

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 describes 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 refers to the use of an interleukin-7 fusion protein in the manufacture of a medicament for treating cancer by increasing a lymphocyte count in a human subject in need thereof, comprising that a dose of 60 µg/kg to 2000 µg/kg every 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 10 days, 20 days, 30 days, 40 days, 50 days, 60 days, 80 days, 90 days, or 100 days is to be administered to the human subject, wherein the interleukin-7 fusion protein comprises: (a) interleukin-7(IL-7); (b) a second domain which is an oligopeptide having 1 to 10 amino acid residues consisting of methionine, glycine, or a combination thereof, wherein the oligopeptide 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; and (c) a third domain which prolongs the half-life of the interleukin-7 fusion protein, wherein the third domain comprises an Fc region of a modified immunoglobulin, 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, wherein the second domain is linked to the N-terminal of IL-7 and the third domain is linked to the C-terminal of IL-7. Another example describes 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 example, there is described 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 example describes 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 example, the solid tumor may be locally advanced or metastatic solid tumors or glioblastoma.

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

[009] In an example, 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).

Claims

1. Use of an interleukin-7 fusion protein in the manufacture of a medicament for treating cancer by increasing a lymphocyte count in a human subject in need thereof, comprising that a dose of 60 µg/kg to 2000 ug/kg every 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 10 days, 20 days, 30 days, 40 days, 50 days, 60 days, 80 days, 90 days, or 100 days is to be administered to the human subject, wherein the interleukin-7 fusion protein comprises:

- (a) interleukin-7(IL-7);
- (b) a second domain which is an oligopeptide having 1 to 10 amino acid residues consisting of methionine, glycine, or a combination thereof, wherein the oligopeptide 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; and
- (c) a third domain which prolongs the half-life of the interleukin-7 fusion protein, wherein the third domain comprises an Fc region of a modified immunoglobulin, 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, wherein the second domain is linked to the N-terminal of IL-7 and the third domain is linked to the C-terminal of IL-7.

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

3. The use of claim 1, 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.

4. The 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.
5. The use of claim 1, wherein the cancer is a solid tumor, a cancer of lymphatic system, or leukemia.
6. The use of claim 5, 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.
7. The use of any one of claims 1 to 6, wherein the human subject has previously received, concurrently receives, or will receive one or more of cancer treatments including surgery, radiation, and/or chemotherapy.
8. The use of any one of claims 1 to 7, wherein the interleukin-7 fusion protein is to be administered at a dose in a range from greater than 720 µg/kg to 1,440 µg /kg.
9. The use of any one of claims 1 to 8, wherein the interleukin-7 fusion protein is to be administered twice or more times at an interval of 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.
10. The use of claims of any one of claims 1 to 9, wherein the interleukin-7 fusion protein is to be administered parenterally, intramuscularly, subcutaneously, ophthalmic, intravenously, intraperitoneally, intradermally, intraorbitally, intracerebrally, intracranially,

intraspinally, intraventricular, intrathecally, intracisternally, intracapsularly, or intratumorally.

11. The use of any one of claims 1 to 10, wherein the interleukin-7 fusion protein comprises the amino acid sequence of SEQ ID NO: 24.

12. The use of any one of claims 1 to 11, wherein the interleukin-7 fusion protein is to be administered 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.

13. The use of claim 5, wherein a number of tumor infiltrating lymphocytes (TILs) in the tumor is increased after the administration of the interleukin-7 fusion protein compared to a number of TILs in a tumor before the administration.