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BRIEF SUMMARY ~~OF THE INVENTION~~

The present disclosure is directed to compositions and methods for the prevention, treatment, and/or functional cure of HIV infection. One ~~aspect~~ example of the present disclosure relates to monoclonal antibodies directed against CD4, compositions thereof, and methods employing such compositions for the prevention, treatment, and functional cure of HIV infection.

One ~~aspect~~ example of the present disclosure relates to an antibody directed against CD4, compositions thereof, and methods employing such compositions for the prevention, treatment, and/or functional cure of HIV infection. In certain ~~embodiments~~examples, the antibody specifically binds to the CDR2 region in domain 1 of CD4. The disclosed antibody exerts potent competitive HIV entry inhibition through its binding to domain 1 of CD4 in both cell-free and cell-to-cell systems. The disclosed antibody also inhibits antigen induced T cell proliferation and cytokine production (IL2 and IFN-gamma) of CD4 positive T cells, which is implicated in the pathogenic cycle of pyroptosis. The disclosed antibody also has the ability to reactivate resting CD4 positive T cells. This property is particularly useful for reactivating latent reservoirs of HIV in resting T cells to make these cells susceptible to treatment with antiretroviral agents. Such high affinity antibodies to CD4 are capable of activating resting HIV infected cells for the release of HIV. Reactivation of HIV infected resting CD4+ T cells allows combinational treatment incorporating antibody of the current invention with HAART in HIV infected patients leading to functional cure.

The present disclosure is directed to methods for the treatment, prevention, and functional cure of HIV infection. In certain ~~embodiments~~examples, the formulations contain antibodies directed against CD4. The present disclosure also includes antiviral agents that can be used in the methods for the treatment, prevention, and functional cure of HIV infection.

In certain ~~embodiments~~examples, ~~the present invention relates to~~disclosed herein are pharmaceutical compositions comprising monoclonal human, humanized or chimeric, anti-CD4 antibodies with the above described binding characteristics that when given, at a dose of about 10 mg/kg or higher on a weekly or biweekly schedule, as a monotherapy, such treatment can reduce viral load down to non-detectable level in treated subjects with no viral load rebound as long the serum antibody level is higher than 10 μg/mL.

In another ~~embodiment~~examples, ~~the present invention relates to~~ disclosed herein are pharmaceutical compositions comprising a monoclonal humanized anti-CD4 antibody with the above described binding characteristics as the key ingredient in an adjunct therapy with HAART, that when given, at about 10 mg/kg or higher on a weekly or biweekly schedule, to treatment naïve HIV patients, will lead to functional cure of the patients.

In one aspect, the present invention refers to use of an antibody directed against domain 1 of CD4 in the manufacture of a medicament for treating a subject exposed to HIV. In another aspect, the present invention refers to use of a) a pharmacologically effective

amount of an antibody directed against domain 1 of CD4; and b) a highly active antiretroviral therapy (HAART), in the manufacture of a medicament for treating a subject with HIV infection, wherein the medicament is to be administered to the subject in a treatment regimen. In yet another aspect, the present invention refers to an antibody directed against a CD4 molecule, wherein the antibody a) binds to an extracellular region of the CD4 molecule; b) competitively inhibits HIV entry into a cell; and c) reduces HIV viral load in an HIV positive patient to less than 50 copies per milliliter of blood without viral load rebound, when the antibody is administered to the HIV positive patient in an amount sufficient to fully coat CD4+ cells. In a further aspect, the present invention refers to a composition comprising the antibody as disclosed herein. In another aspect, the present invention refers to a pharmaceutical composition comprising the antibody disclosed herein and a pharmaceutically acceptable carrier. In another aspect, the present invention refers to a pharmaceutical composition comprising the antibody as disclosed herein in phosphate buffer saline (PBS), 20 mM glycine, and 0.05% (v/v) polysorbate 20. In a further aspect, the present invention refers to a pharmaceutical composition comprising the antibody as disclosed herein in phosphate buffer saline (PBS), 20 mM glycine, 0.05% (v/v) polysorbate 20, and 10 mM histidine. In yet another aspect, the present invention refers to a pharmaceutical composition comprising the antibody as disclosed herein in phosphate buffer saline (PBS), 20 mM glycine, 0.05% (v/v) polysorbate 20, and 10 mM histidine. In one aspect, the present invention refers to a pharmaceutical composition comprising about 1.0 mg/mL to about 200.0 mg/mL of the antibody as disclosed herein in phosphate buffer saline (PBS), 20 mM glycine, 0.05% (v/v) polysorbate 20, and 10 mM histidine. In another aspect, the present invention refers to a pharmaceutical composition comprising about 10.0 mg/mL of the antibody as disclosed herein in phosphate buffer saline (PBS), 20 mM glycine, and 0.05% (v/v) polysorbate 20. In yet another aspect, the present invention refers to a pharmaceutical composition comprising about 10.0 mg/mL of the antibody as disclosed herein in phosphate buffer saline (PBS), 20 mM glycine, 0.05% (v/v) polysorbate 20, and 10 mM histidine. In a further aspect, the present invention refers to a pharmaceutical composition comprising the antibody as disclosed herein and a pharmaceutically acceptable carrier. In another aspect, the present invention refers to use of the antibody as disclosed herein in the manufacture of a medicament for treating a subject exposed to HIV. In one aspect, the prese invention refers to use of a) a pharmacologically effective amount of the antibody of claim 31; and b) a highly active antiretroviral therapy (HAART) in the manufacture of a medicament for treating a subject with HIV infection, wherein the medicament is to be administered to the subject in a

treatment regimen. In another aspect, the present invention refers to use of the antibody as disclosed herein in the manufacture of a medicament for inhibiting HIV entry into a CD4+ cell, comprising exposing the antibody as disclosed herein to the cell. In a further aspect, the present invention refers to use of the antibody as disclosed herein in the manufacture of a medicamentA method for inhibiting gp120 binding to a CD4+ cell, comprising exposing the antibody as disclosed herein to the cell. In another aspect, the present invention refers to use of the antibody as disclosed herein in the manufacture of a medicament for activating a resting CD4+ T cell upon crosslinking, comprising exposing the antibody disclosed herein to the cell. In a further aspect, the present invention refers to use of the antibody disclosed herein in the manufacture of a medicament for activating a latent reservoir of HIV in a resting T cell upon crosslinking, comprising exposing the antibody disclosed herein to the cell. In another aspect, the present invention refers to use of the antibody as disclosed herein and HAART in the manufacture of a medicament for reducing latent HIV reservoirs in a sample of cells infected with HIV, the use comprising a) exposing the antibody as disclosed herein to the sample of cells; and b) exposing HAART to the sample of cells.

CLAIMS

1. Use of an antibody directed against domain 1 of CD4 in the manufacture of a medicament~~A method~~ for treating a subject exposed to HIV ~~comprising: administering to the subject a pharmacologically effective amount of an antibody directed against domain 1 of CD4~~.

2. The ~~method~~ use according to claim 1, wherein the antibody specifically binds to the CDR2 region in domain 1 of CD4.

3. The use ~~method~~ according to claim 2, wherein the antibody is a monoclonal antibody, a polyclonal antibody, or a combination thereof.

4. The use ~~method~~ according to claim 2, wherein the antibody is a humanized monoclonal antibody.

5. The use ~~method~~ according to claim 4, wherein the humanized monoclonal antibody comprises:

a heavy chain amino acid sequence comprising:

CDR1 of SEQ ID NO: 1,

CDR2 of SEQ ID NO: 2, and

CDR3 of SEQ ID NO: 3; and

a light chain amino acid sequence comprising:

CDR1 of SEQ ID NO: 4,

CDR2 of SEQ ID NO: 5, and

CDR3 of SEQ ID NO: 6.

6. The use ~~method~~ according to claim 4, wherein the humanized monoclonal antibody comprises:

a heavy chain comprising an amino acid sequence of SEQ ID NO: 11; and

a light chain comprising an amino acid sequence of SEQ ID NO: 13.

7. The use ~~method~~ according to claim 4, wherein the humanized monoclonal antibody comprises:

a heavy chain comprising an amino acid sequence of SEQ ID NO: 10; and
a light chain comprising an amino acid sequence of SEQ ID NO: 8.

8. The use ~~method~~ according to claim 7, wherein the heavy chain comprising an amino acid sequence of SEQ ID NO: 7.

9. The use ~~method~~ according to claim 8, wherein the humanized antibody is to be administered to the subject prior to exposure to HIV.

10. The use ~~method~~ according to claim 8, wherein the humanized antibody is to be administered to the subject after exposure to HIV.

11. The use ~~method~~ according to claim 10, wherein the humanized antibody is to be administered within 48 hours after exposure to HIV.

12. The use ~~method~~ according to claim 8, wherein the humanized antibody is to be administered to the subject at a dosage of at least about 5 mg/kg body weight.

13. The use ~~method~~ according to claim 12, wherein the humanized antibody is to be administered to the subject multiple times.

14. The use ~~method~~ according to claim 13, wherein the humanized antibody is to be administered to the subject in a weekly or bi-weekly interval.

15. The use ~~method~~ according to claim 13, further comprising a step of ~~administering~~ an antiviral agent to be administered to the subject.

16. The use ~~method~~ according to claim 15, wherein the antiviral agent is a highly active antiretroviral therapy (HAART).

17. The use ~~method~~ according to claim 16, wherein HAART comprises a nucleoside analogue reverse transcriptase inhibitor in combination with a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor.

18. The use ~~method~~ according to claim 16, wherein the humanized antibody is to be administered concurrently with HAART.

19. The use ~~method~~ according to claim 16, wherein the humanized antibody and HAART are to be administered to the subject over the course of a cycle, wherein the cycle comprises:

i) ~~administering~~ the humanized antibody to be administered to the subject for a period of four months in a weekly or bi-weekly interval followed by a two-month treatment holiday; and

ii) ~~administering~~ HAART to be administered to the subject continuously during the six-month period in (i).

20. The use ~~method~~ according to claim 19, wherein the subject is treated over the course of two or more cycles.

21. Use of~~A method for treating a subject with HIV infection, comprising administering to the subject a treatment regimen comprising~~:

a) a pharmacologically effective amount of an antibody directed against domain 1 of CD4; and

b) a highly active antiretroviral therapy (HAART),

in the manufacture of a medicament for treating a subject with HIV infection, wherein the medicament is to be administered to the subject in a treatment regimen.

22. The ~~method~~ use according to claim 21, wherein the antibody specifically binds to the CDR2 region in domain 1 of CD4.

23. The use ~~method~~ according to claim 22, wherein the antibody is a monoclonal antibody, a polyclonal antibody, or a combination thereof.

24. The use ~~method~~ according to claim 22, wherein the antibody is a humanized monoclonal antibody.

25. The use ~~method~~ according to claim 24, wherein the humanized monoclonal antibody comprises:

a heavy chain amino acid sequence comprising:

CDR1 of SEQ ID NO: 1,

CDR2 of SEQ ID NO: 2, and

CDR3 of SEQ ID NO: 3; and

a light chain amino acid sequence comprising:

CDR1 of SEQ ID NO: 4,

CDR2 of SEQ ID NO: 5, and

CDR3 of SEQ ID NO: 6.

26. The use ~~method~~ according to claim 24, wherein the humanized monoclonal antibody comprises:

a heavy chain comprising an amino acid sequence of SEQ ID NO: 11; and

a light chain comprising an amino acid sequence of SEQ ID NO: 13.

27. The use ~~method~~ according to claim 24, wherein the humanized monoclonal antibody comprises:

a heavy chain comprising an amino acid sequence of SEQ ID NO: 10; and

a light chain comprising an amino acid sequence of SEQ ID NO: 8.

28. The use ~~method~~ according to claim 27, wherein the humanized antibody is to be administered to the subject at a dosage of at least about 5 mg/kg body weight.

29. The use ~~method~~ according to claim 21, wherein the treatment regimen is administered to the subject over the course of a cycle, wherein the cycle comprises:

i) administering the humanized antibody to the subject for a period of four months in a weekly or bi-weekly interval followed by a two month treatment holiday; and

ii) administering HAART to the subject continuously during the six-month period in (i).

30. The use ~~method~~ according to claim 29, wherein the subject is treated with two or more cycles.

56. A pharmaceutical composition comprising about 1.0 mg/mL to about 200.0 mg/mL of the antibody of claim 31 in phosphate buffer saline (PBS), 20 mM glycine, 0.05% (v/v) polysorbate 20, and 10 mM histidine.

57. A pharmaceutical composition comprising about 10.0 mg/mL of the antibody of claim 31 in phosphate buffer saline (PBS), 20 mM glycine, and 0.05% (v/v) polysorbate 20.

58. A pharmaceutical composition comprising about 10.0 mg/mL of the antibody of claim 31 in phosphate buffer saline (PBS), 20 mM glycine, 0.05% (v/v) polysorbate 20, and 10 mM histidine.

59. A pharmaceutical composition comprising the antibody of claim 41 and a pharmaceutically acceptable carrier.

60. A pharmaceutical composition comprising the antibody of claim 47 and a pharmaceutically acceptable carrier.

61. Use of the antibody of claim 31 in the manufacture of a medicament~~A method~~ for treating a subject exposed to HIV ~~comprising: administering to the subject a pharmacologically effective amount of the antibody of claim 31~~.

62. The ~~method~~ use of claim 61, wherein the antibody is to be administered to the subject prior to exposure to HIV.

63. The use ~~method~~ according to claim 61, wherein the antibody is to be administered to the subject after exposure to HIV.

64. The use ~~method~~ according to claim 61, wherein the antibody is to be administered within 48 hours after exposure to HIV.

65. The use ~~method~~ according to claim 61, wherein the antibody is to be administered to the subject at a dosage of at least about 5 mg/kg body weight.

66. The use ~~method~~ according to claim 65, wherein the antibody is to be administered to the subject multiple times.

67. The use ~~method~~ according to claim 66, wherein the antibody is to be administered to the subject in a weekly, bi-weekly, or monthly interval.

68. The use ~~method~~ according to claim 66, further comprising a step of ~~administering~~ an antiviral agent to be administered to the subject.

69. The use ~~method~~ according to claim 68, wherein the antiviral agent is a highly active antiretroviral therapy (HAART).

70. The use ~~method~~ according to claim 69, wherein HAART comprises a nucleoside analogue reverse transcriptase inhibitor in combination with a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor.

71. The use ~~method~~ according to claim 69, wherein the antibody is to be administered concurrently with HAART.

72. The use ~~method~~ according to claim 69, wherein the antibody and HAART are to be administered to the subject over the course of a cycle, wherein the cycle comprises:

i) ~~administering~~ the antibody to be administered to the subject for a first period of time followed by a treatment holiday for a second period of time; and

ii) ~~administering~~ HAART to be administered to the subject continuously during the first period of time and the second period of time in (i).

73. The use ~~method~~ according to claim 69, wherein the antibody and HAART are administered to the subject over the course of a cycle, wherein the cycle comprises:

i) ~~administering~~ the antibody to be administered to the subject for a period of four months in a weekly, bi-weekly, or monthly interval followed by a two month treatment holiday; and

ii) ~~administering~~ HAART to be administered to the subject continuously during the six-month period in (i).

74. The use ~~method~~ according to claim 72, wherein the subject is treated over the course of two cycles.

75. The use ~~method~~ according to claim 73, wherein the subject is treated over the course of two cycles.

76. The use ~~method~~ according to claim 69, wherein the antibody is to be administered at a time that is not concurrent with HAART.

77. The use ~~method~~ according to claim 69, wherein the antibody and HAART are to be administered to the subject over the course of a cycle, wherein the cycle comprises:

i) ~~administering~~ the antibody to be administered to the subject for a first period of time followed by a treatment holiday for a second period of time; and

ii) ~~administering~~ HAART to be administered to the subject during the second period of time and not during the first period of time.

78. The use ~~method~~ according to claim 77, wherein the antibody is to be administered in regular intervals during the first time period.

79. The use ~~method~~ according to claim 77, wherein the antibody is to be administered in weekly, bi-weekly, or monthly intervals during the first time period.

80. Use of~~A method for treating a subject with HIV infection, comprising administering to the subject a treatment regimen comprising:~~

a) a pharmacologically effective amount of the antibody of claim 31; and

b) a highly active antiretroviral therapy (HAART)

in the manufacture of a medicament for treating a subject with HIV infection, wherein the medicament is to be administered to the subject in a treatment regimen.

81. The ~~method~~ use of claim 80, wherein the antibody is to be administered to the subject at a dosage of at least about 5 mg/kg body weight.

82. The use ~~method~~ according to claim 80, wherein the antibody and HAART are to be administered to the subject over the course of a cycle, wherein the cycle comprises:

i) ~~administering~~ the antibody to be administered to the subject for a first period of time followed by a treatment holiday for a second period of time; and

ii) ~~administering~~ HAART to be administered the subject continuously during the first period of time and the second period of time in (i).

83. The use ~~method~~ according to claim 80, wherein the antibody and HAART are to be administered to the subject over the course of a cycle, wherein the cycle comprises:

i) ~~administering~~ the antibody to be administered to the subject for a period of four months in a weekly, bi-weekly, or monthly interval followed by a two-month treatment holiday; and

ii) ~~administering~~ HAART to be administered to the subject continuously during the six-month period in (i).

84. The use ~~method~~ according to claim 82, wherein the subject is treated over the course of two or more cycles.

85. The use ~~method~~ according to claim 83, wherein the subject is treated over the course of two or more cycles.

86. The use ~~method~~ according to claim 83, wherein the antibody and HAART are to be administered to the subject over the course of a cycle, wherein the cycle comprises:

i) ~~administering~~ the antibody to be administered to the subject for a period of four months in a weekly, bi-weekly, or monthly interval followed by a two-month treatment holiday; and

ii) ~~administering~~ HAART to be administered to the subject continuously during the six-month period in (i).

87. The use ~~method~~ according to claim 80, wherein the antibody in (a) is administered at a time that is not concurrent with HAART in (b).

88. The use ~~method~~ according to claim 80, wherein the antibody in (a) and HAART in (b) are to be administered to the subject over the course of a cycle, wherein the cycle comprises:

i) ~~administering~~ the antibody to be administered to the subject for a first period of time followed by a treatment holiday for a second period of time; and

ii) ~~administering~~ HAART to be administered to the subject during the second period of time and not during the first period of time.

89. The use ~~method~~ according to claim 88, wherein the antibody is to be administered in regular intervals during the first time period.

90. The use ~~method~~ according to claim 88, wherein the antibody is to be administered in weekly, bi-weekly, or monthly intervals during the first time period.

91. Use of the antibody of claim 31 in the manufacture of a medicament~~A method~~ for inhibiting HIV entry into a CD4+ cell, comprising exposing the antibody of claim 31 to the cell.

92. Use of the antibody of claim 31 in the manufacture of a medicament~~A method~~ for inhibiting gp120 binding to a CD4+ cell, comprising exposing the antibody of claim 31 to the cell.

93. Use of the antibody of claim 31 in the manufacture of a medicament ~~A method~~ for activating a resting CD4+ T cell upon crosslinking, comprising exposing the antibody of claim 31 to the cell.

94. Use of the antibody of claim 31 in the manufacture of a medicament~~A method~~ for activating a latent reservoir of HIV in a resting T cell upon crosslinking, comprising exposing the antibody of claim 31 to the cell.

95. Use of the antibody of claim 31 and HAART in the manufacture of a medicament~~A method~~ for reducing latent HIV reservoirs in a sample of cells infected with HIV, the use comprising

a) exposing the antibody of claim 31 to the sample of cells; and

b) exposing HAART to the sample of cells.