treating cancer in a subject, the method comprising the steps of:

a. determining the immunologic status of the tumor and/or the tumor mutational 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. subsequently surface functionalized particles alone or in combination with a cancer therapeutic are to be administered.

[0007] It is demonstrated herein that surface-functionalized nanoparticles (SFPs) are efficacious against tumors that are immunologically 'cold', immune evasive, immunologically protected, immunologically 'cold', microsatellite stable ("MSS"), microsatellite instability low ("MSI"), have a low immune infiltrate, have a low tumor mutational burden and/or exhibit heterogeneity. For example, without limitation, such tumors may harbor a low TMB, are MSS/MSI-low, and/or exhibit cellular and molecular factors in the TME that are anti-inflammatory or immune suppressive. SFPs can inhibit tumor growth and induce tumor cell death. SFPs, administered alone or in combination with other cancer therapeutics, can be used as an effective treatment option for a wide variety of cancers. In fact, as described herein, the SFPs are not limited to cancer type, and can be used to treat any cancer that may be characterized as immunologically 'cold', immune evasive, immunologically protected, immunologically 'cold', microsatellite stable, microsatellite instability low, have a low immune infiltrate, have a low tumor mutational burden and/or exhibit heterogeneity, or combinations thereof.

[0008] In various ~~embodiment~~examples, the present disclosure provides a method of treating cancer in a subject comprising administering to the subject surface functionalized particles alone or in combination with a cancer therapeutic, wherein the subject has one or more tumors that are characterized as immune evasive, immunologically protected, immunologically 'cold', microsatellite stable, microsatellite instability low, comprising a low immune infiltrate, comprising a low tumor mutational burden and/or exhibiting heterogeneity.

[0009] In various ~~embodiment~~examples, the surface functionalized particle is a negatively charged particle free from attached peptide or antigenic moieties or other bioactive agents.

[0010] In various ~~embodiment~~examples, the present disclosure provides a method of treating cancer in subject comprising administering to the subject a surface functionalized particle alone or in combination with a cancer therapeutic, wherein the subject has one or more tumors with a

low immune infiltrate. In various ~~embodiment~~examples, the administering to a subject with one or more tumors with a low immune infiltrate alters the tumor immune infiltrate. In various ~~embodiment~~examples, the tumor immune infiltrate comprises antigen-presenting cells, myeloid cells, and lymphoid cell. In various ~~embodiment~~examples, antigen-presenting cells in the tumor immune infiltrate comprise macrophages and/or dendritic cells. In various ~~embodiment~~examples, myeloid cells in the tumor immune infiltrate comprise monocytes, neutrophils, myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs). In various ~~embodiment~~examples, the TAMs in the tumor immune infiltrate comprise M1 macrophages, M2 macrophages, and $MARCO^+$ macrophages. In various ~~embodiment~~examples, lymphoid cells in the tumor immune infiltrate comprise T-cells, B-cells, NK T-cells, and NK cells.

[0011] In various ~~embodiment~~examples, the present disclosure provides a method of treating cancer in a subject comprising administering to the subject surface functionalized particles alone or in combination with a cancer therapeutic, wherein the subject has one or more immune evasive tumors. In various ~~embodiment~~examples, the subject has one or more immunologically protected tumors. In various ~~embodiment~~examples, the subject has one or more microsatellite stable tumors. In various ~~embodiment~~examples, the subject has one or more microsatellite low tumors. In various ~~embodiment~~examples, the subject has one or more tumors with moderate microsatellite instability. In various ~~embodiment~~examples, the subject has one or more tumors with a low tumor mutational burden. In various ~~embodiment~~examples, the subject has one or more tumors with a moderate tumor mutational burden. In various ~~embodiment~~examples, the subject has one or more tumors resistant to therapy. In various ~~embodiment~~examples, the subject has one or more immunologically heterogeneous tumors. In various ~~embodiment~~examples, the subject has genetically heterogeneous tumors. In various ~~embodiment~~examples, the subject has one or more refractory tumors. In one or more ~~embodiment~~examples, the subject has a tumor that develops resistance therapy during the course of treatment.

[0012] In various ~~embodiment~~examples, the present disclosure provides a method of treating cancer in a subject comprising administering to the subject surface functionalized particles alone or in combination with a cancer therapeutic, wherein the subject has one or more immune evasive tumors. In various ~~embodiment~~examples, the administering alters the tumor immune infiltrate. In various ~~embodiment~~examples, the administering alters the anti-tumor immune response. In various ~~embodiment~~examples, the administering alters the tumor microenvironment comprising tumor cells, immune cells, cancer stem cells, and stroma. In various ~~embodiment~~examples, the administering transforms an immunologically cold tumor into an immunologically hot tumor. In various ~~embodiment~~examples, the administering reduces tumor size and/or inhibits tumor growth. In various ~~embodiment~~examples, the administering induces tumor cell death, apoptosis, and/or necrosis via direct particle uptake by tumor cells.

[0013] In various ~~embodiment~~examples, the present disclosure provides a method of treating cancer in a subject comprising administering to the subject surface functionalized particles alone or in combination with a cancer therapeutic, wherein the subject has one or more tumors that are characterized as immunologically protected and/or immune evasive. In various ~~embodiment~~examples, the administering alters the tumor-associated stroma comprising fibroblasts, cancer-associated fibroblasts, adipocytes, pericytes, endothelium, vasculature, lymphatic vessels, tumor-associated vasculature, mesenchymal stromal cells, mesenchymal stem cells, and extracellular matrix.

[0014] In various ~~embodiment~~examples, the surface functionalized particles are polyglycolic acid (PGA),particles, polylactic acid (PLA) particles, poly (lactic-co-glycolic acid) (PLGA) particles, polystyrene particles, diamond particles, or iron, zinc, cadmium, gold, or silver particles, or combinations thereof.

[0015] In some ~~embodiment~~examples, the surface functionalized particles are poly(lactic-co-glycolic acid) (PLGA) particles. In various ~~embodiment~~examples, the particle comprises about 50:50, about 80:20 to about 100:0 polylactic acid: polyglycolic acid or from about 50:50, about 80:20 to about 100:0 polyglycolic acid: polylactic acid. In various ~~embodiment~~examples, the particle comprises 50:50 polylactic acid: polyglycolic acid. In various ~~embodiment~~examples, the particle comprises polylactic acid: polyglycolic acid from about 99:1 to about 1:99, e.g., about 99:1, about 95:5, about 90:10, about 85:15, about 80:20, about 75:25, about 70:30, about 65:35, about 60:40, about 55:45, about 50:50, about 45:55, about 40:60, about 35:65, about 30:70, about 25:75, about 20:80, about 15:85, about 10:90, about 5:95, and about 1:99, including all values and ranges that lie in between these values.

[0016] In various ~~embodiment~~examples, surface functionalization is achieved by carboxylation. Carboxylation can produce a negative charge on an otherwise neutral particle, or it can increase the negative charge of negatively charged particle. Without being bound by theory, carboxylation produces negatively charged surface, and this negative charge elicits therapeutic response in immune-evasive tumors. In some ~~embodiment~~examples, the surface functionalized particles do not comprise a therapeutic agent, such as an embedded or attached cancer therapeutic. In further ~~embodiment~~examples, surface functionalized is achieved by the addition of targeting agents. In some ~~embodiment~~examples, the targeting agent comprises polypeptides, antibodies, carbohydrates, nucleic acids, lipids, small molecules, and surfactants. In various ~~embodiment~~examples, surface functionalized nanoparticles are targeted preferentially to monocytes, neutrophils, macrophages, T-cells, B-cells, NK cells, NK T-cells, fibroblasts, cancer associated fibroblasts, endothelial cells, adipocytes, pericytes, endothelium, vasculature, lymphatic vessels, tumor-associated vasculature, mesenchymal stromal cells, mesenchymal stem cells, and/or extracellular matrix.

[0017] In various ~~embodiment~~examples, the particles have a zeta potential between -100 mV and -1 mV. In various ~~embodiment~~examples, the particles have a zeta potential between -80 mV and -30 mV. In some ~~embodiment~~examples, the zeta potential of the particle is from about -100 mV to about -40 mV, from about -75 mV to about -40 mV, from about -70 mV to about -30 mV, from about -60 mV to about -35 mV, or from about -50 mV to about -40 mV. In various ~~embodiment~~examples, the zeta potential is about -30 mV, -35 mV, -40 mV, -45 mV, -50 mV, -55 mV, -60 mV, -65 mV, -70 mV, -75 mV, -80 mV, -85 mV, -90 mV, -95 mV or -100 mV, including all values and ranges that lie in between these values.

[0018] In various ~~embodiment~~examples, the diameter of the negatively charged particle is between 0.1 µm to 10 µm. In various ~~embodiment~~examples, the particle has an average diameter of between about 0.2 µm and about 2 µm; between about 0.3 µm to about 5 µm; between about 0.5 µm to about 3 µm; or between about 0.5 µm to about 1 µm. In some ~~embodiment~~examples, the particle has a diameter of about 100 to 1500 nm, about 200 and 2000 nm, about 100 to 1000 nm, about 300 to 1000 nm, about 400 to 800 nm, or about 200 to 700 nm. In various ~~embodiment~~examples, the particle has an average diameter of about 100nm, 200 nm, 300 nm, 400nm, 500 nm, 600 nm, 700 nm, 800 nm, 900 nm, 1000 nm, 1100 nm, 1200 nm, 1300 nm, 1400 nm, 1500nm, or 2000 nm, including all values and ranges that lie in between these values. In some ~~embodiment~~examples, the diameter of the negatively charged particle is between 400 nm to 800 nm.

[0019] In various ~~embodiment~~examples, the particle is a PLGA particle having a zeta potential between -80 to -30 mV and a diameter between 200 and 2000 nm, optionally surface functionalized by carboxylation.

[0020] In various ~~embodiment~~examples, the present disclosure provides a method of treating cancer in a subject comprising administering to the subject a composition comprising negatively charged PLGA particles alone or in combination with a cancer therapeutic, wherein said particle does not comprise peptides, antigenic moieties or other bioactive agents has a diameter between 400nm and 800nm and a zeta potential between -1 mV and -100 mV, and wherein the subject has one or more immune evasive tumors.

[0021] In various ~~embodiment~~examples, the subject has a cancer selected from the group consisting of brain cancer, skin cancer, eye cancer, breast cancer, prostate cancer, lung cancer, esophageal cancer, head and neck cancer, cervical cancer, liver cancer, colon cancer, bone cancer, uterine cancer, ovarian cancer, bladder cancer, stomach cancer, oral cancer, thyroid cancer, kidney cancer, testicular cancer, leukemia, lymphoma and mesothelioma. Additional cancers contemplated by the methods are disclosed in the Detailed Description.

[0022] In various ~~embodiment~~examples, the cancer therapeutic is a chemotherapeutic selected from the group consisting of growth inhibitors, DNA-replication inhibitors, 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, nucleoside signaling inhibitors, enzyme inhibitors and DNA-damaging agents.

[0023] In various ~~embodiment~~examples, the cancer therapeutic comprises one or more biologic agents selected from the group consisting of cytokines, angiogenesis inhibitors, immune checkpoint modulators, enzymes and monoclonal antibodies.

[0024] In various ~~embodiment~~examples, cytokines are selected from the group consisting of transforming growth factors, tumor necrosis factor, interferons and interleukins. Exemplary cytokines include, but are not limited to, IFN-alpha, IFN-beta, IFN-gamma, IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-11, IL-12, IL-13, IL-15, IL-17, IL-18, IL-21, members of the transforming growth factor beta superfamily, including TGF-β1, TGF-β2 and TGF-β3, tumor necrosis factor alpha, Granulocyte colony-stimulating factor (G-CSF), and Granulocyte macrophage colony-stimulating factor (GM-CSF).

[0025] In various ~~embodiment~~examples, the cancer therapeutic comprises an enzyme. In various ~~embodiment~~examples, the cancer therapeutic comprises an enzyme that targets T-cells, B-cells, APCs, monocytes, MDSCs, TAMs, neutrophils, other monocyte-derived cells, tumor-associated stroma, cancer stem cells, mesenchymal stem cells, extracellular matrix, and amino acids. In various ~~embodiment~~examples, the cancer therapeutic comprises an enzyme selected from the group comprising asparaginase, kynurininase, L-arginine deiminase, L-methionine-γ-lyase, one or more amino acid degrading enzymes, and one or more nucleoside degrading enzymes.

[0026] In various ~~embodiment~~examples the monoclonal antibodies are mono-specific, bi-specific, tri-specific or bispecific T-cell engaging (BiTE) antibodies.

[0027] In various ~~embodiment~~examples the monoclonal antibodies are immune cell co-stimulatory molecule agonists that induce an anti-tumor immune response. Exemplary co-stimulatory molecules include, but are not limited to, ICOS (Inducible T cell Co-stimulator) (CD278), OX40 (CD134), GITR (Glucocorticoid-induced Tumor Necrosis Factor Receptor), CD40 and CD27.

[0028] In various ~~embodiment~~examples, monoclonal antibodies are selected from the group comprising Alemtuzumab, Bevacizumab, Brentuximab, Cetuximab, Denosumab, Ibritumomab, Trastuzumab, Panitumumab, Pertuzumab, and Rituximab. In various ~~embodiment~~examples, monoclonal antibodies target receptor tyrosine kinase, EGFR, VEGF,

VEGFR, PDGF, PDGFR, TGF-β, TGF-β-LAP, SIRP-α, CD47, CD39, CD73, and fibroblast activation protein (FAP).

[0029] In various ~~embodiment~~examples, 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). In various ~~embodiment~~examples, the immune checkpoint modulator is an antibody selected from the group consisting of ipilimumab, tremelimumab, pembrolizumab, nivolumab, atezolizumab, avelumab, cemiplimab and durvalumab.

[0030] In various ~~embodiment~~examples, the cancer therapeutic 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.

[0031] In various ~~embodiment~~examples the cell-based therapy is the adoptive transfer of autologous patient-derived cells. In various ~~embodiment~~examples the cell-based therapy is the adoptive transfer of allogenic donor-derived cells.

[0032] In various ~~embodiment~~examples, the cell-based therapy is the transfer of universal donor-derived or induced pluripotent stem cell-derived cells that are not patient specific and amenable to long-term storage. Such therapies are also referred to as 'off-the-shelf' therapies.

[0033] In various ~~embodiment~~examples, the cancer therapeutic is a hormone therapy. In various ~~embodiment~~examples, the cancer therapeutic comprises one or more antibody-drug conjugates. In various ~~embodiment~~examples, the cancer therapeutic comprises one or more cancer vaccines. In various ~~embodiment~~examples, the cancer vaccine is a protein, polypeptide, and/or nucleic acid vaccine.

[0034] In various ~~embodiment~~examples, the cancer therapeutic is an immunotherapy selected from the group comprising oncolytic virus, bacteria, oncolytic bacteria or other bacterial consortia, tumor cell lysate, bacterial cell lysate, lipopolysaccharide (LPS), Bacillus Calmette-Guerin (BCG), a microbiome modulator, and/or a toll-like receptor (TLR) agonist. In various ~~embodiment~~examples, the TLR agonist is a TLR3, TLR4, TLR5, TLR7, TLR8, TLR9, TLR10, TLR11, TLR12, and/or TLR13 agonist. In various ~~embodiment~~examples, the TLR agonist is derived from virus, bacteria and/or made synthetically. In various ~~embodiment~~examples, the immunotherapy is a STING pathway modulator.

[0035] In various ~~embodiment~~examples, the cancer therapeutic comprises a viral or a bacterial vector. In various ~~embodiment~~examples, the viral vector is selected from the group comprising adenovirus, adeno-associated virus (AAV), herpes simplex virus, lentivirus, retrovirus, alphavirus, flavivirus, rhabdovirus, measles virus, Newcastle disease virus, poxvirus, vaccinia virus, modified Ankara virus, vesicular stomatitis virus, picornavirus, tobacco mosaic virus, potato virus x, comovirus, or cucumber mosaic virus. In various ~~embodiment~~examples, the virus is an oncolytic virus. In various ~~embodiment~~examples the virus is a chimeric virus, a synthetic virus, a mosaic virus or a pseudotyped virus.

[0036] Additional cancer therapeutics contemplated for use in the methods are set out in the Detailed Description.

[0037] In various ~~embodiment~~examples, the surface functionalized 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 every 4 weeks, once every two months, once every three months, once every 6 months or once per year. In various ~~embodiment~~examples, the surface functionalized particle and/or the cancer therapeutic is administered for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52 weeks, or more.

[0038] In various ~~embodiment~~examples, the particle and/or the cancer therapeutic is administered intravenously, orally, nasally, intramuscularly, ocularly, transdermally, or subcutaneously.

[0039] In various ~~embodiment~~examples, the subject is a mammal. In various ~~embodiment~~examples, the subject is human.

[0040] In various ~~embodiment~~examples, the administration improves one or more symptoms of the cancer or proliferative disorder. In various ~~embodiment~~examples, the one or more symptoms are selected from the group consisting of tumor size or tumor burden in the subject, tumor metastasis, and levels of inflammatory cells in the tumor. In various ~~embodiment~~examples, the administration reduces the tumor size or tumor burden by about 10%, 20%, 30% or more. In various ~~embodiment~~examples, the administration reduces the tumor size or tumor burden by about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90% or about 100%, including all values and ranges in between these values.

[0041] In various ~~embodiment~~examples, the particle is formulated in a composition comprising a pharmaceutical acceptable carrier, diluent or excipient. In various ~~embodiment~~examples, the cancer therapeutic is formulated in a composition comprising a pharmaceutical acceptable carrier,

diluent or excipient. In various ~~embodiment~~examples, the particle and cancer therapeutic can be formulated in the same composition or in separate compositions.

[0042] Also contemplated is a composition comprising any of the foregoing surface functionalized particles or cancer therapeutic compositions of the present disclosure, or use thereof in preparation of a medicament, for treatment of any of the disorders described herein associated with inflammation and cancer and/or proliferative diseases.

[0043] It is understood that each feature or embodiment or example, or combination, described herein is a non-limiting, illustrative example of any of the aspects or examples of the ~~invention~~ present disclosure and, as such, is meant to be combinable with any other feature or embodiment or example, or combination, described herein. For example, where features are described with language such as "various embodiments", "one embodiment", "some embodiments", "certain embodiments", "further embodiment", "specific exemplary embodiments", and/or "another embodiment", "various examples", "one example", "some examples", "certain examples", "further example", "specific exemplary examples", and/or "another example", each of these types of embodiments and examples ~~is a~~are non-limiting examples of a feature that is intended to be combined with any other feature, or combination of features, described herein without having to list every possible combination. Such features or combinations of features apply to any of the aspects or examples of the present disclosure. Where examples of values falling within ranges are disclosed, any of these examples are contemplated as possible endpoints of a range, any and all numeric values between such endpoints are contemplated, and any and all combinations of upper and lower endpoints are envisioned.

BRIEF DESCRIPTION OF THE DRAWINGS

[0044] **Figure 1A-1F** shows efficacy of SFP against immunologically "cold" tumors with low TMB. (**Figure 1A**) Effect of indicated treatments on cell viability in the tumor (n=5). (**Figure 1B**) Effect of indicated treatments on B16F10 tumor growth. Treatments were initiated after palpable tumor formation (Day 0) (n=10). (**Figure 1C**) Effect of indicated treatments, administered after palpable tumor formation (Day 0), on the survival of B16F10 tumor-bearing mice (n=10). (**Figure 1D -1F**) Effects of indicated treatment on the frequencies of MDSCs (**Figure 1D**), TAMs (**Figure 1E**) and NK cells (**Figure 1F**) in the tumors (n=5). One-way ANOVA tests were performed to determine statistical significance (n.s = P>0.5; * = p≤0.05; ** = p≤0.01; **** = p≤0.0001)

[0045] **Figure 2A-2B** shows efficacy of treatment with surface functionalized particles after orthotopic 4T1 tumor inoculation inhibits primary growth. (**Figure 2A**) Tumor volumes were measured throughout the course of the experiment and the growth curves are shown for each treatment group. (**Figure 2B**) Shown are average tumor sizes on Day 21 after tumor inoculation in groups treated with Saline, anti-PD1, or CNP-301. CNP-301 treatment

WHAT IS CLAIMED:

1. Use of a surface functionalized particle alone or in combination with a cancer therapeutic in the manufacture of a medicament for ~~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.

2 Use of surface functionalized particles alone or in combination with a cancer therapeutic in the manufacture of a medicament for a~~A~~ method for treating an immune-evasive tumor in a subject, the method comprising

(i) diagnosing the subject as having an immune-evasive tumor, and subsequently (ii) ~~administering~~ surface functionalized particles are to be administered to the subject alone or in combination with a cancer therapeutic.

3. The ~~method~~ use 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.

4. The ~~method~~ use of claim 2 or 3, the method further comprising (iii) determining if the subject's tumor becomes immune responsive, and then (iv) ~~administering~~ surface functionalized particles in combination with an immunotherapy are to be administered.

5. Use of a surface functionalized particle alone or in combination with a cancer therapeutic in the manufacture of a medicament for ~~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~~.

6. The ~~method~~ use 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.

7. The ~~method~~ use of any one of the preceding claims, wherein the surface functionalized particles are poly (lactic-co-glycolic acid) (PLGA) particles.

8. The ~~method~~ use of claim 7, wherein the particle comprises polylactic acid: poly~~-~~glycolic acid ratio from about 1:99 to about 99:1.

9. The ~~method~~ use 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~~ use of any one of the preceding claims, wherein the particle comprises 50:50 poly lactic acid: poly glycolic acid.

11. The ~~method~~ use 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~~ use of any one of the preceding claims, wherein the particle is a negatively charged particle.

13. The ~~method~~ use of claim 12, wherein the particle is free from therapeutic agents.

14. The ~~method~~ use of claim 12 or 13, wherein the particle is free from attached peptide or antigenic moieties or other bioactive agents.

15. The ~~method~~ use of any one of the preceding claims, wherein the particle has a zeta potential between -100 mV and -1 mV.

16. The ~~method~~ use of any one of the preceding claims, wherein the particle has a zeta potential between -80 mV and -30 mV.

17. The ~~method~~ use 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~~ use of any one of the preceding claims, wherein the diameter of the surface functionalized particle is between 400 nm to 800 nm.

19. The ~~method~~ use of any one of claims 1-18 wherein the surface functionalized particle and/or cancer therapeutic are to be administered in a composition.

20. The ~~method~~ use of claim 19 wherein the composition comprises a pharmaceutically acceptable excipient, diluent or carrier.

21. The ~~method~~ use of any one of the preceding claims, wherein the subject has one or more immunologically cold tumors.

22. The ~~method~~ use of any one of the preceding claims, wherein the subject has one or more tumors with a low tumor mutational burden.

23. The ~~method~~ use of any one of the preceding claims, wherein the subject has one or more microsatellite stable tumors.

24. The ~~method~~ use of any one of the preceding claims, wherein the subject has one or more tumors with low microsatellite instability.

25. The ~~method~~ use of any one of the preceding claims wherein the subject has one or more tumors with a low tumor immune infiltrate.

26. The ~~method~~ use of any one of the preceding claims, wherein the ~~administering~~ administration alters the tumor immune infiltrate.

27. The ~~method~~ use of claim 25 or 26, wherein the tumor immune infiltrate comprises antigen-presenting cells, myeloid cells, and lymphoid cells.

28. The ~~method~~ use of claim 27, wherein the antigen presenting cells comprise macrophages and/or dendritic cells.

29. The ~~method~~ use of claim 27, wherein myeloid cells comprise monocytes, neutrophils, myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs).

30. The ~~method~~ use of claim 29, wherein the tumor-associated macrophages comprise M1 macrophages, M2 macrophages, and/or MARCO+ macrophages.

31. The ~~method~~ use of claim 27, wherein lymphoid cells comprise T-cells, B-cells, NK T-cells, and NK cells.

32. The ~~method~~ use of any one of the preceding claims, wherein the ~~administering~~ administration alters the anti-tumor immune response.

33. The ~~method~~ use of any one of the preceding claims, wherein the ~~administering~~ administration alters the tumor microenvironment.

34. The ~~method~~ use of claim 33, wherein the tumor microenvironment comprises tumor cells, cancer stem cells, immune cells, and stroma.

35. The ~~method~~ use of claim 34, wherein the stroma comprises fibroblasts, adipocytes, endothelium, vasculature, mesenchymal stromal cells, and/or extracellular matrix.

36. The ~~method~~ use of any one of the preceding claims, wherein the ~~administering~~ administration transforms an immunologically cold tumor into an immunologically hot tumor.

37. The ~~method~~ use of any one of the preceding claims, wherein the ~~administering~~ administration reduces tumor size and/or inhibits tumor growth.

38. The ~~method~~ use 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, thyroid cancer, kidney cancer, testicular cancer, leukemia, lymphoma, and mesothelioma.

39. The ~~method~~ use of any one of the preceding claims, wherein the cancer therapeutic is to be 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~~ use of any one of claims 1-38, wherein the cancer therapeutic is to be 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~~ use of claim 40, wherein the cytokines are selected form the group consisting of transforming growth factors, tumor necrosis factor, interferons and interleukins.

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

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

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

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

50. The ~~method~~ use of any one of claims 1-38, wherein the cancer therapeutic is to be administered in combination with the particle is one or more immunotherapies comprising 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. Use of surface functionalized particles alone or in combination with a cancer therapeutic in the manufacture of a medicament for a~~A~~ method of treating cancer in a subject, the method comprising the steps of:

a. determining the immunologic status of the tumor and/or the tumor mutational 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. subsequently ~~administering~~ surface functionalized particles alone or in combination with a cancer therapeutic are to be administered.

52. The ~~method~~ use of any one of the preceding claims wherein the particle and/or the cancer therapeutic is to be 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 every 4 weeks, once every two months, once every three months, once every 6 months or once per year.

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

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

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

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

57. The ~~method~~ use 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.