effective interventions that overcome the immune suppressive tumor microenvironment and for treating cancers associated with hypersialylated cancer cells.

SUMMARY OF THE INVENTION

[0006] The invention is based, in part, upon the discovery that it is possible to treat a sialic acid-mediated disorder by administering a sialidase enzyme or a sialidase enzyme conjugated to a serum half-life enhancer. Surprisingly, it has been discovered that a sialidase or a sialidase enzyme conjugated to a serum half-life enhancer that lacks a targeting moiety (*e.g.*, an antibody binding domain directed to a tumor antigen) can effectively treat a sialic acid-mediated disorder (*e.g.*, cancer, *e.g.*, a solid tumor) *in vivo*.

[0007] The invention further relates to recombinant forms of sialidase enzymes, sialidase enzymes conjugated to a serum half-life enhancer, and pharmaceutical compositions thereof, that have suitable substrate specificities and activities to be useful in removing sialic acid and/or sialic acid containing molecules from the surface of cancer cells and/or removing sialic acid and/or sialic acid containing molecules from the tumor microenvironment, and/or reducing the concentration of sialic acid and/or sialic acid containing molecules in the tumor microenvironment.

[0008] Thus, in certain aspects, the invention provides a pharmaceutical composition comprising or consisting essentially of a sialidase conjugated to a serum half-life enhancer that increases the serum half-life of the sialidase when administered to a subject.

[0008a] In one aspect, provided herein is a pharmaceutical composition comprising a sialidase conjugated to a serum half-life enhancer that increases the serum half-life of the sialidase when administered to a subject, wherein the sialidase is a recombinant mutant human Neu2 sialidase comprising:

a substitution of a proline residue at a position corresponding to position 62 of wild-type human Neu2 (P62); and/or

a substitution of an alanine residue at a position corresponding to position 93 of wild-type human Neu2 (A93); and

the sialidase has enzymatic sialidase activity.

[0008b] In another aspect, provided herein is the use of a pharmaceutical composition in the preparation of a medicament for the treatment of cancer in a subject in need thereof, wherein the pharmaceutical composition comprises an effective amount of a sialidase conjugated to a serum half-life enhancer that increases the serum half-life of the sialidase when administered

to a subject, and wherein the sialidase is a recombinant mutant human Neu2 sialidase comprising:

a substitution of a proline residue at a position corresponding to position 62 of wild-type human Neu2 (P62); and/or

a substitution of an alanine residue at a position corresponding to position 93 of wild-type human Neu2 (A93); and

the sialidase has enzymatic sialidase activity.

[0008c] In another aspect, provided herein is the use of a pharmaceutical composition described herein in the preparation of a medicament for the treatment of cancer in a subject.

[0008d] In another aspect, provided herein is the use of a pharmaceutical composition described herein in the preparation of a medicament for removing sialic acid from a cell in a subject.

[0008e] In another aspect, provided herein is the use of a pharmaceutical composition described herein in the preparation of a medicament for increasing phagocytosis of a tumor cell in a subject, so as to increase phagocytosis of the tumor cell.

[0008f] In another aspect, provided herein is the use of a pharmaceutical composition described herein in the preparation of a medicament for activating a dendritic cell (DC) in a subject.

[0008g] In another aspect, provided herein is the use of a pharmaceutical composition described herein in the preparation of a medicament for reducing Siglec-15 binding activity in a subject, so as to increase anti-tumor activity in the subject.

[0008h] In another aspect, provided herein is a pharmaceutical composition described herein for use in therapy.

[0009] In another aspect, the invention provides a method of treating a sialic acid-related disorder in a subject in need thereof. The method includes administering to the subject an effective amount of a pharmaceutical composition comprising or consisting essentially of a sialidase and a serum half-life enhancer that increases the serum half-life of the sialidase when administered to the subject, thereby to treat the disorder.

[0010] In certain embodiments, the sialidase is not conjugated to a cancer antigen targeting agent that binds a cancer antigen associated with a cancerous cell.

[0011] In certain embodiments, the sialidase is a functional fragment of a full-length sialidase or a variant that exhibits at least 50% of the activity of the full-length sialidase.

[0012] In certain embodiments, the sialidase and the serum half-life enhancer are covalently linked together in a fusion protein or are chemically conjugated together.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a sialidase conjugated to a serum half-life enhancer that increases the serum half-life of the sialidase when administered to a subject, wherein the sialidase is a recombinant mutant human Neu2 sialidase comprising:

a substitution of a proline residue at a position corresponding to position 62 of wild-type human Neu2 (P62); and/or

a substitution of an alanine residue at a position corresponding to position 93 of wild-type human Neu2 (A93); and

the sialidase has enzymatic sialidase activity.

2. The pharmaceutical composition of claim 1, wherein the sialidase is not conjugated to a cancer antigen targeting agent that binds a cancer antigen associated with a cancerous cell.

3. The pharmaceutical composition of claim 1 or 2, wherein the sialidase is a functional fragment of a full-length sialidase that exhibits at least 50% of the activity of the full-length sialidase.

4. The pharmaceutical composition of any one of claims 1-3, wherein the sialidase exhibits at least 50% of the activity of the wild-type sialidase.

5. The pharmaceutical composition of any one of claims 1-4, wherein the sialidase and the serum half-life enhancer are covalently linked together in a fusion protein.

6. The pharmaceutical composition of any one of claims 1-4, wherein the sialidase and serum half-life enhancer are chemically conjugated together.

7. The pharmaceutical composition of any one of claims 1-6, wherein the serum half-life enhancer is selected from the group consisting of an Fc domain, transferrin, albumin, XTEN, a homo-amino acid polymer (HAP), a proline-alanine-serine polymer (PAS), an elastin-like peptide (ELP), albumin binding domain, CTP fusion, GLK fusion, and a polyethylene glycol.

8. The pharmaceutical composition of any one of claims 1-7, wherein the serum half-life enhancer is an Fc domain.

9. The pharmaceutical composition of any one of claims 1-7, wherein the serum half-life enhancer is not an Fc domain or polyethylene glycol.

10. The pharmaceutical composition of any one of claims 1-9, wherein the sialidase further comprises:

(a) a substitution or deletion of a methionine residue at a position corresponding to position 1 of wild-type human Neu2 (M1);

(b) a substitution of a valine residue at a position corresponding to position 6 of wild-type human Neu2 (V6);

(c) a substitution of an isoleucine residue at a position corresponding to position 187 of wild-type human Neu2 (I187); or

(d) a substitution of a cysteine residue at a position corresponding to position 332 of wild-type human Neu2 (C332);

or a combination of any of the foregoing substitutions.

11. The pharmaceutical compositions of claim 10, wherein, in the sialidase:

(a) the methionine residue at a position corresponding to position 1 of wild-type human Neu2 is deleted (ΔM1), is substituted by alanine (M1A), or is substituted by aspartic acid (M1D);

(b) the valine residue at a position corresponding to position 6 of wild-type human Neu2 is substituted by tyrosine (V6Y);

(c) the isoleucine residue at a position corresponding to position 187 of wild-type human Neu2 is substituted by lysine (I187K); or

(d) the cysteine residue at a position corresponding to position 332 of wild-type human Neu2 is substituted by alanine (C332A);

or the sialidase comprises a combination of any of the foregoing substitutions.

12. The pharmaceutical composition of any one of claims 1-9, wherein the sialidase further comprises:

(a) a substitution or deletion of a methionine residue at a position corresponding to position 1 of wild-type human Neu2 (M1);

(b) a substitution of a valine residue at a position corresponding to position 6 of wild-type human Neu2 (V6);

(c) a substitution of an isoleucine residue at a position corresponding to position 187 of wild-type human Neu2 (I187);

(d) a substitution of a glutamine residue at a position corresponding to position 126 of wild-type human Neu2 (Q126);

(e) a substitution of an alanine residue at a position corresponding to position 242 of wild-type human Neu2 (A242);

(f) a substitution of a glutamine residue at a position corresponding to position 270 of wild-type human Neu2 (Q270);

(g) a substitution of a serine residue at a position corresponding to position 301 of wild-type human Neu2 (S301);

(h) a substitution of a tryptophan residue at a position corresponding to position 302 of wild-type human Neu2 (W302);

(i) a substitution of a cysteine residue at a position corresponding to position 332 of wild-type human Neu2 (C332);

or a combination of any of the foregoing substitutions.

13. The pharmaceutical composition of any one of claims 1-12, wherein the sialidase comprises a combination of substitutions selected from the group consisting of:

(a) M1D, V6Y, P62G, A93E, I187K, C332A;

(b) M1D, V6Y, P62G, A93E, I187K, S301A, W302R, C332A;

(c) M1D, V6Y, P62G, A93E, Q126Y, I187K, A242F, Q270T, C332A;

(d) M1D, V6Y, P62G, A93E, Q126Y, I187K, C332A; and

(e) A93E, Q126Y, I187K, A242F, Q270T, C332A.

14. The pharmaceutical composition of claim 13, wherein the sialidase conjugated to a serum half-life enhancer comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 115, 152, 180, 184, and 188, or an amino acid sequence that has at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% to an amino acid sequence selected from the group consisting of SEQ ID NOs: 115, 152, 180, 184, and 188.

15. The pharmaceutical composition of any one of claims 1-9, wherein the sialidase further comprises:

(a) a substitution of a proline residue at a position corresponding to position 5 of wild-type human Neu2 (P5);

(b) a substitution of a lysine residue at a position corresponding to position 9 of wild-type human Neu2 (K9);

(c) a substitution of a lysine residue at a position corresponding to position 44 of wild-type human Neu2 (K44);

(d) a substitution of a lysine residue at a position corresponding to position 45 of wild-type human Neu2 (K45);

(e) a substitution of a leucine residue at a position corresponding to position 54 of

wild-type human Neu2 (L54);

(f) a substitution of a glutamine residue at a position corresponding to position 69 of wild-type human Neu2 (Q69);

(g) a substitution of an arginine residue at a position corresponding to position 78 of wild-type human Neu2 (R78);

(h) a substitution of an aspartic acid residue at a position corresponding to position 80 of wild-type human Neu2 (D80);

(i) a substitution of a glycine residue at a position corresponding to position 107 of wild-type human Neu2 (G107);

(j) a substitution of a glutamine residue at a position corresponding to position 108 of wild-type human Neu2 (Q108);

(k) a substitution of a glutamine residue at a position corresponding to position 112 of wild-type human Neu2 (Q112);

(l) a substitution of a cysteine residue at a position corresponding to position 125 of wild-type human Neu2 (C125);

(m) a substitution of a glutamine residue at a position corresponding to position 126 of wild-type human Neu2 (Q126);

(n) a substitution of an alanine residue at a position corresponding to position 150 of wild-type human Neu2 (A150);

(o) a substitution of a cysteine residue at a position corresponding to position 164 of wild-type human Neu2 (C164);

(p) a substitution of an arginine residue at a position corresponding to position 170 of wild-type human Neu2 (R170);

(q) a substitution of an alanine residue at a position corresponding to position 171 of wild-type human Neu2 (A171);

(r) a substitution of a glutamine residue at a position corresponding to position 188 of wild-type human Neu2 (Q188);

(s) a substitution of an arginine residue at a position corresponding to position 189 of wild-type human Neu2 (R189);

(t) a substitution of an alanine residue at a position corresponding to position 213 of wild-type human Neu2 (A213);

(u) a substitution of a leucine residue at a position corresponding to position 217 of wild-type human Neu2 (L217);

(v) a substitution of a glutamic acid residue at a position corresponding to position

225 of wild-type human Neu2 (E225);

(w) a substitution of a histidine residue at a position corresponding to position 239 of wild-type human Neu2 (H239);

(x) a substitution of a leucine residue at a position corresponding to position 240 of wild-type human Neu2 (L240);

(y) a substitution of an arginine residue at a position corresponding to position 241 of wild-type human Neu2 (R241);

(z) a substitution of an alanine residue at a position corresponding to position 242 of wild-type human Neu2 (A242);

(aa) a substitution of a valine residue at a position corresponding to position 244 of wild-type human Neu2 (V244);

(bb) a substitution of a threonine residue at a position corresponding to position 249 of wild-type human Neu2 (T249);

(cc) a substitution of an aspartic acid residue at a position corresponding to position 251 of wild-type human Neu2 (D251);

(dd) a substitution of a glutamic acid residue at a position corresponding to position 257 of wild-type human Neu2 (E257);

(ee) a substitution of a serine residue at a position corresponding to position 258 of wild-type human Neu2 (S258);

(ff) a substitution of a leucine residue at a position corresponding to position 260 of wild-type human Neu2 (L260);

(gg) a substitution of a valine residue at a position corresponding to position 265 of wild-type human Neu2 (V265);

(hh) a substitution of a glutamine residue at a position corresponding to position 270 of wild-type human Neu2 (Q270);

(ii) a substitution of a tryptophan residue at a position corresponding to position 292 of wild-type human Neu2 (W292);

(jj) a substitution of a serine residue at a position corresponding to position 301 of wild-type human Neu2 (S301);

(kk) a substitution of a tryptophan residue at a position corresponding to position 302 of wild-type human Neu2 (W302);

(ll) a substitution of a cysteine residue at a position corresponding to position 332 of wild-type human Neu2 (C332);

(mm) a substitution of a valine residue at a position corresponding to position 363 of

wild-type human Neu2 (V363); or

(nn) a substitution of a leucine residue at a position corresponding to position 365 of wild-type human Neu2 (L365);

or a combination of any of the foregoing substitutions.

16. The pharmaceutical composition of any one of claims 1-15, comprising from 0.01 mg/kg to 100 mg/kg of the sialidase.

17. The pharmaceutical composition of any one of claims 1-16, wherein the pharmaceutical composition comprises a second therapeutic agent.

18. The pharmaceutical composition of claim 17, wherein the second therapeutic agent is selected from the group consisting of an anti-inflammatory agent, anti-angiogenic agent, anti-fibrotic agent, or an anti-proliferative compound.

19. The pharmaceutical composition of any one of claims 1-18, wherein the pharmaceutical composition further comprises a stabilizing amount of a sialidase stabilizing agent.

20. The pharmaceutical composition of claim 19, wherein the sialidase stabilizing agent is a cation.

21. The pharmaceutical composition of claim 20, wherein the cation is selected from the group consisting of calcium and magnesium.

22. The pharmaceutical composition of any one of claims 1-21, wherein the pharmaceutical composition is disposed in a sterile container.

23. The pharmaceutical composition of claim 22, wherein the pharmaceutical composition is lyophilized in the sterile container.

24. The pharmaceutical composition of claim 22, wherein the pharmaceutical composition is present as a solution in the sterile container.

25. The pharmaceutical composition of any one of claims 22-24, wherein the sterile container is sealed with a septum.

26. The pharmaceutical composition of any one of claims 22-25, wherein the sterile container has a label disposed thereon identifying the pharmaceutical composition contained in the container.

27. Use of a pharmaceutical composition in the preparation of a medicament for the

treatment of cancer in a subject in need thereof, wherein the pharmaceutical composition comprises an effective amount of a sialidase conjugated to a serum half-life enhancer that increases the serum half-life of the sialidase when administered to a subject, and wherein the sialidase is a recombinant mutant human Neu2 sialidase comprising:

a substitution of a proline residue at a position corresponding to position 62 of wild-type human Neu2 (P62); and/or

a substitution of an alanine residue at a position corresponding to position 93 of wild-type human Neu2 (A93); and

the sialidase has enzymatic sialidase activity.

28. The use of claim 27, wherein the sialidase is not conjugated to a cancer antigen targeting agent that binds a cancer antigen associated with a cancerous cell.

29. The use of claim 27 or 28, wherein the sialidase is a functional fragment of a full-length sialidase that exhibits at least 50% of the activity of the full-length sialidase.

30. The use of any one of claims 27-29, wherein the sialidase exhibits at least 50% of the activity of the wild-type sialidase.

31. The use of any one of claims 27-30, wherein the sialidase and the serum half-life enhancer are covalently linked together in a fusion protein.

32. The use of any one of claims 27-30, wherein the sialidase and serum half-life enhancer are chemically conjugated together.

33. The use of any one of claims 27-31, wherein the serum half-life enhancer is selected from the group consisting of an Fc domain, transferrin, albumin, XTEN, a homo-amino acid polymer (HAP), a proline-alanine-serine polymer (PAS), an elastin-like peptide (ELP), and a polyethylene glycol.

34. The use of any one of claims 27-33, wherein the serum half-life enhancer is an Fc domain.

35. The use of any one of claims 27-33, wherein the serum half-life enhancer is not an Fc domain or polyethylene glycol.

36. The use of any one of claims 27-35, wherein the sialidase further comprises:

(a) a substitution or deletion of a methionine residue at a position corresponding to position 1 of wild-type human Neu2 (M1);

(b) a substitution of a valine residue at a position corresponding to position 6 of wild-

type human Neu2 (V6);

(c) a substitution of an isoleucine residue at a position corresponding to position 187 of wild-type human Neu2 (I187); or

(d) a substitution of a cysteine residue at a position corresponding to position 332 of wild-type human Neu2 (C332);

or a combination of any of the foregoing substitutions.

37. The use of claim 36, wherein, in the sialidase:

(a) the methionine residue at a position corresponding to position 1 of wild-type human Neu2 is deleted (ΔM1), is substituted by alanine (M1A), or is substituted by aspartic acid (M1D);

(b) the valine residue at a position corresponding to position 6 of wild-type human Neu2 is substituted by tyrosine (V6Y);

(c) the isoleucine residue at a position corresponding to position 187 of wild-type human Neu2 is substituted by lysine (I187K); or

(d) the cysteine residue at a position corresponding to position 332 of wild-type human Neu2 is substituted by alanine (C332A);

or the sialidase comprises a combination of any of the foregoing substitutions.

38. The use of any one of claims 27-35, wherein the sialidase further comprises:

(a) a substitution or deletion of a methionine residue at a position corresponding to position 1 of wild-type human Neu2 (M1);

(b) a substitution of a valine residue at a position corresponding to position 6 of wild-type human Neu2 (V6);

(c) a substitution of an isoleucine residue at a position corresponding to position 187 of wild-type human Neu2 (I187);

(d) a substitution of a glutamine residue at a position corresponding to position 126 of wild-type human Neu2 (Q126);

(e) a substitution of an alanine residue at a position corresponding to position 242 of wild-type human Neu2 (A242);

(f) a substitution of a glutamine residue at a position corresponding to position 270 of wild-type human Neu2 (Q270);

(g) a substitution of a serine residue at a position corresponding to position 301 of wild-type human Neu2 (S301);

(h) a substitution of a tryptophan residue at a position corresponding to position 302 of wild-type human Neu2 (W302);

(i) a substitution of a cysteine residue at a position corresponding to position 332 of wild-type human Neu2 (C332);

or a combination of any of the foregoing substitutions.

39. The use of any one of claims 27-38, wherein the sialidase comprises a combination of substitutions selected from the group consisting of:

(a) M1D, V6Y, P62G, A93E, I187K, C332A;

(b) M1D, V6Y, P62G, A93E, I187K, S301A, W302R, C332A;

(c) M1D, V6Y, P62G, A93E, Q126Y, I187K, A242F, Q270T, C332A;

(d) M1D, V6Y, P62G, A93E, Q126Y, I187K, C332A; and

(e) A93E, Q126Y, I187K, A242F, Q270T, C332A.

40. The use of claim 39, wherein the sialidase conjugated to a serum half-life enhancer comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 115, 152, 180, 184, and 188, or an amino acid sequence that has at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% to an amino acid sequence selected from the group consisting of SEQ ID NOs: 115, 152, 180, 184, and 188.

41. The use of any one of claims 27-35, wherein the sialidase further comprises:

(a) a substitution of a proline residue at a position corresponding to position 5 of wild-type human Neu2 (P5);

(b) a substitution of a lysine residue at a position corresponding to position 9 of wild-type human Neu2 (K9);

(c) a substitution of a lysine residue at a position corresponding to position 44 of wild-type human Neu2 (K44);

(d) a substitution of a lysine residue at a position corresponding to position 45 of wild-type human Neu2 (K45);

(e) a substitution of a leucine residue at a position corresponding to position 54 of wild-type human Neu2 (L54);

(f) a substitution of a glutamine residue at a position corresponding to position 69 of wild-type human Neu2 (Q69);

(g) a substitution of an arginine residue at a position corresponding to position 78 of wild-type human Neu2 (R78);

(h) a substitution of an aspartic acid residue at a position corresponding to position 80 of wild-type human Neu2 (D80);

(i) a substitution of a glycine residue at a position corresponding to position 107 of wild-type human Neu2 (G107);

(j) a substitution of a glutamine residue at a position corresponding to position 108 of wild-type human Neu2 (Q108);

(k) a substitution of a glutamine residue at a position corresponding to position 112 of wild-type human Neu2 (Q112);

(l) a substitution of a cysteine residue at a position corresponding to position 125 of wild-type human Neu2 (C125);

(m) a substitution of a glutamine residue at a position corresponding to position 126 of wild-type human Neu2 (Q126);

(n) a substitution of an alanine residue at a position corresponding to position 150 of wild-type human Neu2 (A150);

(o) a substitution of a cysteine residue at a position corresponding to position 164 of wild-type human Neu2 (C164);

(p) a substitution of an arginine residue at a position corresponding to position 170 of wild-type human Neu2 (R170);

(q) a substitution of an alanine residue at a position corresponding to position 171 of wild-type human Neu2 (A171);

(r) a substitution of a glutamine residue at a position corresponding to position 188 of wild-type human Neu2 (Q188);

(s) a substitution of an arginine residue at a position corresponding to position 189 of wild-type human Neu2 (R189);

(t) a substitution of an alanine residue at a position corresponding to position 213 of wild-type human Neu2 (A213);

(u) a substitution of a leucine residue at a position corresponding to position 217 of wild-type human Neu2 (L217);

(v) a substitution of a glutamic acid residue at a position corresponding to position 225 of wild-type human Neu2 (E225);

(w) a substitution of a histidine residue at a position corresponding to position 239 of wild-type human Neu2 (H239);

(x) a substitution of a leucine residue at a position corresponding to position 240 of wild-type human Neu2 (L240);

(y) a substitution of an arginine residue at a position corresponding to position 241 of wild-type human Neu2 (R241);

(z) a substitution of an alanine residue at a position corresponding to position 242 of wild-type human Neu2 (A242);

(aa) a substitution of a valine residue at a position corresponding to position 244 of wild-type human Neu2 (V244);

(bb) a substitution of a threonine residue at a position corresponding to position 249 of wild-type human Neu2 (T249);

(cc) a substitution of an aspartic acid residue at a position corresponding to position 251 of wild-type human Neu2 (D251);

(dd) a substitution of a glutamic acid residue at a position corresponding to position 257 of wild-type human Neu2 (E257);

(ee) a substitution of a serine residue at a position corresponding to position 258 of wild-type human Neu2 (S258);

(ff) a substitution of a leucine residue at a position corresponding to position 260 of wild-type human Neu2 (L260);

(gg) a substitution of a valine residue at a position corresponding to position 265 of wild-type human Neu2 (V265);

(hh) a substitution of a glutamine residue at a position corresponding to position 270 of wild-type human Neu2 (Q270);

(ii) a substitution of a tryptophan residue at a position corresponding to position 292 of wild-type human Neu2 (W292);

(jj) a substitution of a serine residue at a position corresponding to position 301 of wild-type human Neu2 (S301);

(kk) a substitution of a tryptophan residue at a position corresponding to position 302 of wild-type human Neu2 (W302);

(ll) a substitution of a cysteine residue at a position corresponding to position 332 of wild-type human Neu2 (C332);

(mm) a substitution of a valine residue at a position corresponding to position 363 of wild-type human Neu2 (V363); or

(nn) a substitution of a leucine residue at a position corresponding to position 365 of wild-type human Neu2 (L365);

or a combination of any of the foregoing substitutions.

42. The use of any one of claims 27-41, wherein from 0.01 mg/kg to 100 mg/kg of the sialidase is to be administered to the subject.

43. The use of any one of claims 27-42, wherein the cancer is a solid tumor, soft tissue tumor, hematopoietic tumor or metastatic lesion.

44. The use of claim 43, wherein the solid tumor is a sarcoma, adenocarcinoma, or carcinoma.

45. The use of claim 43 or 44, wherein the solid tumor is a head and neck, thyroid, lung, breast, lymphoid, gastrointestinal, genital or genitourinary tract, CNS, or skin tumor.

46. The use of claim 43, wherein the hematopoietic tumor is a leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, hairy cell leukemia, myelodysplastic syndrome (MDS), lymphoma, Hodgkin's disease, malignant lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, or Richter's Syndrome (Richter's Transformation).

47. The use of claim 43, wherein the cancer is breast cancer.

48. The use of claim 43, wherein the cancer is lymphoma.

49. The use of any one of claims 27-48, wherein administration of the pharmaceutical composition increases expression of granzyme B, IFNγ, IL-10, IL-6, or IL-17A in the subject.

50. The use of any one of claims 27-49, wherein the pharmaceutical composition is to be administered to the subject in combination with another therapeutic agent.

51. The use of claim 50, wherein the therapeutic agent is selected from the group consisting of an anti-inflammatory agent, anti-angiogenic agent, anti-fibrotic agent, or an anti-proliferative compound.

52. The use of any one of claims 27-51, wherein the pharmaceutical composition further comprises a stabilizing amount of a sialidase stabilizing agent.

53. The use of claim 52, wherein the sialidase stabilizing agent is a cation.

54. The use of claim 53, wherein the cation is selected from the group consisting of calcium and magnesium.

55. The use of claim 54, wherein the pharmaceutical composition, prior to administration,

is disposed in a sterile container.

56. Use of the pharmaceutical composition of any one of claims 1-26 in the preparation of a medicament for the treatment of cancer in a subject.

57. Use of the pharmaceutical composition of any one of claims 1-26 in the preparation of a medicament for removing sialic acid from a cell in a subject.

58. The use of claim 57, wherein the cell is a tumor cell, dendritic cell (DC), or monocyte.

59. The use of claim 58, wherein the cell is a monocyte, and administration of the pharmaceutical composition to the subject results in increased expression of an MHC-II molecule on the monocyte.

60. Use of the pharmaceutical composition of any one of claims 1-26 in the preparation of a medicament for increasing phagocytosis of a tumor cell in a subject, so as to increase phagocytosis of the tumor cell.

61. Use of the pharmaceutical composition of any one of claims 1-26 in the preparation of a medicament for activating a dendritic cell (DC) in a subject.

62. Use of the pharmaceutical composition of any one of claims 1-26 in the preparation of a medicament for reducing Siglec-15 binding activity in a subject, so as to increase anti-tumor activity in the subject.

63. The pharmaceutical composition of any one of claims 1-26 for use in therapy.