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 poly (lactic-co-glycolic acid) (PLGA) particles in the manufacture of a medicament for use in combinatorial therapy for treating cancer for which an anti-programmed cell death protein (PD-1) antibody is effective in a subject, wherein the negatively charged PLGA particles are free from attached antigens, peptides, or other bioactive agents, wherein the medicament is to be administered in combination with the anti-programmed cell death protein (PD-1) antibody, wherein the cancer is skin cancer, breast cancer, melanoma, pancreatic cancer, prostate cancer, lung cancer, esophageal cancer, head and neck cancer, cervical cancer, liver cancer, colon cancer, colorectal cancer, rectal cancer, uterine cancer, ovarian cancer, bladder cancer, stomach cancer, oral cancer, thyroid cancer, gastrointestinal cancer and kidney cancer.

[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 poly (lactic-co-glycolic acid) (PLGA) particles in the manufacture of a medicament for use in combinatorial therapy for treating cancer for which an anti-programmed cell death protein (PD-1) antibody is effective in a subject, wherein the negatively charged PLGA particles are free from attached antigens, peptides, or other bioactive agents, wherein the medicament is to be administered in combination with the anti-programmed cell death protein (PD-1) antibody, wherein the cancer is skin cancer, breast cancer, melanoma, pancreatic cancer, prostate cancer, lung cancer, esophageal cancer, head and neck cancer, cervical cancer, liver cancer, colon cancer, colorectal cancer, rectal cancer, uterine cancer, ovarian cancer, bladder cancer, stomach cancer, oral cancer, thyroid cancer, gastrointestinal cancer and kidney cancer.
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 PLGA particles comprise from 100:0 to 0:100 or from 80:20 to 20:80 polylactic acid:polyglycolic acid.
9. The use of any one of the preceding claims, wherein the negatively charged PLGA particles comprise 50:50 polylactic acid:polyglycolic acid.

10. The use of any one of the preceding claims, wherein the negatively charged PLGA particles are carboxylated.

11. The use of any one of the preceding claims, wherein the negatively charged PLGA particles have a zeta potential between -100 mV and -1 mV.

12. The use of any one of the preceding claims, wherein the negatively charged PLGA particles have a zeta potential between -80 mV and -30 mV.

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

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

15. The use of any one of the preceding claims, wherein the subject has a cancer selected from the group consisting of skin 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, uterine cancer, ovarian cancer, bladder cancer, stomach cancer, oral cancer, thyroid cancer, and kidney cancer.

16. The use of any one of the preceding claims, wherein the anti-PD-1 antibody targets PD-L1 and PD-L2 binding to the PD-1 receptor.

17. The use of any one of the preceding claims, wherein the anti-PD-1 antibody is a monoclonal antibody.

18. The use of claim 17, wherein the monoclonal antibody is mono-specific, bi-specific, tri-specific or bi-specific T-cell engager (BiTE).

19. The use of any one of the preceding claims, wherein the anti-PD-1 antibody is pembrolizumab or nivolumab.

20. The use of any one of the preceding claims, wherein the negatively charged PLGA 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.

21. The use of any one of the preceding claims, wherein the negatively charged PLGA particles are to be administered intravenously, orally, nasally, intramuscularly, ocularly, transdermally, or subcutaneously.

22. The use of any one of the preceding claims, wherein the subject is human.

23. The use of any one of the preceding claims, wherein the administration improves one or more symptoms of the cancer.

24. The use of claim 23, 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.

25. The use of claim 24, wherein the administration reduces the tumor size or tumor burden by 10%, 20%, 30% or more.

26. The use of claim 25, wherein the administration reduces the number of monocytes, macrophages, granulocytes and/or neutrophils at the tumor.

27. The use of any one of the preceding claims, wherein the negatively charged PLGA particles are formulated in a composition comprising a pharmaceutical acceptable carrier, diluent or excipient.

28. 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.

29. The use of any one of the preceding claims, wherein the subject has lung carcinoma, colon carcinoma, metastatic melanoma, metastatic squamous non-small cell lung cancer (NSCLC), bladder cancer, head and neck cancer, or gastrointestinal cancer.

30. The use of any one of the preceding claims, wherein the subject has lung carcinoma or colon carcinoma.