

apparent in the finger flexors and knee extensors. Inflammation is evident from the invasion of muscle fibers by immune cells. Large granular lymphocyte expansions are present in both blood and muscle and provides additional biomarkers for IBM and suggests a mechanistic relationship to the neoplastic disease T-cell large granular lymphocytic leukemia. Most (58%) patients with IBM have aberrant populations of large granular lymphocytes in their blood meeting standard diagnostic criteria for T-cell LGLL. Muscle immunohistochemistry analysis has demonstrated invasion of large granular lymphocytes into muscle in 15/15 IBM patients but in only 1/28 patients with dermatomyositis or polymyositis.

[0011] Current therapies for diseases involving large granular lymphocytes (LGLs) do not selectively reduce the levels of or deplete LGL or NK cells. Accordingly, it would be beneficial to develop more efficacious and safer therapies for treating diseases mediated by LGL and NK cells.

SUMMARY OF THE DISCLOSURE

[0011a] In an aspect of the present disclosure, there is provided a use of an antibody that specifically binds to human CD94 in the manufacture of a medicament for treating a disease or disorder in a subject, wherein the antibody is to be administered to the subject, wherein the antibody comprises a human IgG1 Fc region that is non-fucosylated and/or the antibody specifically binds to a human cellular Fc gamma receptor IIIA to a greater extent than an antibody comprising a wild type human IgG1 Fc region, and wherein the disease or disorder is selected from the group consisting of chronic lymphoproliferative disorder of NK cells (CLPD-NK), LGL leukemia, Felty's syndrome, rheumatoid arthritis, aggressive NK leukemia, inclusion body myositis, and inflammatory bowel disease.

[0011b] In another aspect of the present disclosure, there is provided a use of an antibody that specifically binds to human CD94 in the manufacture of a medicament for inducing ADCC activity in a subject, wherein the antibody is to be administered to the subject, wherein the antibody comprises a human IgG1 Fc region that is non-fucosylated and/or the antibody specifically binds to a human cellular Fc gamma receptor IIIA to a greater extent than an antibody comprising a wild type human IgG1 Fc region, wherein the subject has a disease or disorder selected from the group consisting of chronic lymphoproliferative disorder of NK cells (CLPD-NK), LGL leukemia, Felty's syndrome, rheumatoid arthritis, aggressive NK leukemia, inclusion body myositis, and inflammatory bowel disease, and wherein the antibody reduces the number of peripheral blood LGL and/or NK cells in the subject.

[0011c] In a further aspect of the present disclosure, there is provided a use of an antibody that specifically binds to human CD94 in the manufacture of a medicament for treating CLPD-NK in a human subject in need thereof, wherein the antibody is to be administered to the human subject, wherein the antibody comprises a human IgG1 Fc region that is non-fucosylated and/or the antibody specifically binds to a human cellular Fc gamma receptor IIIA to a greater extent than an antibody comprising a wild type human IgG1 Fc region.

[0012] The present disclosure relates to a method of depleting or reducing the numbers of large granular lymphocytes and natural killer cells in a human subject upon administration of CD94 or CD57 or NKG2A binding molecule that consists of a part that specifically binds to the CD94 or CD57 or NKG2A receptors and an immunoglobulin Fc part.

[0013] The disclosure provides a method of treating for treating LGL leukemia, Felty's syndrome, rheumatoid arthritis, aggressive NK leukemia, IBM, or IBD in a subject, comprising administering to said subject an effective amount of an antibody that specifically binds to human CD94, human CD57 or human NKG2A, wherein the antibody comprises a human immunoglobulin Fc region having enhanced ADCC activity as compared to wild type IgG1 Fc region.

[0014] The disclosure provides a method of reducing the number or depleting of peripheral blood LGL or NK cells in a human subject by administering to said subject between about 0.01 to about 25 mg/kg of antibody that is specific for either CD94 or CD57 or NKG2A or an additional cell surface protein that is specific for LGL cells and comprising an immunoglobulin Fc region including no fucose or Fc mutations that enhance its binding to CD16 in which the administration of the antibody reduces the number of peripheral blood LGL or NK cells below the limit of detection and the level remains below detection for at least about 1 week after dosing of the antibody. In some examples, the reduction of LGL or NK cells takes place within the first 24 hours after administration. In some examples, the reduction of LGL or NK cells is reversible. In some examples, the reduction in LGL or NK cells leads to a reduction in LGL leukemia symptoms. In some examples, the reduction in LGL or NK cells leads to a reduction in Felty's syndrome symptoms. In some examples, the reduction in LGL or NK cells leads to a reduction in IBM symptoms. In some examples, the reduction in LGL or NK cells leads to a reduction in aggressive NK leukemia symptoms.

[0015] In one example, provided herein is a method for treating LGL leukemia, Felty's syndrome, rheumatoid arthritis, aggressive NK leukemia, IBM, or IBD in a subject, comprising administering to said subject an effective amount of an antibody that specifically binds to human CD94, human CD57 or human NKG2A, wherein the antibody comprises a human immunoglobulin Fc region having enhanced ADCC

activity as compared to wild type IgG1 Fc region. In some examples, the administration of the antibody reduces the number of peripheral blood LGL or NK cells below the limit of detection and/or the level remains below detection for at least about 1 week after dosing of the antibody. In some examples, the reduction of LGL or NK cells takes place within the first 24 hours after administration. In some examples, the reduction of LGL or NK cells is reversible. In some examples, said reduction in LGL or NK cells leads to a reduction in LGL leukemia symptoms. In some examples, said reduction in LGL or NK cells leads to a reduction in Felty's syndrome symptoms. In some examples, said reduction in LGL or NK cells leads to a reduction in IBM symptoms. In some examples, said reduction in LGL or NK cells leads to a reduction in aggressive NK leukemia symptoms. In some examples, the subject is a mammal. In some examples, the subject is a human. In some examples, the Fc region of the antibody comprises a human IgG1 Fc which is non-fucosylated.

[0016] In another example, provided herein is a method for treating a disease or disorder in a subject, comprising administering to the subject an effective amount of an antibody that specifically binds to a cell surface protein selected from human CD94, human CD57, or human NKG2A, wherein the antibody comprises a human immunoglobulin Fc region comprising enhanced ADCC activity compared to a wild type IgG1 Fc region, and wherein the disease or disorder is selected from chronic lymphoproliferative disorder of NK cells (CLPD-NK), LGL leukemia, Felty's syndrome, rheumatoid arthritis, aggressive NK leukemia, inclusion body myositis, or inflammatory bowel disease. In some examples, administration of the antibody results in a reduction in the number of peripheral blood LGL or NK cells in the subject.

[0017] In another example, provided herein is a method for reducing the number of peripheral blood LGL and/or NK cells in a subject, comprising administering to the subject an effective amount of an antibody that specifically binds to a cell surface protein selected from human CD94, human CD57, or human NKG2A, wherein the antibody comprises a human immunoglobulin Fc region comprising enhanced ADCC activity compared to a wild type IgG1 Fc region, and wherein the subject has a disease or disorder selected from LGL leukemia, Felty's syndrome, rheumatoid arthritis, aggressive NK leukemia, inclusion body myositis, or inflammatory bowel disease.

[0018] In another example, provided herein is a method for inducing ADCC activity in a subject, comprising administering to the subject an effective amount of an antibody that specifically binds to a cell surface protein selected from human CD94, human CD57, or human NKG2A, wherein the antibody comprises a human immunoglobulin Fc region comprising enhanced ADCC activity compared to a wild type IgG1 Fc region, wherein the subject has a disease or disorder selected from chronic lymphoproliferative disorder of NK cells (CLPD-NK), LGL leukemia, Felty's syndrome, rheumatoid arthritis, aggressive NK leukemia, inclusion body myositis, or inflammatory bowel disease, and wherein administration of the antibody to the subject results in a reduction in the number of peripheral blood LGL and/or NK cells in the subject.

[0019] In some examples, which may be combined with any of the preceding examples, at least about 1,000 receptors per cell, at least about 2,000 receptors per cell, at least about 3,000 receptors per cell, at least about 4,000 receptors per cell, at least about 5,000 receptors per cell, or at least about 7,000 receptors per cell of the cell surface protein are expressed on the surface of the peripheral blood LGL and/or NK cells in the subject.

[0020] In some examples, which may be combined with any of the preceding examples, the reduction in the number of peripheral blood LGL or NK cells in the subject comprises a reduction of at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or about 10% to about 80% compared to the number of peripheral blood NK cells in the human subject prior to administration of the antibody. In some examples, the reduction in the number of peripheral blood LGL and/or NK cells in the subject occurs within the first 24 hours after administration of the antibody to the subject. In some examples, the number of peripheral blood LGL and/or NK cells in the subject is reduced to below the limit for clinical diagnosis of the disease or disorder. In some examples, the number of peripheral blood LGL and/or NK cells in the subject is reduced to less than or equal to 2×10^9 cells/L (*e.g.*, in a peripheral blood sample obtained from the subject). In some examples, the reduction in the number of peripheral blood LGL and/or NK cells in the subject to below the limit for clinical diagnosis of the disease or disorder is present in the subject for at least about 1 week after administration of the antibody to the subject. In some examples, the reduction in the number of peripheral blood LGL and/or NK cells in the subject to less than or equal to 2×10^9 cells/L (*e.g.*, in a peripheral blood sample obtained from the subject) for at least about 1 week after administration of the antibody to the subject. In some examples, the number of peripheral blood LGL and/or NK cells in the subject is reduced to below the limit of detection for the peripheral blood LGL and/or NK cells in the subject. In some examples, the reduction in the number of peripheral blood LGL and/or NK cells in the subject to below the limit of detection for the peripheral blood LGL and/or NK cells is present in the subject for at least about 1 week after administration of the antibody to the subject. In some examples, the reduction in the number of peripheral blood LGL and/or NK cells in the subject is reversible.

[0021] In some examples, which may be combined with any of the preceding examples, administration of the antibody to the subject results in a reduction in the number of peripheral blood NK cells in the subject. In some examples, the NK cells in the subject are CD3 negative and CD56 positive, CD3 negative and CD16 positive, CD3 negative and CD57 positive, CD3 negative and CD94 positive, or CD3 negative and NKG2A positive. In some examples, the antibody has an EC50 of between about 3 ng/ml and about 40 ng/ml.

[0022] In some examples, which may be combined with any of the preceding examples, administration of the antibody to the subject does not result in a reduction of T cells in the subject. In some examples, the T cells in the subject are CD3 positive and CD4 positive or CD3 positive and CD16 negative.

[0023] In some examples, which may be combined with any of the preceding examples, the subject is a human.

[0024] In some examples, which may be combined with any of the preceding examples, administration of the antibody to the subject does not result in tumor lysis syndrome in the subject.

[0025] In some examples, which may be combined with any of the preceding examples, the antibody comprises a human IgG1 Fc region that is non-fucosylated.

[0026] In some examples, which may be combined with any of the preceding examples, the antibody binds to a human cellular Fc gamma receptor IIIA to a greater extent than an antibody comprising a wild type human IgG1 Fc region. In some examples, the human cellular Fc gamma receptor IIIA comprises a valine residue or a phenylalanine residue at amino acid residue position 158. In some examples, the human cellular Fc gamma receptor IIIA comprises the sequence of SEQ ID NO: 8 or 9.

[0027] In some examples, which may be combined with any of the preceding examples, the antibody: (a) specifically binds to human CD94, wherein the antibody does not bind to the same epitope on human CD94 as anti-CD94 antibody clones HP-3D9, DX22, 131412, or 12K45; (b) specifically binds to human CD57, wherein the antibody does not bind to the same epitope on human CD57 as anti-CD57 antibody clone NK-1; or (c) specifically binds to human NKG2A, wherein the antibody does not bind to the same epitope on human NKG2A as anti-NKG2A antibody clone Z199.

[0028] In some examples, which may be combined with any of the preceding examples, the antibody: (a) specifically binds to human CD94, wherein the antibody binds to human CD94 with a greater affinity than anti-CD94 antibody clones HP-3D9, DX22, 131412, and 12K45; (b) specifically binds to human CD57, wherein the antibody binds to human CD57 with greater affinity than anti-CD57 antibody clone NK-1; or (c) specifically binds to human NKG2A, wherein the antibody binds to human NKG2A with a greater affinity than anti-NKG2A antibody clone Z199.

[0029] In some examples, the disease or disorder is Felty's syndrome, wherein administration of the antibody to the subject results in a reduction of one or more Felty's syndrome symptoms in the subject.

[0030] In some examples, the disease or disorder is inclusion body myositis, wherein administration of the antibody to the subject results in a reduction of one or more inclusion body myositis symptoms in the subject.

[0031] In some examples, the disease or disorder is aggressive NK leukemia, wherein administration of the antibody to the subject results in a reduction of one or more aggressive NK leukemia symptoms in the subject.

[0032] In some examples, the disease or disorder is rheumatoid arthritis, wherein administration of the antibody to the subject results in a reduction of one or more rheumatoid arthritis symptoms in the subject.

[0033] In some examples, the disease or disorder is LGL leukemia, wherein administration of the antibody to the subject results in a reduction of one or more LGL leukemia symptoms in the subject.

[0034] In some examples, the disease or disorder is CLPD-NK, wherein administration of the antibody to the subject results in a reduction of one or more CLPD-NK symptoms in the subject.

[0035] In another example, provided herein is a method for treating CLPD-NK in a human subject in need thereof, comprising administering to the human subject an effective amount of an antibody, wherein the antibody specifically binds to human NKG2A, and wherein the antibody comprises a human immunoglobulin Fc region comprising enhanced ADCC activity compared to a wild type IgG1 Fc region. In some examples, the antibody does not bind to the same epitope on human NKG2A as anti-NKG2A antibody clone Z199. In some examples, the antibody binds to human NKG2A with a greater affinity than anti-NKG2A antibody clone Z199.

[0036] In another example, provided herein is a method for treating CLPD-NK in a human subject in need thereof, comprising administering to the human subject an effective amount of an antibody, wherein the antibody specifically binds to human CD94, and wherein the antibody comprises a human immunoglobulin Fc region comprising enhanced ADCC activity compared to a wild type IgG1 Fc region. In some examples, the antibody does not bind to the same epitope on human CD94 as anti-CD94 antibody clones HP-3D9, DX22, 131412, or 12K45. In some examples, the antibody binds to human CD94 with a greater affinity than anti-CD94 antibody clones HP-3D9, DX22, 131412, and 12K45.

[0037] In some examples, which may be combined with any of the preceding examples, administration of the antibody to the human subject results in a reduction in the number of peripheral blood LGL or NK cells in the human subject of 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%, or about 10% to about 90%, compared to the number of peripheral blood NK cells in the human subject prior to administration of the antibody. In some examples, the NK cells in the human subject are CD3 negative and CD56 positive, CD3 negative and CD16 positive, CD3 negative and CD57 positive, CD3 negative and CD94 positive, or CD3 negative and NKG2A positive. In some examples, administration of the antibody to the human subject does not result in a reduction of T cells in the human. In some examples, the T cells in the human subject are CD3 positive and CD4 positive or CD3 positive and CD16 negative. In some examples, administration of the antibody to the human subject does not result in tumor lysis syndrome in the human. In some examples, the antibody comprises a human IgG1 Fc region that is non-fucosylated. In some examples, the antibody binds to a human cellular Fc gamma receptor IIIA to a greater extent than an antibody comprising a wild type human IgG1 Fc region. In some examples, the human cellular Fc gamma receptor IIIA comprises a valine residue or a phenylalanine residue at amino acid residue position 158. In some examples, the human cellular Fc gamma receptor IIIA comprises the sequence of SEQ ID NO: 8 or 9. In some examples, administration of the antibody to the human subject results in an improvement of one or more CLPD-NK symptoms in the human.

[0038] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

CLAIMS

What is claimed is:

1. A use of an antibody that specifically binds to human CD94 in the manufacture of a medicament for treating a disease or disorder in a subject, wherein the antibody is to be administered to the subject, wherein the antibody comprises a human IgG1 Fc region that is non-fucosylated and/or the antibody specifically binds to a human cellular Fc gamma receptor IIIA to a greater extent than an antibody comprising a wild type human IgG1 Fc region, and wherein the disease or disorder is selected from the group consisting of chronic lymphoproliferative disorder of NK cells (CLPD-NK), LGL leukemia, Felty's syndrome, rheumatoid arthritis, aggressive NK leukemia, inclusion body myositis, and inflammatory bowel disease.
2. The use of claim 1, wherein the antibody reduces in the number of peripheral blood LGL or NK cells in the subject.
3. A use of an antibody that specifically binds to human CD94 in the manufacture of a medicament for inducing ADCC activity in a subject, wherein the antibody is to be administered to the subject, wherein the antibody comprises a human IgG1 Fc region that is non-fucosylated and/or the antibody specifically binds to a human cellular Fc gamma receptor IIIA to a greater extent than an antibody comprising a wild type human IgG1 Fc region, wherein the subject has a disease or disorder selected from the group consisting of chronic lymphoproliferative disorder of NK cells (CLPD-NK), LGL leukemia, Felty's syndrome, rheumatoid arthritis, aggressive NK leukemia, inclusion body myositis, and inflammatory bowel disease, and wherein the antibody reduces the number of peripheral blood LGL and/or NK cells in the subject.
4. The use of any one of claims 2-3, wherein at least 2,000 receptors per cell of the cell surface protein are expressed on the surface of the peripheral blood LGL and/or NK cells in the subject.
5. The use of any one of claims 2-4, wherein the reduction in the number of peripheral blood LGL or NK cells in the subject comprises a reduction of at least 25% compared to the number of peripheral blood LGL or NK cells in the human subject before the antibody is to be administered.
6. The use of any one of claims 2-5, wherein the reduction in the number of peripheral blood LGL and/or NK cells in the subject occurs within the first 24 hours after the antibody is to be administered.
7. The use of any one of claims 2-6, wherein the number of peripheral blood LGL and/or NK cells in the subject is reduced to below the limit for clinical diagnosis of the disease or disorder.
8. The use of claim 7, wherein the reduction in the number of peripheral blood LGL and/or NK cells in the subject to below the limit for clinical diagnosis of the disease or disorder is present in the subject for at least 1 week after the antibody is to be administered.

9. The use of any one of claims 2-8, wherein the number of peripheral blood LGL and/or NK cells in the subject is reduced to below the limit of detection for the peripheral blood LGL and/or NK cells in the subject.
10. The use of claim 9, wherein the reduction in the number of peripheral blood LGL and/or NK cells in the subject to below the limit of detection for the peripheral blood LGL and/or NK cells is present in the subject for at least 1 week after the antibody is to be administered.
11. The use of any one of claims 2-10, wherein the reduction in the number of peripheral blood LGL and/or NK cells in the subject is reversible.
12. The use of any one of claims 1-11, wherein the antibody results in a reduction in the number of peripheral blood NK cells in the subject.
13. The use of claim 12, wherein the NK cells in the subject are CD3 negative and CD56 positive, CD3 negative and CD16 positive, CD3 negative and CD57 positive, CD3 negative and CD94 positive, or CD3 negative and NKG2A positive.
14. The use of any one of claims 1-13, wherein the antibody does not result in a reduction of T cells in the subject.
15. The use of claim 14, wherein the T cells in the subject are CD3 positive and CD4 positive or CD3 positive and CD16 negative.
16. The use of any one of claims 1-15, wherein the subject is a human.
17. The use of any one of claims 1-16, wherein the antibody does not result in tumor lysis syndrome in the subject.
18. The use of any one of claims 1-17, wherein the human cellular Fc gamma receptor IIIA comprises the sequence of SEQ ID NO: 8 or 9.
19. The use of any one of claims 1-18, wherein the disease or disorder is Felty's syndrome, and wherein the antibody results in a reduction of one or more Felty's syndrome symptoms in the subject.
20. The use of any one of claims 1-18, wherein the disease or disorder is inclusion body myositis, and wherein the antibody results in a reduction of one or more inclusion body myositis symptoms in the subject.
21. The use of any one of claims 1-18, wherein the disease or disorder is aggressive NK leukemia, and wherein the antibody results in a reduction of one or more aggressive NK leukemia symptoms in the subject.

22. The use of any one of claims 1-18, wherein the disease or disorder is rheumatoid arthritis, and wherein the antibody results in a reduction of one or more rheumatoid arthritis symptoms in the subject.
23. The use of any one of claims 1-18, wherein the disease or disorder is LGL leukemia, and wherein the antibody results in a reduction of one or more LGL leukemia symptoms in the subject.
24. The use of any one of claims 1-18, wherein the disease or disorder is CLPD-NK, and wherein the antibody results in a reduction of one or more CLPD-NK symptoms in the subject.
25. A use of an antibody that specifically binds to human CD94 in the manufacture of a medicament for treating CLPD-NK in a human subject in need thereof, wherein the antibody is to be administered to the human subject, wherein the antibody comprises a human IgG1 Fc region that is non-fucosylated and/or the antibody specifically binds to a human cellular Fc gamma receptor IIIA to a greater extent than an antibody comprising a wild type human IgG1 Fc region.
26. The use of claim 25, wherein the antibody results in a reduction in the number of peripheral blood LGL or NK cells in the human subject of at least 25% compared to the number of peripheral blood LGL or NK cells in the human subject before the antibody is to be administered.
27. The use of any one of claims 25-26, wherein the NK cells in the human subject are CD3 negative and CD56 positive, CD3 negative and CD16 positive, CD3 negative and CD57 positive, CD3 negative and CD94 positive, or CD3 negative and NKG2A positive.
28. The use of any one of claims 25-27, wherein the antibody does not result in a reduction of T cells in the human.
29. The use of claim 28, wherein the T cells in the human subject are CD3 positive and CD4 positive or CD3 positive and CD16 negative.
30. The use of any one of claims 25-29, wherein the antibody does not result in tumor lysis syndrome in the human.
31. The use of any one of claims 25-30, wherein the human cellular Fc gamma receptor IIIA comprises the sequence of SEQ ID NO: 8 or 9.
32. The use of any one of claims 25-31, wherein the antibody results in an improvement of one or more CLPD-NK symptoms in the human.