

increased T cells, IL-7 moves into the cell (transcytosis). It maintains homeostasis and is known as the homeostatic cytokine. Therefore, severe immune-related side effects such as cytokine storm caused by excessive immune response, which have been a major problem in the clinical safety of other cytokine treatments, have not been reported in previous clinical trials with recombinant human IL-7 (rhIL-7) by Cytheris under codename CYT107.

[003] IL-7 is encoded by the gene IL7 and binds to IL-7 receptor (CD127). IL-7 is an immunostimulatory cytokine which can promote immune responses mediated by B cells and T cells. IL-7 plays an important role in an adaptive immune system.

[004] In copending application (US Application No. 15/126,313), of which the entire content is incorporated herein by reference, a modified IL-7 protein with enhanced expression and half-life, a fusion protein containing the modified IL-7, and their production method have been provided.

SUMMARY

[005] The present disclosure provides a method of increasing a lymphocyte count by employing the modified IL-7 or a fusion protein containing the modified IL-7.

[005a] In one aspect, the present disclosure provides a use of the following (i) and/or (ii) in the manufacture of a medicament for increasing a lymphocyte count in a subject in need thereof, comprising that a dose of greater than about 600 µg/kg of (i) or a dose of greater than about 60 µg/kg of (ii) is to be administered to the subject,

(i) a modified interleukin-7 of the following formula (I):

A - IL-7 formula (I)

wherein A is an oligopeptide consisting of 1 to 10 amino acid residues, and

the IL-7 is a polypeptide which is capable of binding to IL-7 receptor; or

(ii) an interleukin-7 fusion protein comprising

(a) the modified interleukin-7,

(b) a second domain comprising an oligopeptide having 1 to 10 amino acid residues consisting of methionine, glycine, or a combination thereof; and

(c) a third domain which prolongs the half-life of the interleukin-7 fusion protein.

[005b] In another aspect, the present disclosure provides a pharmaceutical composition for use in increasing a lymphocyte count in a subject in need thereof, comprising as an active ingredient,

(i) a modified interleukin-7 of the following formula (I):

A - IL-7 formula (I)

wherein A is an oligopeptide consisting of 1 to 10 amino acid residues, and

the IL-7 is a polypeptide which is capable of binding to IL-7 receptor; and/or

(ii) an interleukin-7 fusion protein comprising

(a) the modified interleukin-7,

(b) a second domain comprising an oligopeptide having 1 to 10 amino acid residues consisting of methionine, glycine, or a combination thereof; and

(c) a third domain which prolongs the half-life of the interleukin-7 fusion protein,

wherein said pharmaceutical composition is to be administered to the subject at a dose of greater than about 600 µg/kg of (i) or a dose of greater than about 60 µg/kg of (ii).

[006] An embodimentexample provides a method of increasing a lymphocyte count in a subject in need thereof, comprising administering the modified IL-7 or its fusion protein to the subject.

[007] The subject in need thereof may be a mammal suffering from a cancer or a malignant tumor. The cancer may be a solid tumor. In an exemplary embodimentexample, the solid tumor may be locally advanced or metastatic solid tumors or glioblastoma.

[008] In an embodimentexample, the subject may be human.

[009] In an embodimentexample, the subject may previously or concurrently undergo a cancer treatment. The modified IL-7 or its fusion protein may be administered separately or simultaneously with another anti-cancer drug(s).

[0010] Therefore, various aspectexamples of the disclosure include the following embodimentexamples.

[0011] 1. A method for increasing a lymphocyte count in a subject in need thereof, comprising administering

(i) a modified interleukin-7 of the following formula (I):

A - IL-7 formula (I)

wherein A is an oligopeptide consisting of 1 to 10 amino acid residues, and

the IL-7 is a polypeptide which is capable of binding to IL-7 receptor; or

(ii) an interleukin-7 fusion protein comprising

a first domain comprising the modified interleukin-7 of formula (I),

a second domain comprising an oligopeptide having 1 to 10 amino acid residues consisting of methionine, glycine, or a combination thereof; and

a third domain which prolongs the half-life of the interleukin-7 fusion protein, to the subject at a dose of greater than 600 µg/kg.

[0012] 2. The method of above 1, wherein the subject is suffering from a cancer, infection, chronic failure of the right ventricle of the heart, Hodgkin's disease and cancers of the lymphatic system, leukemia, a leak or rupture in the thoracic duct, side effects of prescription medications including anticancer agents (*e.g.*, chemotherapy), antiviral agents, and glucocorticoids, malnutrition resulting from diets that are low in protein, radiation therapy, uremia, autoimmune disorders, immune deficiency syndromes, high stress levels, trauma, thymectomy, or a combination thereof; or idiopathic, acute radiation syndrome(ARS) or a combination thereof.

[0013] 3. The method of above 1 or 2, the IL-7 has an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 6.

[0014] 4. The method of any one of above 1-3, wherein the A is linked to the N-terminal of the IL-7.

[0015] 5. The method of any one of above 1-4, wherein A is methionine(M), glycine(G), methionine-methionine, glycine-glycine, methionine-glycine, glycine-methionine, methionine-methionine-methionine, methionine-methionine-glycine, methionine-glycine-methionine,

glycine-methionine-methionine, methionine-glycine-glycine, glycine-methionine-glycine, glycine-glycine-methionine, glycine-glycine-glycine, MMMM, MGMM, MGGM, MGGG, MGMG, GMMM, GMGG, GGGG, MMMMM, MMGMM, MMGGM, MGMMG, MMMMG, GGGGG, GGMMM, GGGMG, MGMGMG, MMMGGG, MMGGMM, GGMMGG, MGMGMGMG, MMMMGGGG, MMGGMMGG, MMMMGGGG, MGMGMGMGMG, or and MMMMMGGGGG.

[0016] 6. The method of above 5, wherein the third domain is linked to the N-terminal or C-terminal of the first domain or the second domain. In an embodiment example, the third domain is linked to the C-terminal of the second domain.

[0017] 7. The method of any one of above 1-6, wherein the third domain is any one selected from the group consisting of an Fc region of immunoglobulin or a part thereof, albumin, an albumin-binding polypeptide, Pro/Ala/Ser (PAS), a C-terminal peptide (CTP) of the β subunit of human chorionic gonadotropin, polyethylene glycol (PEG), long unstructured hydrophilic sequences of amino acids (XTEN), hydroxyethyl starch (HES), an albumin-binding small molecule, and a combination thereof.

[0018] 8. The method of any one of above 1-7, wherein the third domain comprises an Fc region of a modified immunoglobulin.

[0019] 9. The method of any one of above 1-8, wherein the modified immunoglobulin is selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE and a combination thereof.

[0020] 10. The method of any one of above 1-9, wherein the Fc region of the modified immunoglobulin comprises a hinge region, a CH2 domain, and a CH3 domain from the N-terminal to the C-terminal direction,

wherein the hinge region comprises a human IgD hinge region,

the CH2 domain comprises a part of the amino acid residues of CH2 domain of human IgD and human IgG4, and

the CH3 domain comprises a part of the amino acid residues of the human IgG4 CH3 domain.

[0021] 11. The method of any one of above 1-10, wherein the Fc region of the modified immunoglobulin is represented by the following Formula (I):

Formula (I)

$N'-(Z1)_p-Y-Z2-Z3-Z4-C'$

wherein N' is the N-terminal of a polypeptide and C' is the C-terminal of a polypeptide;
p is an integer of 0 or 1;

Z1 is an amino acid sequence having 5 to 9 consecutive amino acid residues from the amino acid residue at position 98 toward the N-terminal, among the amino acid residues at positions from 90 to 98 of SEQ ID NO: 7;

Y is an amino acid sequence having 5 to 64 consecutive amino acid residues from the amino acid residue at position 162 toward the N-terminal, among the amino acid residues at positions from 99 to 162 of SEQ ID NO: 7;

Z2 is an amino acid sequence having 4 to 37 consecutive amino acid residues from the amino acid residue at position 163 toward the C-terminal, among the amino acid residues at positions from 163 to 199 of SEQ ID NO: 7;

Z3 is an amino acid sequence having 71 to 106 consecutive amino acid residues from the amino acid residue at position 220 toward the N-terminal, among the amino acid residues at positions from 115 to 220 of SEQ ID NO: 8; and

Z4 is an amino acid sequence having 80 to 107 consecutive amino acid residues from the amino acid residue at position 221 toward the C-terminal, among the amino acid residues at positions from 221 to 327 of SEQ ID NO: 8.

[0022] 12. The method of any one of above 1-11, wherein the third domain has an amino acid sequence selected from the group consisting of SEQ ID NOS: 9 to 14.

[0023] 13. The method of any one of above 2-12, wherein the cancer is a solid tumor, a cancer of lymphatic system, or leukemia.

[0024] 14. The method of above 13, wherein the solid tumor is synovial sarcoma, infiltrating duct carcinoma, rectal cancer, colon cancer, ovary cancer, ascending colon cancer, anal cancer, invasive ductal carcinoma, adenocarcinoma, rectal cancer with paraaortic in metastasis, neuroendocrine carcinoma (cervix), sigmoid colon cancer, or glioblastoma.

[0025] 15. The method of any one of above 1-14, wherein the subject has previously received or concurrently receives one or more of cancer treatments including surgery, radiation, and/or chemotherapy.

[0026] 16. The method of any one of above 1-15, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose in a range from greater than 600 µg/kg to about 2,000 µg /kg.

[0027] 17. The method of any one of above 1-16, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose of about 720 µg/kg or above, about 960 µg/kg or above, about 1,200 µg/kg or above, about 1,700 µg/kg or above, or about 2,000 µg/kg.

[0028] 18. The method of any one of above 1-16, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose of about 720 µg/kg or above, about 840 µg/kg or above, or about 1,440 µg/kg or above.

[0029] 19. The method of any one of above 1-16, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at 720 µg/kg or above, 840 µg/kg or above, 960 µg/kg or above, 1,200 µg/kg or above, 1,440 µg/kg or above, 1,700 µg/kg or above, or 2,000 µg/kg.

[0030] 20. The method of any one of above 1-19, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered twice or more times at an interval of 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, or 12 weeks.

[0031] 21. The method of any one of above 1-19, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered twice or more times at an interval of 10 days, 20 days, 30 days, 40 days, 50 days, 60 days, 70 days, 80 days, 90 days, or 100 days.

[0032] 22. The method of any one of above 1-21, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered parenterally, intramuscularly, subcutaneously, ophthalmic, intravenously, intraperitoneally, intradermally, intraorbitally, intracerebrally, intracranially, intraspinally, intraventricular, intrathecally, intracisternally, intracapsularly, or intratumorally.

[0033] 23. The method of any one of above 1-22, comprising administering the (ii) interleukin-7 fusion protein.

[0034] 24. The method of any one of above 1-23, wherein the (i) modified interleukin-7 has the amino acid sequence of SEQ ID NO: 18, and (ii) interleukin-7 fusion protein comprises the amino acid sequence of SEQ ID NO: 24.

[0035] 25. The method of any one of above 1-24, wherein the subject has a lymphocyte count of 1000 lymphocyte cells or less/µl of blood and/or serum, as determined according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

[0036] 26. The method of any one of above 1-25, wherein the lymphocyte is T-cell.

[0037] 27. The method of any one of above 1-26, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered twice or more times in an amount of about 720 $\mu\text{g/kg}$ at an interval of about 1 week, about 2 weeks, about 3 weeks, or about 4 weeks.

[0038] 28. The method of any one of above 1-26, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered twice or more times in an amount of about 840 $\mu\text{g/kg}$ at an interval of about 2 weeks, about 3 weeks, about 4 weeks, or about 5 weeks.

[0039] 29. The method of any one of above 1-26, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered twice or more times in an amount of about 960 $\mu\text{g/kg}$ at an interval of about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, or about 6 weeks.

[0040] 30. The method of any one of above 1-26, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered twice or more times in an amount of about 1200 $\mu\text{g/kg}$ at an interval of about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, or about 8 weeks.

[0041] 31. The method of any one of above 1-26, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered twice or more times in an amount of about 1440 $\mu\text{g/kg}$ at an interval of about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 10 weeks, or about 12 weeks, or about 2 months or 3 months.

[0042] 32. The method of any one of above 1-26, wherein (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose of greater than about 600 $\mu\text{g/kg}$, greater than about 700 $\mu\text{g/kg}$, greater than about 800 $\mu\text{g/kg}$, greater than about 900 $\mu\text{g/kg}$, greater than about 1,000 $\mu\text{g/kg}$, greater than about 1,100 $\mu\text{g/kg}$, greater than about 1,200 $\mu\text{g/kg}$, greater than about 1,300 $\mu\text{g/kg}$, greater than about 1,400 $\mu\text{g/kg}$, greater than about 1,500 $\mu\text{g/kg}$, greater than about 1,600 $\mu\text{g/kg}$, greater than about 1,700 $\mu\text{g/kg}$, greater than about 1,800 $\mu\text{g/kg}$, greater than about 1,900 $\mu\text{g/kg}$, or about 2,000 $\mu\text{g/kg}$.

[0043] 33. The method of any one of above 1-26, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose of between about 610 $\mu\text{g/kg}$ and about 1,200 $\mu\text{g/kg}$, between about 650 $\mu\text{g/kg}$ and about 1,200 $\mu\text{g/kg}$, between about 700 $\mu\text{g/kg}$ and about 1,200 $\mu\text{g/kg}$, between about 750 $\mu\text{g/kg}$ and about 1,200 $\mu\text{g/kg}$, between about 800 $\mu\text{g/kg}$ and about 1,200 $\mu\text{g/kg}$, between about 850 $\mu\text{g/kg}$ and about 1,200 $\mu\text{g/kg}$, between about 900 $\mu\text{g/kg}$ and about 1,200 $\mu\text{g/kg}$, between about 950 $\mu\text{g/kg}$ and about 1,200 $\mu\text{g/kg}$, between about 1,000 $\mu\text{g/kg}$ and about 1,200 $\mu\text{g/kg}$, between about 1,050 $\mu\text{g/kg}$ and about 1,200 $\mu\text{g/kg}$,

between about 1,100 µg/kg and about 1,200 µg/kg, between about 1,200 µg/kg and about 2,000 µg/kg, between about 1,300 µg/kg and about 2,000 µg/kg, between about 1,500 µg/kg and about 2,000 µg/kg, between about 1,700 µg/kg and about 2,000 µg/kg, between about 610 µg/kg and about 1,000 µg/kg, between about 650 µg/kg and about 1,000 µg/kg, between about 700 µg/kg and about 1,000 µg/kg, between about 750 µg/kg and about 1,000 µg/kg, between about 800 µg/kg and about 1,000 µg/kg, between about 850 µg/kg and about 1,000 µg/kg, between about 900 µg/kg and about 1,000 µg/kg, or between about 950 µg/kg and about 1,000 µg/kg.

[0044] 34. The method of any one of above 1-26, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose of between about 700 µg/kg and about 900 µg/kg, between about 750 µg/kg and about 950 µg/kg, between about 700 µg/kg and about 850 µg/kg, between about 750 µg/kg and about 850 µg/kg, between about 700 µg/kg and about 800 µg/kg, between about 800 µg/kg and about 900 µg/kg, between about 750 µg/kg and about 850 µg/kg, or between about 850 µg/kg and about 950 µg/kg.

[0045] 35. The method of any one of above 1-26, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose of about 650 µg/kg, about 680 µg/kg, about 700 µg/kg, about 720 µg/kg, about 740 µg/kg, about 750 µg/kg, about 760 µg/kg, about 780 µg/kg, about 800 µg/kg, about 820 µg/kg, about 840 µg/kg, about 850 µg/kg, about 860 µg/kg, about 880 µg/kg, about 900 µg/kg, about 920 µg/kg, about 940 µg/kg, about 950 µg/kg, about 960 µg/kg, about 980 µg/kg, about 1,000 µg/kg, about 1,020 µg/kg, about 1,040 µg/kg, about 1,060 µg/kg, about 1,080 µg/kg, about 1,100 µg/kg, about 1,120 µg/kg, about 1,140 µg/kg, about 1,160 µg/kg, about 1,180 µg/kg, about 1,200 µg/kg, about 1,220 µg/kg, about 1,240 µg/kg, about 1,260 µg/kg, about 1,280 µg/kg, about 1,300 µg/kg, about 1,320 µg/kg, about 1,340 µg/kg, about 1,360 µg/kg, about 1,380 µg/kg, about 1,400 µg/kg, about 1,420 µg/kg, about 1,440 µg/kg, about 1,460 µg/kg, about 1,480 µg/kg, about 1,500 µg/kg, about 1,520 µg/kg, about 1,540 µg/kg, about 1,560 µg/kg, about 1,580 µg/kg, about 1,600 µg/kg, about 1,620 µg/kg, about 1,640 µg/kg, about 1,660 µg/kg, about 1,680 µg/kg, about 1,700 µg/kg, about 1,720 µg/kg, about 1,740 µg/kg, about 1,760 µg/kg, about 1,780 µg/kg, about 1,800 µg/kg, about 1,820 µg/kg, about 1,840 µg/kg, about 1,860 µg/kg, about 1,880 µg/kg, about 1,900 µg/kg, about 1,920 µg/kg, about 1,940 µg/kg, about 1,960 µg/kg, about 1,980 µg/kg, or about 2,000 µg/kg.

[0046] 36. The method of any one of above 32-35, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dosing frequency of once a week, once in two weeks, once in three weeks, once in four weeks, once in five weeks, once in six weeks, once

in seven weeks, once in eight weeks, once in nine weeks, once in 10 weeks, once in 11 weeks, or once in 12 weeks.

[0047] 37. The method of above 26, wherein the T-cell is CD4⁺ T-cell and/or CD8⁺ T-cell.

[0048] 38. The method of above 26, wherein the T-cell is CD4⁺/CD8⁺ T-cell.

[0049] 39. The method of any one of above 1-38, wherein the the subject has a lymphocyte count of 800 lymphocyte cells or less/ μ l of blood.

[0050] 40. The method of any one of above 1-39, wherein the the subject has a lymphocyte count of 500 lymphocyte cells or less/ μ l of blood.

[0051] 41. The method of any one of above 1-40, wherein the the subject has a lymphocyte count of 200 lymphocyte cells or less/ μ l of blood.

[0052] 42. The method of any one of above 15-41, wherein the subject is concurrently administered with an anti-cancer agent.

[0053] 43. The method of above 42, wherein the anti-cancer agent is an anti-cancer chemical compound.

[0054] 44. The method of any one of above 1-43, wherein a number of tumor infiltrating lymphocytes (TILs) in the tumor is increased after the administration of the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein compared to a number of TILs in a tumor before administration.

[0055] 45. The method of any one of above 1-44, wherein the TILs are CD4⁺ TILs.

[0056] 46. The method of any one of above 1-44, wherein the TILs are CD8⁺ TILs.

[0057] 47. The method of any one of above 44-46, wherein the number of TILs is increased by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 125%, at least about 150%, at least about 200%, at least about 250%, or at least about 300% after the administration.

[0058] 48. The method of any one of above 1-26, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose of about 650 μ g/kg - 680 μ g/kg, about 680 μ g/kg - 700 μ g/kg, about 700 μ g/kg - 720 μ g/kg, about 720 μ g/kg - 740 μ g/kg, about 740 μ g/kg - 750 μ g/kg, about 750 μ g/kg - 760 μ g/kg, about 760 μ g/kg - 780 μ g/kg, about 780 μ g/kg - 800 μ g/kg, about 800 μ g/kg - 820 μ g/kg, about 820 μ g/kg - 840 μ g/kg, about 840 μ g/kg - 850 μ g/kg, about 850 μ g/kg - 860 μ g/kg, about 860 μ g/kg - 880 μ g/kg, about 880 μ g/kg - 900

$\mu\text{g/kg}$, about 900 $\mu\text{g/kg}$ - 920 $\mu\text{g/kg}$, about 920 $\mu\text{g/kg}$ - 940 $\mu\text{g/kg}$, about 940 $\mu\text{g/kg}$ - 950 $\mu\text{g/kg}$,
 about 950 $\mu\text{g/kg}$ - 960 $\mu\text{g/kg}$, about 960 $\mu\text{g/kg}$ - 980 $\mu\text{g/kg}$, about 980 $\mu\text{g/kg}$ - 1000 $\mu\text{g/kg}$, about
 1,000 $\mu\text{g/kg}$ - 1,020 $\mu\text{g/kg}$, about 1,020 $\mu\text{g/kg}$ - 1,040 $\mu\text{g/kg}$, about 1,040 $\mu\text{g/kg}$ - 1,060 $\mu\text{g/kg}$,
 about 1,060 $\mu\text{g/kg}$ - 1,080 $\mu\text{g/kg}$, about 1,080 $\mu\text{g/kg}$ - 1,100 $\mu\text{g/kg}$, about 1,100 $\mu\text{g/kg}$ - 1,120
 $\mu\text{g/kg}$, about 1,120 $\mu\text{g/kg}$ - 1,140 $\mu\text{g/kg}$, about 1,140 $\mu\text{g/kg}$ - 1,160 $\mu\text{g/kg}$, about 1,160 $\mu\text{g/kg}$ -
 1,180 $\mu\text{g/kg}$, about 1,180 $\mu\text{g/kg}$ - 1,200 $\mu\text{g/kg}$, about 1,200 $\mu\text{g/kg}$ - 1,220 $\mu\text{g/kg}$, about 1,220
 $\mu\text{g/kg}$ - 1,240 $\mu\text{g/kg}$, about 1,240 $\mu\text{g/kg}$ - 1,260 $\mu\text{g/kg}$, about 1,260 $\mu\text{g/kg}$ - 1,280 $\mu\text{g/kg}$, about
 1,280 $\mu\text{g/kg}$ - 1,300 $\mu\text{g/kg}$, about 1,300 $\mu\text{g/kg}$ - 1,320 $\mu\text{g/kg}$, about 1,320 $\mu\text{g/kg}$ - 1,340 $\mu\text{g/kg}$,
 about 1,340 $\mu\text{g/kg}$ - 1,360 $\mu\text{g/kg}$, about 1,360 $\mu\text{g/kg}$ - 1,380 $\mu\text{g/kg}$, about 1,380 $\mu\text{g/kg}$ - 1,400
 $\mu\text{g/kg}$, about 1,400 $\mu\text{g/kg}$ - 1,420 $\mu\text{g/kg}$, about 1,420 $\mu\text{g/kg}$ - 1,440 $\mu\text{g/kg}$, about 1,440 $\mu\text{g/kg}$ -
 1,460 $\mu\text{g/kg}$, about 1,480 $\mu\text{g/kg}$, about 1,480 $\mu\text{g/kg}$ - 1,500 $\mu\text{g/kg}$, about 1,500 $\mu\text{g/kg}$ - 1,520
 $\mu\text{g/kg}$, about 1,520 $\mu\text{g/kg}$ - 1,540 $\mu\text{g/kg}$, about 1,540 $\mu\text{g/kg}$ - 1,560 $\mu\text{g/kg}$, about 1,560 $\mu\text{g/kg}$ -
 1,580 $\mu\text{g/kg}$, about 1,580 $\mu\text{g/kg}$ - 1,600 $\mu\text{g/kg}$, about 1,600 $\mu\text{g/kg}$ - 1,620 $\mu\text{g/kg}$, about 1,620
 $\mu\text{g/kg}$ - 1,640 $\mu\text{g/kg}$, about 1,640 $\mu\text{g/kg}$ - 1,660 $\mu\text{g/kg}$, about 1,660 $\mu\text{g/kg}$ - 1,680 $\mu\text{g/kg}$, about
 1,680 $\mu\text{g/kg}$ - 1,700 $\mu\text{g/kg}$, about 1,700 $\mu\text{g/kg}$ - 1,720 $\mu\text{g/kg}$, about 1,720 $\mu\text{g/kg}$ - 1,740 $\mu\text{g/kg}$,
 about 1,740 $\mu\text{g/kg}$ - 1,760 $\mu\text{g/kg}$, about 1,760 $\mu\text{g/kg}$ - 1,780 $\mu\text{g/kg}$, about 1,780 $\mu\text{g/kg}$ - 1,800
 $\mu\text{g/kg}$, about 1,800 $\mu\text{g/kg}$ - 1,820 $\mu\text{g/kg}$, about 1,820 $\mu\text{g/kg}$ - 1,840 $\mu\text{g/kg}$, about 1,840 $\mu\text{g/kg}$ -
 1,860 $\mu\text{g/kg}$, about 1,860 $\mu\text{g/kg}$ - 1,880 $\mu\text{g/kg}$, about 1,880 $\mu\text{g/kg}$ - 1,900 $\mu\text{g/kg}$, about 1,900
 $\mu\text{g/kg}$ - 1,920 $\mu\text{g/kg}$, about 1,920 $\mu\text{g/kg}$ - 1,940 $\mu\text{g/kg}$, about 1,940 $\mu\text{g/kg}$ - 1,960 $\mu\text{g/kg}$, about
 1,960 $\mu\text{g/kg}$ - 1,980 $\mu\text{g/kg}$, or about 1,980 $\mu\text{g/kg}$ - 2,000 $\mu\text{g/kg}$.

[0059] 49. The method of above 48, wherein the (i) modified interleukin-7 or the (ii)
 interleukin-7 fusion protein is administered twice, three times, four times, or five times with the
 above dose at an interval of about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about
 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about
 12 weeks, about 13 weeks, about 14 weeks, or about 15 weeks.

BRIEF DESCRIPTION OF DRAWINGS

[0060] FIGS. 1A, 1B, and 1C show pharmacokinetic profiles by IV, SC, and IM route in
 rats, respectively.

[0061] FIGS. 2A and 2B show GX-I7 concentration-time Profiles by Dose, shown in linear
 scale and log scale.

[0062] FIGS. 3A and 3B show serum exposure ($C_{\max}$ and AUC_{last}) vs dose correlation, respectively.

[0063] FIGS. 4A and 4B show changes in absolute lymphocyte count (ALC) in comparison with the baseline value in low dose (60-120 $\mu\text{g/kg}$), medium dose (240-480 $\mu\text{g/kg}$), and high dose (720-1,200 $\mu\text{g/kg}$) groups. FIG. 4A shows the results from solid cancer patient group and FIG. 4B shows the results from glioblastoma patient group.

Claims

1. ~~A method for increasing a lymphocyte count in a subject in need thereof, comprising administering~~ Use of the following (i) and/or (ii) in the manufacture of a medicament for increasing a lymphocyte count in a subject in need thereof, comprising that a dose of greater than about 600 µg/kg of (i) or a dose of greater than about 60 µg/kg of (ii) is to be administered to the subject,

(i) a modified interleukin-7 of the following formula (I):

A - IL-7 formula (I)

wherein A is an oligopeptide consisting of 1 to 10 amino acid residues, and

the IL-7 is a polypeptide which is capable of binding to IL-7 receptor; or

(ii) an interleukin-7 fusion protein comprising

(a) the modified interleukin-7,

(b) a second domain comprising an oligopeptide having 1 to 10 amino acid residues consisting of methionine, glycine, or a combination thereof; and

(c) a third domain which prolongs the half-life of the interleukin-7 fusion protein;

~~to the subject at a dose of greater than about 600 µg/kg.~~

2. The ~~method-use~~ of claim 1, wherein the subject is suffering from a cancer; infection; chronic failure of the right ventricle of the heart; Hodgkin's disease; a leak or rupture in the thoracic duct; side effects of prescription medications including anticancer agents (*e.g.*, chemotherapy), antiviral agents, or glucocorticoids; malnutrition resulting from diets that are low in protein, radiation therapy, uremia, autoimmune disorders, immune deficiency syndromes, thymectomy, or a combination thereof; or idiopathic, acute radiation syndrome(ARS) or a combination thereof.

3. The methoduse of claim 1 or 2, wherein the IL-7 has an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 6.

~~4. The method of claim 3, wherein the A is linked to the N-terminal of the IL-7.~~

45. The methoduse of claim 3, wherein A is methionine, glycine, methionine-methionine, glycine-glycine, methionine-glycine, glycine-methionine, methionine-methionine-methionine, methionine-methionine-glycine, methionine-glycine-methionine, glycine-methionine-methionine, methionine-glycine-glycine, glycine-methionine-glycine, glycine-glycine-methionine, or glycine-glycine-glycine.

~~6. The method of claim 5, wherein the third domain is linked to the N-terminal or C-terminal of the first domain or the second domain.~~

~~7. The method of any one of claims 4-6, wherein the third domain is any one selected from the group consisting of an Fc region of immunoglobulin or a part thereof, albumin, an albumin-binding polypeptide, Pro/Ala/Ser (PAS), a C-terminal peptide (CTP) of the β subunit of human chorionic gonadotropin, polyethylene glycol (PEG), long unstructured hydrophilic sequences of amino acids (XTEN), hydroxyethyl starch (HES), an albumin-binding small molecule, and a combination thereof.~~

58. The methoduse of claim 17, wherein the third domain comprises an Fc region of a modified immunoglobulin.

69. The ~~method~~use of claim 58, wherein the modified immunoglobulin is selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE and a combination thereof.

710. The ~~method~~use of claim 69, wherein the Fc region of the modified immunoglobulin comprises a hinge region, a CH2 domain, and a CH3 domain from the N-terminal to the C-terminal direction,

wherein the hinge region comprises a human IgD hinge region,

the CH2 domain comprises a part of the amino acid residues of CH2 domain of human IgD and human IgG4, and

the CH3 domain comprises a part of the amino acid residues of the human IgG4 CH3 domain.

811. The ~~method~~use of claim 710, wherein the Fc region of the modified immunoglobulin is represented by the following Formula (I):

Formula (I)

$N'-(Z1)_p-Y-Z2-Z3-Z4-C'$

wherein N' is the N-terminal of a polypeptide and C' is the C-terminal of a polypeptide;

p is an integer of 0 or 1;

Z1 is an amino acid sequence having 5 to 9 consecutive amino acid residues from the amino acid residue at position 98 toward the N-terminal, among the amino acid residues at positions from 90 to 98 of SEQ ID NO: 7;

Y is an amino acid sequence having 5 to 64 consecutive amino acid residues from the amino acid residue at position 162 toward the N-terminal, among the amino acid residues at positions from 99 to 162 of SEQ ID NO: 7;

Z2 is an amino acid sequence having 4 to 37 consecutive amino acid residues from the amino acid residue at position 163 toward the C-terminal, among the amino acid residues at positions from 163 to 199 of SEQ ID NO: 7;

Z3 is an amino acid sequence having 71 to 106 consecutive amino acid residues from the amino acid residue at position 220 toward the N-terminal, among the amino acid residues at positions from 115 to 220 of SEQ ID NO: 8; and

Z4 is an amino acid sequence having 80 to 107 consecutive amino acid residues from the amino acid residue at position 221 toward the C-terminal, among the amino acid residues at positions from 221 to 327 of SEQ ID NO: 8.

912. The ~~method~~use of claim 1, wherein the third domain has an amino acid sequence selected from the group consisting of SEQ ID NOS: 9 to 14.

1013. The ~~method~~use of claim 2, wherein the cancer is a solid tumor, a cancer of lymphatic system, or leukemia.

1114. The ~~method~~use of claim 1013, wherein the solid tumor is synovial sarcoma, infiltrating duct carcinoma, rectal cancer, colon cancer, ovary cancer, ascending colon cancer, anal cancer, invasive ductal carcinoma, adenocarcinoma, rectal cancer with paraaortic in metastasis, neuroendocrine carcinoma (cervix), sigmoid colon cancer, or glioblastoma.

1215. The ~~method~~use of any one of claims 1, 2, 1013, or 1114, wherein the subject has previously received, concurrently receives, or will receive one or more of cancer treatments including surgery, radiation, and/or chemotherapy.

~~1316.~~ The ~~method~~use of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is to be administered at a dose in a range from greater than ~~about~~ 600 µg/kg to ~~about~~ 2,000 µg /kg.

~~17. The method of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose of about 720 µg/kg or above, about 960 µg/kg or above, about µg/kg or above, 1,200 µg/kg or above, about 1,700 µg/kg or above, or about 2,000 µg/kg.~~

~~18. The method of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose at a dose of about 720 µg/kg or above, about 840 µg/kg or above, or about 1,440 µg/kg or above.~~

~~19. The method of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose of about 720 µg/kg or above, about 840 µg/kg or above, about 960 µg/kg or above, about 1,200 µg/kg or above, about 1,440 µg/kg or above, about 1,700 µg/kg or above, or about 2,000 µg/kg.~~

~~1420.~~ The ~~method~~use of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is to be administered twice or more times at an interval of 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, or 15 weeks.

~~21. The method of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered twice or more times at an interval of 10 days, 20 days, 30 days, 40 days, 50 days, 60 days, 70 days, 80 days, 90 days, or 100 days.~~

~~1522.~~ The ~~method~~use of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is to be administered parenthetically, intramuscularly, subcutaneously, ophthalmic, intravenously, intraperitoneally, intradermally, intraorbitally, intracerebrally, intracranially, intraspinally, intraventricular, intrathecally, intracistemally, intracapsularly, or intratumorally.

~~23. The method of claims 1 or 2, comprising administering the (ii) interleukin-7 fusion protein.~~

~~1624.~~ The ~~method~~use of claim ~~123~~, wherein the (ii) interleukin-7 fusion protein comprises the amino acid sequence of SEQ ID NO: 24.

~~25. The method of claims 1 or 2, wherein the subject has a lymphocyte count of about 1000 lymphocyte cells or less/ μ l of blood, as determined according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.~~

~~26. The method of claim 25, wherein the lymphocyte is T-cell.~~

~~27. The method of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered twice or more times in an amount of about 720 μ g/kg at~~

~~an interval of about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 week, or about 6 weeks.~~

~~28. The method of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered twice or more times in an amount of about 840 µg/kg at an interval of about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, or about 6 weeks.~~

~~29. The method of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered twice or more times in an amount of about 960 µg/kg at an interval of about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, or about 9 weeks.~~

~~30. The method of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered twice or more times in an amount of about 1,200 µg/kg at an interval of about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, or about 10 weeks.~~

~~31. The method of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered twice or more times in an amount of about 1,440 µg/kg at an interval of about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 2 months, or about 3 months.~~

~~32. The method of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose of greater than about 600 µg/kg, greater than about 700 µg/kg, greater than about 800 µg/kg, greater than about 900 µg/kg, greater than about~~

~~1,000 µg/kg, greater than about 1,100 µg/kg, greater than about 1,200 µg/kg, greater than about 1,300 µg/kg, greater than about 1,400 µg/kg, greater than about 1,500 µg/kg, greater than about 1,600 µg/kg, greater than about 1,700 µg/kg, greater than about 1,800 µg/kg, greater than about 1,900 µg/kg, or greater than about 2,000 µg/kg.~~

33. — ~~The method of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose of between about 610 µg/kg and about 1,200 µg/kg, between about 650 µg/kg and about 1,200 µg/kg, between about 700 µg/kg and about 1,200 µg/kg, between about 750 µg/kg and about 1,200 µg/kg, between about 800 µg/kg and about 1,200 µg/kg, between about 850 µg/kg and about 1,200 µg/kg, between about 900 µg/kg and about 1,200 µg/kg, between about 950 µg/kg and about 1,200 µg/kg, between about 1,000 µg/kg and about 1,200 µg/kg, between about 1,050 µg/kg and about 1,200 µg/kg, between about 1,100 µg/kg and about 1,200 µg/kg, between about 1,200 µg/kg and about 2,000 µg/kg, between about 1,300 µg/kg and about 2,000 µg/kg, between about 1,500 µg/kg and about 2,000 µg/kg, between about 1,700 µg/kg and about 2,000 µg/kg, between about 610 µg/kg and about 1,000 µg/kg, between about 650 µg/kg and about 1,000 µg/kg, between about 700 µg/kg and about 1,000 µg/kg, between about 750 µg/kg and about 1,000 µg/kg, between about 800 µg/kg and about 1,000 µg/kg, between about 850 µg/kg and about 1,000 µg/kg, between about 900 µg/kg and about 1,000 µg/kg, or between about 950 µg/kg and about 1,000 µg/kg.~~

34. — ~~The method of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose of between about 700 µg/kg and about 900 µg/kg, between about 750 µg/kg and about 950 µg/kg, between about 700 µg/kg and about 850 µg/kg, between about 750 µg/kg and about 850 µg/kg, between about 700 µg/kg and about 800 µg/kg, between about 800 µg/kg and about 900 µg/kg, between about 750 µg/kg and about 850 µg/kg, or between about 850 µg/kg and about 950 µg/kg.~~

~~35. The method of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is administered at a dose of about 650 µg/kg, about 680 µg/kg, about 700 µg/kg, about 720 µg/kg, about 740 µg/kg, about 750 µg/kg, about 760 µg/kg, about 780 µg/kg, about 800 µg/kg, about 820 µg/kg, about 840 µg/kg, about 850 µg/kg, about 860 µg/kg, about 880 µg/kg, about 900 µg/kg, about 920 µg/kg, about 940 µg/kg, about 950 µg/kg, about 960 µg/kg, about 980 µg/kg, about 1,000 µg/kg, about 1,020 µg/kg, about 1,040 µg/kg, about 1,060 µg/kg, about 1,080 µg/kg, about 1,100 µg/kg, about 1,120 µg/kg, about 1,140 µg/kg, about 1,160 µg/kg, about 1,180 µg/kg, about 1,200 µg/kg, about 1,220 µg/kg, about 1,240 µg/kg, about 1,260 µg/kg, about 1,280 µg/kg, about 1,300 µg/kg, about 1,320 µg/kg, about 1,340 µg/kg, about 1,360 µg/kg, about 1,380 µg/kg, about 1,400 µg/kg, about 1,420 µg/kg, about 1,440 µg/kg, about 1,460 µg/kg, about 1,480 µg/kg, about 1,500 µg/kg, about 1,520 µg/kg, about 1,540 µg/kg, about 1,560 µg/kg, about 1,580 µg/kg, about 1,600 µg/kg, about 1,620 µg/kg, about 1,640 µg/kg, about 1,660 µg/kg, about 1,680 µg/kg, about 1,700 µg/kg, about 1,720 µg/kg, about 1,740 µg/kg, about 1,760 µg/kg, about 1,780 µg/kg, about 1,800 µg/kg, about 1,820 µg/kg, about 1,840 µg/kg, about 1,860 µg/kg, about 1,880 µg/kg, about 1,900 µg/kg, about 1,920 µg/kg, about 1,940 µg/kg, about 1,960 µg/kg, about 1,980 µg/kg, or about 2,000 µg/kg.~~

1736. The method of claims 1 or 2, wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is to be administered at a dose of about 60 µg/kg or above, about 120 µg/kg or above, about 240 µg/kg or above, about 360 µg/kg or above, about 480 µg/kg or above, about 600 µg/kg or above, about 720 µg/kg or above, about 840 µg/kg or above, about 960 µg/kg or above, about 1,200 µg/kg or above, about 1,440 µg/kg or above, about 1,700 µg/kg or above, or about 2,000 µg/kg, and wherein the (i) modified interleukin-7 or the (ii) interleukin-7 fusion protein is to be administered at a dosing frequency of once a week, once in every two weeks, once in every three weeks, once in every four weeks, once in every five weeks, once in every six weeks, once in every seven weeks, once in every eight weeks, once in every nine weeks, once in every 10 weeks, once in

every 11 weeks, once in every 12 weeks, once in every 13 weeks, once in every 14 weeks, or once in every 15 weeks.

~~37. The method of claim 26, wherein the T-cell is CD4⁺ and/or CD8⁺ T-cell.~~

~~38. The method of claim 26, wherein the T-cell is CD4⁺/CD8⁺ T-cell.~~

~~39. The method of claim 25, wherein the the subject has a lymphocyte count of about 800 lymphocyte cells or less/ μ l of blood.~~

~~40. The method of claim 25, wherein the the subject has a lymphocyte count of about 500 lymphocyte cells or less/ μ l of blood.~~

~~41. The method of claim 25, wherein the the subject has a lymphocyte count of about 200 lymphocyte cells or less/ μ l of blood.~~

~~42. The method of claims 1 or 2, wherein the subject has been, is to be concurrently, or will be administered with an anti-cancer agent.~~

~~43. The method of claim 42, wherein the anti-cancer agent is an anti-cancer chemical compound.~~

1844. The ~~method~~use of claims ~~1025 or 42~~, wherein a number of tumor infiltrating lymphocytes (TILs) in the tumor is increased after the administration of the (i) modified interleukin-7

or the (ii) interleukin-7 fusion protein compared to a number of TILs in a tumor before the administration.

~~45. The method of claim 44, wherein the TILs are CD4⁺ TILs.~~

~~46. The method of claim 44, wherein the TILs are CD8⁺ TILs.~~

~~47. The method of claim 44, wherein the number of TILs is increased by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 125%, at least about 150%, at least about 200%, at least about 250%, or at least about 300% after the administration.~~

~~48. A use of the following (i) and/or (ii) for increasing a lymphocyte count in a subject in need thereof, comprising administering~~

~~(i) a modified interleukin-7 of the following formula (I):~~

~~A-IL-7—formula (I)~~

~~wherein A is an oligopeptide consisting of 1 to 10 amino acid residues, and~~

~~the IL-7 is a polypeptide which is capable of binding to IL-7 receptor; and/or~~

~~(ii) an interleukin-7 fusion protein comprising~~

~~—(a) the modified interleukin-7,~~

~~—(b) a second domain comprising an oligopeptide having 1 to 10 amino acid residues consisting of methionine, glycine, or a combination thereof; and~~

~~—(c) a third domain which prolongs the half-life of the interleukin-7 fusion protein,~~

~~to the subject at a dose of greater than about 600 µg/kg.~~

~~49.~~ A use of the following (i) and/or (ii) in manufacturing a medicament for use in increasing a lymphocyte count in a subject in need thereof, said medicament being administered to the patient at a dose of greater than about 600 µg/kg,

~~(i) a modified interleukin-7 of the following formula (I):~~

~~A - IL-7 ————— formula (I)~~

~~wherein A is an oligopeptide consisting of 1 to 10 amino acid residues, and~~

~~the IL-7 is a polypeptide which is capable of binding to IL-7 receptor; and/or~~

~~(ii) an interleukin-7 fusion protein comprising~~

~~————— (a) the modified interleukin-7,~~

~~————— (b) a second domain comprising an oligopeptide having 1 to 10 amino acid residues consisting of methionine, glycine, or a combination thereof; and~~

~~————— (c) a third domain which prolongs the half-life of the interleukin-7 fusion protein.~~

5019. A pharmaceutical composition for use in increasing a lymphocyte count in a subject in need thereof, comprising as an active ingredient,

(i) a modified interleukin-7 of the following formula (I):

A - IL-7 formula (I)

wherein A is an oligopeptide consisting of 1 to 10 amino acid residues, and

the IL-7 is a polypeptide which is capable of binding to IL-7 receptor; and/or

(ii) an interleukin-7 fusion protein comprising

(a) the modified interleukin-7,

(b) a second domain comprising an oligopeptide having 1 to 10 amino acid residues consisting of methionine, glycine, or a combination thereof; and

(c) a third domain which prolongs the half-life of the interleukin-7 fusion

protein,

wherein said pharmaceutical composition is to be administered to the subject at a dose of greater than about 600 µg/kg of (i) or a dose of greater than about 60 µg/kg of (ii).