suggested herein that combination therapies using IMPs and cancer therapeutics that can target both tumor cells and overcome the immunosuppressive tumor microenvironment by targeting MDSCs, TAMs, neutrophils, other monocyte-derived cells, and the tumor-associated stroma may be able to provide enhanced therapeutic benefit compared to monotherapy with cancer therapeutics, such as immune checkpoint inhibitors.

[0008] In various examples, the disclosure provides a method of treating cancer in a subject comprising administering to the subject negatively charged particles in combination with a cancer therapeutic, wherein said particle is free from attached peptide or antigenic moieties or other bioactive agents and wherein the administering alters the population of myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), neutrophils, monocytes, dendritic cells, and/or stroma at the tumor site.

[0008a] In one aspect, the present disclosure refers to use of negatively charged particles in the manufacture of a medicament for use in combinatorial therapy for treating cancer or a proliferative disease in a subject, wherein the particles are biodegradable particles that are ~~is~~ free of associated antigens, peptides, or other bioactive agents,~~from attached peptide or antigenic moieties or other bioactive agents, and~~ wherein the medicament is to be administered in combination with a cancer therapeutic, and wherein the cancer therapeutic is an immune modulator.

[0009] In various examples, the disclosure provides a method of treating cancer in a subject comprising administering to the subject negatively charged particles in combination with a cancer therapeutic, wherein said particle is free from attached peptide or antigenic moieties or other bioactive agents and wherein the administering alters the tumor-associated stroma.

[0010] In various examples, the disclosure provides a method of treating cancer in a subject comprising administering to the subject negatively charged particles in combination with a cancer therapeutic, wherein said particle is free from attached peptide or antigenic moieties or other bioactive agents and wherein the administering alters stromal connective tissue, fibroblasts, endothelium, adipose tissue, extracellular matrix, pericytes, cancer stem cells, mesenchymal stem cells, and/or mesenchymal stromal cells.

[0011] In various examples, the disclosure provides a method of treating cancer in a subject comprising administering to the subject negatively charged particles in combination with a cancer therapeutic, wherein said particle is free from attached peptide or antigenic moieties or other bioactive agents and wherein the administering reduces tumor size and/or tumor growth. In various examples, the administering induces tumor cell death, apoptosis, and/or necrosis via direct particle uptake by tumor cells.

[0012] In various examples, the disclosure provides a method of treating cancer in a subject comprising administering to the subject negatively charged particles in combination with a cancer therapeutic, wherein said particle is free from attached peptide or antigenic moieties or other bioactive agents and wherein the administering regulates the anti-tumor immune response.

WHAT IS CLAIMED:

1. Use of negatively charged particles in the manufacture of a medicament for use in combinatorial therapy for treating cancer or a proliferative disease in a subject, wherein the particles are biodegradable particles that are~~is~~ free of associated antigens, peptides, or other bioactive agents,~~from attached peptide or antigenic moieties or other bioactive agents, and~~ wherein the medicament is to be administered in combination with a cancer therapeutic, and wherein the cancer therapeutic is an immune modulator.

2. The use of claim 1, wherein the medicament alters myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), neutrophils and/or monocytes at the tumor site.

3. The use of claim 1 or claim 2, wherein the medicament reduces tumor size and/or tumor growth in the subject.

4. The use of any one of claims 1 to 3, wherein the medicament regulates the anti-tumor immune response.

5. The use of any one of claims 1 to 4, wherein the medicament alters cancer stem cells and/or mesenchymal stem cells.

6. The use of any one of claims 1 to 5, wherein the medicament alters the tumor-associated stroma.

7. The use of any one of claims 1 to 6, wherein the medicament alters fibroblasts, adipocytes, endothelial cells, mesenchymal stromal cells, and/or the ECM in the tumor-associated stroma.

8. The use of any one of the preceding claims wherein the negatively charged particles comprise ~~are~~ polyglycolic acid ~~polymers~~ (PGA), polylactic acid (PLA), ~~polystyrene particles,~~ or poly (lactic-co-glycolic acid) (PLGA) ~~particles, diamond particles, or iron, zinc, cadmium, gold, or silver particles~~.

9. The use of any one of the preceding claims, wherein the negatively charged particles comprise ~~are~~ poly (lactic-co-glycolic acid) (PLGA) ~~particles~~.

10. The use of claim 8 or 9, wherein the particles comprise~~s~~ from ~~about 50:50, about 80:20 to about~~ 100:0 to 0:100 or from 80:20 to 20:80 polylactic acid:polyglycolic acid ~~or from about 50:50, about 80:20 to about 100:0 polyglycolic acid:polylactic acid~~.

11. The use of any one of the preceding claims, wherein the particles comprises 50:50 polylactic acid:polyglycolic acid.

12. The use of any one of the preceding claims, wherein the particles areis carboxylated.

13. The use of any one of the preceding claims, wherein the particles has have a zeta potential between -100 mV and -1 mV.

14. The use of any one of the preceding claims, wherein the particles has have a zeta potential between -80 mV and -30 mV.

15. The use of any one of the preceding claims, wherein the diameter of the negatively charged particles is between 0.1 μm to 10 μm.

16. The use of any one of the preceding claims, wherein the diameter of the negatively charged particles is between 400 nm to 800 nm.

17. The 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, pancreatic cancer, prostate cancer, lung cancer, esophageal cancer, head and neck cancer, cervical cancer, liver cancer, colon cancer, colorectal cancer, rectal cancer, bone cancer, uterine cancer, ovarian cancer, bladder cancer, stomach cancer, oral cancer, thyroid cancer, kidney cancer, testicular cancer, leukemia, lymphoma and mesothelioma.

18. The use of any one of the preceding claims, wherein 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, enzyme inhibitors, nucleoside signaling inhibitors and DNA-damaging agents.

19. The use of any one of claims 1-17, wherein the immune modulator is a cancer therapeutic comprises one or more biologic agents selected from the group consisting of cytokines, enzymes, angiogenesis inhibitors, immune checkpoint modulators, and or monoclonal antibodyies.

20. The use of claim 19, wherein the cytokines are selected from the group consisting of is a transforming growth factors, tumor necrosis factor, interferons and interleukins.

21. The use of claim 19, wherein the immune checkpoint modulator~~s~~ target~~s~~ 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).

22. The use of claim 21, wherein the immune checkpoint modulator is an antibody selected from the group consisting of ipilimumab, tremelimumab, pembrolizumab, nivolumab, atezolizumab, avelumab,cemiplimab and durvalumab.

23. The use of claim 19, wherein the monoclonal antibody is mono-specific, bi-specific, tri-specific or bi-specific T-cell engager (BiTE).

24. The use of claim 19, wherein the monoclonal antibody ~~comprises~~ is Alemtuzumab, Bevacizumab, Brentuximab, Cetuximab, Denosumab, Ibritumomab, Trastuzumab, Panitumumab, Pertuzumab, ~~and~~ or Rituximab.

25. The use of claim 19, wherein the monoclonal antibody targets receptor tyrosine kinase, EGFR, VEGF, VEGFR, PDGF, PDGFR, TGF-β, TGF-β-LAP, SIRP-α, CD47, CD39, CD73 and/or fibroblast activating protein (FAP).

26. The use of claim 19, wherein the cytokine is a transforming growth factor, tumor necrosis factor, interferon, or interleukin.

27. The use of claim 19, wherein the cytokine is 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, TGF-bI , TGF-82 , TGF-83, tumor necrosis factor alpha, Granulocyte colony-stimulating factor (G-CSF), or Granulocyte macrophage colony- stimulating factor (GM-CSF).

28. The use of claim 19, wherein the enzyme is an enzyme that targets T-cells, B-cells, APCs, macrophages, dendritic cells, monocytes, MDSCs, TAMs, neutrophils, other monocyte-derived cells, tumor-associated stroma, cancer stem cells, mesenchymal stem cells, extracellular matrix, or amino acids or asparaginase, kynurininase, L-arginine deiminase, L- methionine-y-lyase, amino acid degrading enzyme, or nucleoside degrading enzyme.

~~26. The use of any one of claims 1-17, wherein 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.~~

~~27. The use of any one of claims 1-17, wherein the cancer therapeutic is a hormone therapy.~~

~~28. The use of any one of claims 1-17, wherein the cancer therapeutic comprises one or more antibody-drug conjugates.~~

~~29. The use of any one of claims 1-17, wherein the cancer therapeutic comprises one or more cancer vaccines.~~

~~30. The use of any one of claims 1-17, wherein the cancer therapeutic is an immunotherapy comprising oncolytic virus, oncolytic bacteria or other bacterial compositions, Bacillus Calmette-Guerin (BCG), a microbiome modulator, a STING pathway modulator and/or a toll-like receptor (TLR) agonist.~~

29~~31~~. The use of any one of the preceding claims wherein the particles and or the cancer therapeutic is to be administered 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.

30~~2~~. The use of any one of the preceding claims, wherein the particles are to be administered intravenously, orally, nasally, intramuscularly, ocularly, transdermally, or subcutaneously.

31~~3~~. The use of any one of the preceding claims, wherein the subject is human.

32~~4~~. The use of any one of the preceding claims wherein the administration improves one or more symptoms of the cancer of proliferative disorder.

33~~5~~. The use of claim 32~~4~~, wherein 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.

34~~6~~. The use of claim 33~~5~~, wherein the administration reduces the tumor size or tumor burden by 10%, 20%, 30% or more.

35~~7~~. The use of claim 32~~4~~, wherein the administration reduces of the number of monocytes, macrophages, granulocytes and/or neutrophils at the tumor.

36~~8~~. The use of any one of the preceding claims, wherein the particles are~~is~~ formulated in a composition comprising a pharmaceutical acceptable carrier, diluent or excipient.

37~~9~~. The use of any one of the preceding claims, wherein the cancer therapeutic is formulated in a composition comprising a pharmaceutical acceptable carrier, diluent or excipient.