

CLAIMS

1. A composition comprising:

an extracellular vesicle comprising a cell membrane bounding an enclosed volume, ~~said cell membrane having~~ wherein the extracellular vesicle comprises a fusion protein comprising a prostaglandin F2 receptor negative regulator (PTGFRN) or a fragment thereof fused to an interior surface and an exterior surface; and

~~a first immunomodulating component associated with said cell membrane or enclosed within said enclosed volume.~~

~~1.—.~~

2. The composition of claim ~~1~~, wherein ~~said first~~ the immunomodulating component ~~is an inhibitor for a negative checkpoint regulator or an inhibitor for a binding partner of~~ comprises a ~~negative checkpoint regulator.~~

~~2.—~~ cytokine.

3. The composition of claim ~~2~~, wherein ~~said negative checkpoint regulator~~ 2, wherein the cytokine is IL-7.

4. The composition of claim 2, wherein the cytokine is selected from the group consisting IL-12.

5. The composition of: ~~cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), lymphocyte-activated gene 3 (LAG-3), T-cell immunoglobulin mucin-containing protein 3 (TIM-3), B and T lymphocyte attenuator (BTLA), T-cell immunoreceptor with Ig and ITIM domains (TIGIT), V-domain Ig suppressor~~ claim 2, wherein the cytokine is IL-15.

6. The composition of ~~T-cell activation (VISTA), adenosine A2a-receptor (A2aR), killer-cell immunoglobulin-like receptor (KIR), indoleamine 2,3-dioxygenase (IDO), CD20, CD39, and CD73.~~

~~3.—~~ claim 2, wherein the cytokine is IL-2, IL-7, IL-10, IL-12, or IL-15.

7. The composition of claim 1, wherein said first1, wherein the extracellular vesicle is an exosome.

8. The composition of claim 1, wherein the extracellular vesicle is a nanovesicle.

9. The composition of claim 1, further comprising a pharmaceutically-acceptable carrier.

10. The composition of claim 1, wherein the immunomodulating component is an activator for a positive co-stimulatory molecule or an activator for a binding partner of a positive co-stimulatory molecule.

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11. The composition of claim 4,10, wherein said positive co-stimulatory molecule is the immunomodulating component comprises a TNF receptor superfamily member.

5.—

12. The composition of claim 5,11, wherein said the TNF receptor superfamily member is selected from the group consisting of: comprises CD120a, CD120b, CD18, OX40, CD40, Fas receptor, M68, CD27, CD30, 4-1BB, TRAILR1, TRAILR2, TRAILR3, TRAILR4, RANK, OCIF, TWEAK receptor, TACI, BAFF receptor, ATAR, CD271, CD269, AITRGITR, TROY, CD358, TRAMP, and or XEDAR.

6.—

13. The composition of claim 4,1, wherein said activator for a positive co-stimulatory molecule is the immunomodulating component comprises a TNF superfamily member.

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14. The composition of claim 7,13, wherein said the TNF superfamily member is selected from the group consisting of: comprises TNF α , TNF-C, OX40L, CD40L, FasL, LIGHT, TL1A, CD27L, Siva, CD153, 4-1BB ligand, TRAIL, RANKL, TWEAK, APRIL, BAFF, CAMLG, NGF, BDNF, NT-3, NT-4, GITR ligand, and EDA-2 or EDA-2.

15. The composition of claim 14, wherein the TNF superfamily member is CD40L.

16. The composition of claim 1, wherein the immunomodulating component comprises IFN γ .

17. The composition of claim 1, wherein the fragment of the PTGFRN comprises the region before the C-terminal-most IgV domain, the transmembrane domain, and the intracellular domain of PTGFRN.

18. The composition of claim 1, wherein the PTGFRN comprises the full-length PTGFRN.

19. The composition of claim 1, wherein the immunomodulating component comprises an inhibitor of cytotoxic T-lymphocyte-associate protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), programmed death-ligand 2 (PD-L2), lymphocyte-activated gene 3 (LAG3), T-cell immunoglobulin mucin-containing protein 3 (TIM-3), B and T lymphocyte attenuator (BTLA), T cell immunoreceptor with Ig and ITIM domains (TIGIT), V-domain Ig suppressor of T cell activation (VISTA), adenosine A2a receptor (A2aR), killer cell immunoglobulin like receptor (KIR), indoleamine 2,3-dioxygenase (IDO), CD20, CD39, or CD73.

~~7. The composition of claim 8, wherein said TNF superfamily member is CD40L.~~

~~8. The composition of claim 8, wherein said TNF superfamily member is CD27L.~~

~~9. The composition of claim 8, wherein said TNF superfamily member is OX40L.~~

~~10. The composition of claim 4, wherein said positive co-stimulatory molecule is a CD28-superfamily co-stimulatory molecule.~~

~~11. The composition of claim 12, wherein said CD28-superfamily co-stimulatory molecule is ICOS or CD28.~~

~~12. The composition of claim 4, wherein said activator for a positive co-stimulatory molecule is ICOSL, CD80, or CD86.~~

~~13. The composition of claim 14, wherein said activator for a positive co-stimulatory molecule is CD80.~~

~~14. The composition of claim 1, wherein said first immunomodulating component is a cytokine or a binding partner of a cytokine.~~

~~15. The composition of claim 16, wherein said cytokine is selected from the group consisting of: IL-2, IL-7, IL-10, IL-12, and IL-15.~~

~~16. The composition of claim 16, wherein said cytokine is IL-7.~~

~~17. The composition of claim 16, wherein said cytokine is IL-12.~~

- ~~18. The composition of claim 16, wherein said cytokine is IL-15.~~
- ~~19. The composition of claim 1, wherein said first immunomodulating component is a T-cell receptor (TCR), a T-cell co-receptor, a major histocompatibility complex (MHC), a human leukocyte antigen (HLA), or a derivative thereof.~~
- ~~20. The composition of claim 1, wherein said first immunomodulating component is an activator of a T-cell receptor or co-receptor.~~
- ~~21. The composition of claim 22, wherein said activator of a T-cell receptor or co-receptor is an activator of CD3, optionally an agonist antibody of CD3.~~
- ~~22. The composition of claim 1, wherein said first immunomodulating component is a tumor antigen.~~
- ~~23. The composition of claim 24, wherein said tumor antigen is selected from the group consisting of: alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), epithelial tumor antigen (ETA), mucin 1 (MUC1), Tn-MUC1, mucin 16 (MUC16), tyrosinase, melanoma-associated antigen (MAGE), tumor protein p53 (p53), CD4, CD8, CD45, CD80, CD86, programmed death ligand 1 (PD-L1), programmed death ligand 2 (PD-L2), NY-ESO-1, PSMA, TAG-72, HER2, GD2, cMET, EGFR, Mesothelin, VEGFR, alpha-folate receptor, CE7R, IL-3, Cancer-testis antigen, MART-1 gp100, and TNF-related apoptosis-inducing ligand.~~
- ~~24. The composition of claim 24 or 25, wherein said tumor antigen is derived from a reference genome sequence.~~
- ~~25. The composition of claim 24 or 25, wherein said tumor antigen is derived from a genome sequence of a subject.~~
- ~~26. The composition of any of claims 1 to 27, wherein said first immunomodulating component is an agonist or an antagonist.~~
- ~~27. The composition of any of claims 1 to 27, wherein said first immunomodulating component is an antibody or an antigen-binding fragment.~~
- ~~28. The composition of any of claims 1 to 27, wherein said first immunomodulating component is a polynucleotide.~~

~~29. The composition of claim 30, wherein said polynucleotide is selected from the group consisting of: an mRNA, a miRNA, an siRNA, an antisense RNA, an shRNA, a lncRNA, and a dsDNA.~~

~~30. The composition of claim 1 to 27, wherein said first immunomodulating component is a protein, a peptide, a glycolipid, or a glycoprotein.~~

~~31. The composition of any of claims 1 to 32, wherein said first immunomodulating component is expressed as a fusion protein displayed on the exterior surface of said extracellular vesicle.~~

~~32. The composition of claim 33, wherein said fusion protein comprises PTCFRN or a fragment or a variant thereof.~~

~~33. The composition of claim 34, wherein the sequence of said fusion protein is SEQ ID NO: 3.~~

~~34. The composition of any of claims 1 to 35, wherein said extracellular vesicle is an exosome.~~

~~35. The composition of any of claims 1 to 32, wherein said extracellular vesicle is a nanovesicle.~~

~~36. The composition of any of claims 1 to 37, further comprising a pharmaceutically-acceptable carrier.~~

~~37. The composition of any of claims 1 to 38, wherein the extracellular vesicle additionally comprises a second immunomodulating component.~~

~~38. The composition of claim 39, wherein said second immunomodulating component is an inhibitor for a negative checkpoint regulator or an inhibitor for a binding partner of a negative checkpoint regulator.~~

~~39. The composition of claim 40, wherein said negative checkpoint regulator is selected from the group consisting of: cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), lymphocyte-activated gene 3 (LAG-3), T-cell immunoglobulin mucin-containing protein 3 (TIM-3), B and T lymphocyte attenuator (BTLA), T-cell immunoreceptor with Ig and ITIM domains (TIGIT), V-domain Ig suppressor of T cell activation (VISTA), adenosine A2a receptor (A2aR), killer cell immunoglobulin like receptor (KIR), indoleamine 2,3-dioxygenase (IDO), CD20, CD39, and CD73.~~

- ~~40. The composition of claim 39, wherein said second immunomodulating component is an activator for a positive co-stimulatory molecule or an activator for a binding partner of a positive co-stimulatory molecule.~~
- ~~41. The composition of claim 42, wherein said positive co-stimulatory molecule is a TNF receptor superfamily member.~~
- ~~42. The composition of claim 43, wherein said TNF receptor superfamily member is selected from the group consisting of: CD120a, CD120b, CD18, OX40, CD40, Fas receptor, M68, CD27, CD30, 4-1BB, TRAILR1, TRAILR2, TRAILR3, TRAILR4, RANK, OCIF, TWEAK receptor, TACI, BAFF receptor, ATAR, CD271, CD269, AITR, TROY, CD358, TRAMP, and XEDAR.~~
- ~~43. The composition of claim 42, wherein said activator for a positive co-stimulatory molecule is a TNF superfamily member.~~
- ~~44. The composition of claim 45, wherein said TNF superfamily member is selected from the group consisting of: TNF α , TNF-C, OX40L, CD40L, FasL, LIGHT, TL1A, CD27L, Siva, CD153, 4-1BB ligand, TRAIL, RANKL, TWEAK, APRIL, BAFF, CAMLG, NGF, BDNF, NT-3, NT-4, GITR ligand, and EDA-2.~~
- ~~45. The composition of claim 46, wherein said TNF superfamily member is CD40L.~~
- ~~46. The composition of claim 46, wherein said TNF superfamily member is CD27L.~~
- ~~47. The composition of claim 46, wherein said TNF superfamily member is OX40L.~~
- ~~48. The composition of claim 42, wherein said positive co-stimulatory molecule is a CD28-superfamily co-stimulatory molecule.~~
- ~~49. The composition of claim 50, wherein said CD28-superfamily co-stimulatory molecule is ICOS or CD28.~~
- ~~50. The composition of claim 42, wherein said activator for a positive co-stimulatory molecule is ICOSL, CD80, or CD86.~~
- ~~51. The composition of claim 52, wherein said activator for a positive co-stimulatory molecule is CD80.~~
- ~~52. The composition of claim 39, wherein said second immunomodulating component is a cytokine or a binding partner of a cytokine.~~

~~53. The composition of claim 54, wherein said cytokine is selected from the group consisting of: IL-2, IL-7, IL-10, IL-12, and IL-15.~~

~~54. The composition of claim 54, wherein said cytokine is IL-7.~~

~~55. The composition of claim 54, wherein said cytokine is IL-12.~~

~~56. The composition of claim 54, wherein said cytokine is IL-15.~~

~~57. The composition of claim 39, wherein said second immunomodulating component is a T-cell receptor (TCR), a T-cell co-receptor, a major histocompatibility complex (MHC), a human leukocyte antigen (HLA), or a derivative thereof.~~

~~58. The composition of claim 39, wherein said second immunomodulating component is an activator of a T-cell receptor or co-receptor.~~

~~59. The composition of claim 60, wherein said activator of a T-cell receptor or co-receptor is an activator of CD3, optionally an agonist antibody of CD3.~~

~~60. The composition of claim 39, wherein said second immunomodulating component is a tumor antigen.~~

~~61. The composition of claim 62, wherein said tumor antigen is selected from the group consisting of: alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), epithelial tumor antigen (ETA), mucin 1 (MUC1), Tn-MUC1, mucin 16 (MUC16), tyrosinase, melanoma-associated antigen (MAGE), tumor protein p53 (p53), CD4, CD8, CD45, CD80, CD86, programmed death ligand 1 (PD-L1), programmed death ligand 2 (PD-L2), NY-ESO-1, PSMA, TAG-72, HER2, GD2, cMET, EGFR, Mesothelin, VEGFR, alpha-folate receptor, CE7R, IL-3, Cancer-testis antigen, MART-1 gp100, and TNF-related apoptosis-inducing ligand.~~

~~62. The composition of claim 62 or 63, wherein said tumor antigen is derived from a reference genome sequence.~~

~~63. The composition of claim 62 or 63, wherein said tumor antigen is derived from a genome sequence of a subject.~~

~~64. The composition of any of claims 39 to 65, wherein said second immunomodulating component is an agonist or an antagonist.~~

~~65. The composition of any of claims 39 to 65, wherein said second immunomodulating component is an antibody or an antigen-binding fragment.~~

~~66. The composition of any of claims 39 to 65, wherein said second immunomodulating component is a polynucleotide.~~

~~67. The composition of claim 68, wherein said polynucleotide is selected from the group consisting of: an mRNA, a miRNA, an siRNA, an antisense RNA, an shRNA, a lncRNA, and a dsDNA.~~

~~68. The composition of claim 39 to 65, wherein said second immunomodulating component is a protein, a peptide, a glycolipid, or a glycoprotein.~~

~~69. The composition of any of claims 39 to 70, wherein said second immunomodulating component is expressed as a fusion protein displayed on the exterior surface of said extracellular vesicle.~~

~~70. The composition of claim 71, wherein said fusion protein comprises PTGFRN or a fragment or a variant thereof.~~

~~71. The composition of claim 72, wherein the sequence of said fusion protein is SEQ ID NO: 3.~~

~~72. The composition of any of claims 39 to 73, wherein said second immunomodulating component is different from said first immunomodulating component.~~

~~73. The composition of any of claims 39 to 74, wherein the extracellular vesicle additionally comprises a third immunomodulating component.~~

~~74. The composition of claim 75, wherein said third immunomodulating component is different from said first and second immunomodulating components.~~

~~75. A method of producing said composition of any of claims 1 to 38, comprising:~~

~~modifying a producer cell with said first, second, and/or third immunomodulating components;~~

~~obtaining said extracellular vesicle from said producer cell; and~~

~~optionally isolating said obtained extracellular vesicles.~~

~~76. A method of producing said composition of any of claims 1 to 38, comprising:~~

~~obtaining said extracellular vesicle from a producer cell;~~

~~isolating said obtained extracellular vesicles; and~~

~~modifying said isolated extracellular vesicle with said first, second, and/or third immunomodulating components.~~

~~77. The method of claim 77 or 78, further comprising formulating said isolated extracellular vesicles into a pharmaceutical composition.~~

~~78. A method of treating cancer in a subject comprising:~~

~~administering to said subject a therapeutically effective amount of said composition of any of claims 1 to 38, wherein said composition is capable of up-regulating an immune response in said subject, thereby enhancing the tumor targeting of said subject's immune system.~~

79. A method of treating graft-versus-host disease (GvHD) in a subject comprising:

administering to said subject a therapeutically effective amount of said composition of any of claims 1 to 38, wherein said composition is capable of down-regulating an immune response in said subject, thereby alleviating the symptoms of GvHD.

80. A method of treating an autoimmune disease in a subject comprising:

administering to said subject a therapeutically effective amount of said composition of any of claims 1 to 38, wherein said composition is capable of down-regulating an immune response in said subject, thereby suppressing the immune activity of said subject.

81. A method of treating or preventing cancer in a subject comprising:

administering to said subject a therapeutically effective amount of said composition of any of claims 24 to 27, wherein said composition is capable of potentiating an immune response to said tumor antigen, thereby enhancing the immune response of said subject to cancer.