CLAIMS

1. An extracellular vesicle comprising one or more immunomodulating component(s) that, upon contact with a macrophage, selectively repolarizes the macrophage from an M2 to an M1 phenotype.

2. The extracellular vesicle of claim 1, wherein the one or more immunomodulating component(s) inhibit(s) at least one macrophage target gene.

3. The extracellular vesicle of claim 1 or 2, wherein the extracellular vesicle is an exosome.

4. The extracellular vesicle of any one of claims 1 to 3, wherein the immunomodulating component is a nucleic acid.

5. The extracellular vesicle of claim 4, wherein the nucleic acid is an inhibitory RNA.

6. The extracellular vesicle of claim 5, wherein the inhibitory RNA is an antisense RNA, an siRNA, an shRNA, a miRNA, a lncRNA, a pri-miRNA or a pre-miRNA.

7. The extracellular vesicle of claim 4, wherein the nucleic acid is an antisense oligonucleotide (ASO).

8. The extracellular vesicle of any one of claims 1-7, wherein the immunomodulating component inhibits at least one gene is selected from the group consisting of: KRAS, HRAS, NRAS, HIF1-alpha, HIF1-beta, Sp1, P300, LKB1, AMPK, STAT3, STAT6, n-MYC, c-MYC, HCAR1, A2AB, IDO, TDO, Arginase, Glutaminase, CEBP/β, Pi3Kγ, and PKM2.

9. The extracellular vesicle of claim 8, wherein the at least one gene is selected from the group consisting of: STAT3, STAT6, CEBP/β, Pi3Kγ, KRAS, and HIF1-alpha.

10. The extracellular vesicle of claim 9, wherein the immunomodulating component is an antisense oligonucleotide comprising a sequence at least 95% identical to a sequence selected from SEQ ID NOs:1-6.

11. The extracellular vesicle of claim 10, wherein the immunomodulating component is an antisense oligonucleotide comprising a sequence selected from SEQ ID NOs:1-6.

12. The extracellular vesicle of claim 9, wherein the at least one gene is STAT3.

13. The extracellular vesicle of claim 12, wherein the immunomodulating component is an antisense oligonucleotide that targets STAT3.

14. The extracellular vesicle of claim 9, wherein the at least one gene is KRAS.

15. The extracellular vesicle of claim 14, wherein the immunomodulating component is an inhibitory RNA that targets wild-type human KRAS.

16. The extracellular vesicle of claim 15, wherein the inhibitory RNA also targets mouse $Kras^{G12D}$.

17. The extracellular vesicle of any one of claims 1-16, wherein the macrophage is a tumor resident macrophage.

18. The extracellular vesicle of claim 17, wherein the tumor is a pancreatic tumor.

19. The extracellular vesicle of any one of claims 1-18, further comprising an additional immunomodulating component.

20. The extracellular vesicle of claim 19, wherein the additional immunomodulating component is a small molecule drug, an antibody or active fragment thereof or a therapeutic protein or active fragment thereof.

21. The extracellular vesicle of claim 20, wherein the additional immunomodulating component is an antibody or active fragment thereof.

22. The extracellular vesicle of claim 21, wherein the antibody or active fragment thereof is an immune checkpoint inhibitor that binds to CTLA-4, PD-1, or PD-L1 or an inhibitor that binds to CSF1-R.

23. The extracellular vesicle of claim 22, wherein the antibody or active fragment thereof comprises CDRs that are at least 95% identical to the CDRs of Ipilimumab, or at least 95% identical to the CDRs of Nivolumab, or at least 95% identical to the CDRs of Cemiplimab, or at least 95% identical to the CDRs of Pembrolizumab, or at least 95% identical to the CDRs of Atezolizumab, or at least 95% identical to the CDRs of Avelumab, or at least 95% identical to the CDRs of Durvalumab, or at least 95% identical to the CDRs of Pexidartinib, or at least 95% identical to the CDRs of PLX7486, or at least 95% identical to the CDRs of ARRY-382, or at least 95% identical to the CDRs of JNJ-40346527, or at least 95% identical to the CDRs of BLZ945, or at least 95% identical to the CDRs of Emactuzumab, or at least

95% identical to the CDRs of AMG820, or at least 95% identical to the CDRs of IMC-CS4, or at least 95% identical to the CDRs of Cabiralizumab.

24. The extracellular vesicle of claim 23, wherein the antibody or active fragment thereof is at least one antibody selected from the group consisting of Ipilimumab, Nivolumab, Cemiplimab, Pembrolizumab, Atezolizumab, Avelumab, Durvalumab, Pexidartinib, PLX7486, ARRY-382, JNJ-40346527, BLZ945, Emactuzumab, AMG820, IMC-CS4 and Cabiralizumab.

25. The extracellular vesicle of claim 22, wherein the antibody or active fragment thereof is at least one antibody that competes for binding with antibody selected from the group consisting of Ipilimumab, Nivolumab, Cemiplimab, Pembrolizumab, Atezolizumab, Avelumab, Durvalumab, Pexidartinib, PLX7486, ARRY-382, JNJ-40346527, BLZ945, Emactuzumab, AMG820, IMC-CS4 and Cabiralizumab.

26. The extracellular vesicle of any one of claims 20-25, further comprising PTGFRN or a fragment thereof.

27. The extracellular vesicle of claim 26, wherein the antibody or fragment thereof is fused to the PTGFRN or fragment thereof.

28. The extracellular vesicle of any one of claims 1-27, wherein the comparison is determined using an assay selected from the group consisting of an extracellular vesicle uptake assay, a target gene expression assay, a downstream gene expression assay, a cytokine release assay and a macrophage cell surface protein assay.

29. The extracellular vesicle of any one of the above claims wherein the M2 macrophage is a tumor associated macrophage selected from the group consisting of a M2a, M2b, and M2c macrophage.

30. The extracellular vesicle of any one of the above claims wherein the M1 macrophage exhibits increased secretion of inflammatory cytokines and chemokines selected from the group consisting of INFγ, IL-12, IL-23, TNFα, IL-6, IL-1, CSCL9, CXCL10 and CXCL11 compared to the M2 macrophage prior to polarization.

31. The extracellular vesicle of any one of the above claims wherein the M1 macrophage exhibits decreased secretion of immunosuppressive cytokines and chemokines selected from the group consisting IL-10, TGFβ, PGE2, CCL2, CCL17, CCL18, CCL22 and CCL24 compared to the M2 macrophage prior to polarization.

32. The extracellular vesicle of any one of the above claims wherein the M1 macrophage expresses increased tumor associated antigen compared to the M2 macrophage prior to polarization.

33. The extracellular vesicle of any one of the above claims wherein the M1 macrophage increases stimulation of $CD8^+$ T-Cells and/or Natural Killer cells compared to the M2 macrophage prior to polarization.

34. A pharmaceutical composition comprising the extracellular vesicle of any one of claims 1-33.

35. A method of treating a disease in a patient in need thereof comprising administering the extracellular vesicle of any one of claims 1-33 or the pharmaceutical composition of claim 34 to the patient, thereby treating the disease in the patient.

36. The method of claim 35, wherein the disease is a cancer.

37. The method of claim 35 or 36, wherein the patient is human.

38. The method of claim any one of claims 35-37, wherein the immunomodulating component is an inhibitory RNA targeting a proto-oncogene.

39. The method of claim 38, wherein the proto-oncogene is human KRAS.

40. The method of claim 39, wherein the cancer is pancreatic cancer.

41. The method of any one of claims 35-40, further comprising performing at least a second therapy.

42. The method of claim 41, wherein the second therapy comprises a surgical therapy, chemotherapy, radiation therapy, cryotherapy, hormonal therapy, or immunotherapy.

43. The method of any one of claims 26-33, wherein the administering is via a route selected from the group consisting of intravenous, intraperitoneal and intratumoral administration.

44. A method of modulating gene expression in a macrophage, comprising:
contacting the macrophage with an extracellular vesicle comprising one or more immunomodulating components that inhibit at least one gene and thereby increase macrophage polarization from an M2 to an M1 phenotype, as compared to contacting the macrophage with equimolar amount(s) of the immunomodulating components alone.

45. The method of claim 44, wherein the contacting is *ex vivo* or *in vivo*.

46. The method of claim 45, wherein the contacting is *in vivo*.

47. The method of claim 46, wherein the contacting *in vivo* comprises administering the extracellular vesicle to a subject.

48. The method of claim 46, wherein the administering is via a route selected from the group consisting of intravenous, intraperitoneal and intratumoral administration.

49. The method of any one of claims 46-48, wherein the subject is human.

50. The method of any one of claims 46-49, wherein the subject is suffering from a condition selected from cancer and fibrosis.

51. The method of claim 50, wherein the condition is pancreatic cancer.

52. The method of any one of claims 44-51, wherein the extracellular vesicle is an exosome.

53. The method of any one of claims 44-50, wherein the immunomodulating component is a nucleic acid.

54. The method of claim 53, wherein the nucleic acid is an inhibitory RNA.

55. The method of claim 54, wherein the inhibitory RNA is an antisense RNA, an siRNA, an shRNA, a miRNA, a lncRNA, a pri-miRNA or a pre-miRNA.

56. The method of claim 55, wherein the nucleic acid is an antisense oligonucleotide (ASO).

57. The method of any one of claims 44-56, wherein the at least one gene is selected from the group consisting of: KRAS, HRAS, NRAS, HIF1-alpha, HIF1-beta, Sp1, P300, LKB1, AMPK, STAT3, STAT6, n-MYC, c-MYC, HCAR1, A2AB, IDO, TDO, Arginase, Glutaminase, CEBP/β, Pi3Kγ, and PKM2.

58. The method of claim 57, wherein the at least one gene is selected from the group consisting of: STAT3, STAT6, CEBP/β, Pi3Kγ, KRAS, and HIF1-alpha.

59. The method of claim 58, wherein the immunomodulating component is an antisense oligonucleotide comprising a sequence at least 95% identical to a sequence selected from SEQ ID NOs:1-6.

60. The method of claim 59, wherein the immunomodulating component is an antisense oligonucleotide comprising a sequence selected from SEQ ID NOs:1-6.

61. The method of claim 58, wherein the at least one gene is STAT3.

62. The method of claim 61, wherein the immunomodulating component is an antisense oligonucleotide that targets STAT3.

63. The method of claim 58, wherein the at least one gene is KRAS.

64. The method of claim 63, wherein the immunomodulating component is an inhibitory RNA that targets wild-type human KRAS.

65. A method of treating pancreatic cancer in a subject comprising: administering to the subject an extracellular vesicle comprising an inhibitory RNA targeting human wild-type KRAS; wherein the treatment increases the percentage of polarization of tumor-resident macrophages from an M2 to an M1 phenotype to a greater level than that observed in a patient treated with an inhibitory RNA targeting human $KRAS^{G12D}$.

66. The method of claim 65, wherein the percentage of polarization of tumor-resident macrophages is determined using an *ex-vivo* assay of tumor-resident macrophages obtained from a tumor sample.