

CLAIMS:

1. ~~A method of treating a disease or disorder characterized by expression of CD38, the method comprising administering to a subject with the disease or disorder an antibody comprising:
a first polypeptide having binding affinity to a first epitope on CD38; and
a second polypeptide having binding affinity to a second, non-overlapping epitope on CD38.~~
2. ~~The method of claim 1, wherein the disease or disorder is characterized by a hydrolase enzymatic activity of CD38, a cyclase enzymatic activity of CD38, or a combination thereof.~~
3. ~~The method of claim 1 or 2, wherein the disease or disorder is a telomere shortening disease.~~
4. ~~The method of claim 3, wherein the telomere shortening disease is accelerated aging.~~
5. ~~The method of claim 3, wherein the telomere shortening disease is aplastic anemia.~~
6. ~~The method of claim 3, wherein the telomere shortening disease is dyskeratosis congenita.~~
7. ~~The method of claim 3, wherein the telomere shortening disease is Franconi's anemia.~~
8. ~~The method of claim 3, wherein the telomere shortening disease is idiopathic pulmonary fibrosis.~~
9. ~~The method of claim 1 or 2, wherein the disease or disorder is an inflammatory disease.~~
10. ~~The method of claim 9, wherein the inflammatory disease is ulcerative colitis.~~

~~11.—The method of claim 9, wherein the inflammatory disease is graft versus host disease (GvHD).~~

~~12.—The method of claim 11, wherein the GvHD is acute GvHD.~~

~~13.—The method of claim 11, wherein the GvHD is chronic GvHD.~~

~~14.—The method of claim 11, wherein the GvHD is transplant-associated GvHD.~~

~~15.—The method of claim 9, wherein the inflammatory disease is acute kidney injury.~~

~~16.—The method of claim 1 or 2, wherein the disease or disorder is fibrosis-associated disorder.~~

~~17.—The method of claim 16, wherein the fibrosis-associated disorder is scleroderma.~~

~~18.—The method of claim 1 or 2, wherein the disease or disorder is a metabolic syndrome.~~

~~19.—The method of claim 18, wherein the metabolic syndrome is type II diabetes mellitus (T2DM).~~

~~20.—The method of claim 18, wherein the metabolic syndrome is obesity.~~

~~21.—The method of claim 18, wherein the metabolic syndrome is systemic inflammation.~~

~~22.—A method of treating a disease or disorder characterized by reduced sirtuin activity, the method comprising administering to a subject with the disease or disorder an antibody comprising:~~

~~a first polypeptide having binding affinity to a first epitope on CD38; and~~

~~a second polypeptide having binding affinity to a second, non-overlapping epitope on CD38.~~

23. — ~~The method of claim 22, further comprising administering nicotinamide mononucleotide (NMN) to the subject.~~

24. — ~~The method of claim 22 or 23, wherein the disease or disorder is a metabolic disease or disorder.~~

25. — ~~The method of claim 22 or 23, wherein the disease or disorder is a cardiovascular disease or disorder.~~

26. — ~~The method of claim 22 or 23, wherein the disease or disorder is a neurodegenerative disease or disorder.~~

27. — ~~The method of claim 22 or 23, wherein the disease or disorder is a cancer.~~

28. — ~~The method according to any one of claims 1-27, wherein the antibody is administered to the subject as a pharmaceutical composition.~~

29. — ~~A method of increasing nicotinamide adenine dinucleotide (NAD⁺) concentration in a cell, the method comprising contacting the cell with an antibody comprising:
a first polypeptide having binding affinity to a first epitope on CD38; and
a second polypeptide having binding affinity to a second, non-overlapping epitope on CD38.~~

30. — ~~The method of claim 29, further comprising contacting the cell with NMN.~~

31. — ~~A method of increasing sirtuin activity in a cell, the method comprising contacting the cell with an antibody comprising:
a first polypeptide having binding affinity to a first epitope on CD38; and
a second polypeptide having binding affinity to a second, non-overlapping epitope on CD38.~~

32. — ~~The method of claim 31, further comprising contacting the cell with NMN.~~

~~33. The method of any one of claims 1-32, wherein the first polypeptide comprises an antigen-binding domain of a heavy-chain antibody having binding affinity to the first epitope or the second epitope on CD38, and comprises:~~

- ~~(i) a CDR1 sequence having two or fewer substitutions in any of the amino acid sequences of SEQ ID NOs: 1-5; and/or~~
- ~~(ii) a CDR2 sequence having two or fewer substitutions in any of the amino acid sequences of SEQ ID NOs: 6-12; and/or~~
- ~~(iii) a CDR3 sequence having two or fewer substitutions in any of the amino acid sequences of SEQ ID NOs: 13-17.~~

~~34. The method of claim 33, wherein the CDR1, CDR2, and CDR3 sequences are present in a human framework.~~

~~35. The method of any one of claims 33-34, wherein the first polypeptide comprises:~~

- ~~(i) a CDR1 sequence comprising any one of SEQ ID NOs: 1-5; and/or~~
- ~~(ii) a CDR2 sequence comprising any one of SEQ ID NOs: 6-12; and/or~~
- ~~(iii) a CDR3 sequence comprising any one of SEQ ID NOs: 13-17.~~

~~36. The method of claim 35, wherein the first polypeptide comprises:~~

- ~~(i) a CDR1 sequence comprising any one of SEQ ID NOs: 1-5; and~~
- ~~(ii) a CDR2 sequence comprising any one of SEQ ID NOs: 6-12; and~~
- ~~(iii) a CDR3 sequence comprising any one of SEQ ID NOs: 13-17.~~

~~37. The method of claim 36, wherein the first polypeptide comprises:~~

~~—— a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 13; or~~
~~a CDR1 sequence of SEQ ID NO: 3, a CDR2 sequence of SEQ ID NO: 9, and a CDR3 sequence of SEQ ID NO: 16; or~~
~~a CDR1 sequence of SEQ ID NO: 4, a CDR2 sequence of SEQ ID NO: 11, and a CDR3 sequence of SEQ ID NO: 17.~~

~~38. The method of claim 37, wherein the antibody comprises:~~

~~an antigen-binding domain of a heavy chain antibody having binding affinity to the first epitope on CD38, comprising a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 13; and~~

~~an antigen-binding domain of a heavy chain antibody having binding affinity to the second epitope on CD38, comprising a CDR1 sequence of SEQ ID NO: 3, a CDR2 sequence of SEQ ID NO: 9, and a CDR3 sequence of SEQ ID NO: 16.~~

~~39. The method of any one of claims 34-38, wherein the antibody comprises a variable region sequence having at least 95% sequence identity to any of the sequences of SEQ ID NOs: 18-28.~~

~~40. The method of claim 39, wherein the antibody comprises a variable region sequence selected from the group consisting of SEQ ID NOs: 18-28.~~

~~41. The method of claim 40, wherein the antibody comprises:~~

~~—— an antigen-binding domain of a heavy chain antibody having binding affinity to the first epitope on CD38, comprising a variable region sequence of SEQ ID NO: 18; and~~

~~—— an antigen-binding domain of a heavy chain antibody having binding affinity to the second epitope on CD38, comprising a variable region sequence of SEQ ID NO: 23.~~

~~42. The method of any one of claims 1-41, wherein the antibody further comprises a heavy chain constant region sequence in the absence of a CH1 sequence.~~

~~43. The method of any one of claims 1-42, wherein the antibody is multi-specific.~~

~~44. The method of claim 43, wherein the antibody is bispecific.~~

~~45. The method of claim 43, wherein the antibody has binding affinity to an effector cell.~~

~~46. The method of claim 45, wherein the antibody has binding affinity to a T-cell antigen.~~

~~47. The method of claim 46, wherein the antibody has binding affinity to CD3.~~

~~48. The method according to any one of claims 1-47, wherein the antibody is in a CAR-T format.~~

~~49. The method according to any one of claims 1-32, wherein the antibody is a bispecific antibody comprising:~~

~~— (a) — a first polypeptide having binding affinity to the first CD38 epitope comprising:~~

~~(i) — an antigen-binding domain of a heavy-chain antibody comprising a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 13;~~

~~(ii) — at least a portion of a hinge region; and~~

~~(iii) — a CH domain comprising a CH2 domain and a CH3 domain; and~~

~~(b) — a second polypeptide having binding affinity to the second CD38 epitope comprising:~~

~~(i) — an antigen-binding domain of a heavy-chain antibody comprising a CDR1 sequence of SEQ ID NO: 3, a CDR2 sequence of SEQ ID NO: 9, and a CDR3 sequence of SEQ ID NO: 16;~~

~~(ii) — at least a portion of a hinge region; and~~

~~(iii) — a CH domain comprising a CH2 domain and a CH3 domain; and~~

~~(c) — an asymmetric interface between the CH3 domain of the first polypeptide and the CH3 domain of the second polypeptide.~~

~~50. The method of claim 49, wherein the antibody comprises an Fc region selected from the group consisting of: a human IgG1 Fc region, a human IgG4 Fc region, a silenced human IgG1 Fc region, and a silenced human IgG4 Fc region.~~

~~51. The method according to any one of claims 1-32, wherein the antibody is a bispecific antibody comprising:~~

~~(i) — a first antigen-binding domain of a heavy-chain antibody having binding affinity to the first CD38 epitope, comprising a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 13;~~

- (ii) ~~—a second antigen-binding domain of a heavy chain antibody having binding affinity to the second CD38 epitope, comprising a CDR1 sequence of SEQ ID NO: 3, a CDR2 sequence of SEQ ID NO: 9, and a CDR3 sequence of SEQ ID NO: 16;~~
- (iii) ~~—at least a portion of a hinge region; and~~
- (iv) ~~—a CH domain comprising a CH2 domain and a CH3 domain.~~

52. ~~—The method of claim 51, wherein the antibody comprises an Fc region selected from the group consisting of: a human IgG1 Fc region, a human IgG4 Fc region, a silenced human IgG1 Fc region, and a silenced human IgG4 Fc region.~~

53. ~~—The method according to any one of claims 1–32, wherein the antibody is a bispecific antibody comprising:~~

- ~~—(a) —a first and a second heavy chain polypeptide, each comprising:

 - (i) ~~—an antigen-binding domain of a heavy chain antibody having binding affinity to the first CD38 epitope, comprising a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 13;~~
 - (ii) ~~—at least a portion of a hinge region; and~~
 - (iii) ~~—a CH domain comprising a CH1 domain, a CH2 domain and a CH3 domain; and~~~~
- ~~—(b) —a first and a second light chain polypeptide, each comprising:

 - (i) ~~—an antigen-binding domain of a heavy chain antibody having binding affinity to the second CD38 epitope, comprising a CDR1 sequence of SEQ ID NO: 3, a CDR2 sequence of SEQ ID NO: 9, and a CDR3 sequence of SEQ ID NO: 16; and~~
 - (ii) ~~—a CL domain.~~~~

54. ~~—The method of claim 53, wherein the antibody comprises an Fc region selected from the group consisting of: a human IgG1 Fc region, a human IgG4 Fc region, a silenced human IgG1 Fc region, and a silenced human IgG4 Fc region.~~

155. ~~Use of The method according to any one of claims 1–32, wherein the antibody is a~~
bispecific antibody comprising:

(a) a first polypeptide subunit comprising a heavy chain variable region comprising a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 13 in a human heavy chain framework;

(b) a second polypeptide subunit comprising a light chain variable region comprising a CDR1 sequence of SEQ ID NO: 49, a CDR2 sequence of SEQ ID NO: 50, and a CDR3 sequence of SEQ ID NO: 51, in a human light chain framework;

wherein the first polypeptide subunit and the second polypeptide subunit together have binding affinity to the first CD38 epitope; and

(c) a third polypeptide subunit comprising an antigen-binding domain of a heavy-chain antibody comprising a CDR1 sequence of SEQ ID NO: 3, a CDR2 sequence of SEQ ID NO: 9, and a CDR3 sequence of SEQ ID NO: 16 in a human heavy chain framework, in a monovalent or bivalent configuration;

wherein the third polypeptide subunit has binding affinity to the second, non-overlapping CD38 epitope in the manufacture of a medicament for treating a disease or disorder characterized by expression of CD38.

~~56. The method of claim 55, wherein the first polypeptide subunit further comprises a CH1 domain, at least a portion of a hinge region, a CH2 domain, and a CH3 domain.~~

~~57. The method of claim 55 or 56, wherein the third polypeptide subunit further comprises a constant region sequence comprising at least a portion of a hinge region, a CH2 domain, and a CH3 domain, in the absence of a CH1 domain.~~

~~58. The method of any one of claims 55-57, wherein the human light chain framework is a human kappa light chain framework or a human lambda light chain framework.~~

~~59. The method of any one of claims 55-58, wherein the second polypeptide subunit further comprises a CL domain.~~

260. The usemethod of ~~any one of~~ claims 155-59, wherein the bispecific antibody further comprises an Fc region selected from the group consisting of: a human IgG1 Fc region, a

human IgG4 Fc region, a silenced human IgG1 Fc region, and a silenced human IgG4 Fc region.

~~613.~~ The ~~use~~~~method~~ of ~~any one of~~ claims ~~155-60~~, wherein the bispecific antibody comprises an asymmetric interface between ~~a~~~~the~~ CH3 domain of the first polypeptide subunit and ~~a~~~~the~~ CH3 domain of the third polypeptide subunit.

4. The use of claim 1, wherein the bispecific antibody comprises:

(a) a first heavy chain polypeptide comprising the sequence of SEQ ID NO: 46;

(b) a first light chain polypeptide comprising the sequence of SEQ ID NO: 48;

and

(c) a second heavy chain polypeptide comprising the sequence of SEQ ID NO: 47.

5. The use of claim 1, wherein the disease or disorder is characterized by a hydrolase enzymatic activity of CD38, a cyclase enzymatic activity of CD38, or a combination thereof.

6. The use of claim 1, wherein the disease or disorder is a telomere shortening disease.

7. The use of claim 6, wherein the telomere shortening disease is selected from the group consisting of: accelerated aging, aplastic anemia, dyskeratosis congenita, Franconi's anemia, and idiopathic pulmonary fibrosis.

8. The use of claim 1, wherein the disease or disorder is an inflammatory disease.

9. The use of claim 8, wherein the inflammatory disease is selected from the group consisting of: ulcerative colitis, graft versus host disease (GvHD), acute GvHD, chronic GvHD, transplant-associated GvHD, and acute kidney injury.

10. The use of claim 1, wherein the disease or disorder is a fibrosis-associated disorder.

11. The use of claim 10, wherein the fibrosis-associated disorder is scleroderma.

12. The use of claim 1, wherein the disease or disorder is a metabolic syndrome.

13. The use of claim 12, wherein the metabolic syndrome is selected from the group consisting of: type II diabetes mellitus (T2DM), obesity, and systemic inflammation.

1462. Use of~~The method of any one of claims 1-32, wherein the antibody is~~ a bispecific antibody comprising:

- (a) a first heavy chain polypeptide comprising the sequence of SEQ ID NO: 46;
- (b) a first light chain polypeptide comprising the sequence of SEQ ID NO: 48;

and

- (c) a second heavy chain polypeptide comprising the sequence of SEQ ID NO: 47

in the manufacture of a medicament for treating a disease or disorder characterized by reduced sirtuin activity, wherein the bispecific antibody is to be administered to a subject with the disease or disorder.

15. The use of claim 14, wherein nicotinamide mononucleotide (NMN) is to be further administered to the subject.

16. The use of claim 14, wherein the disease or disorder is a metabolic disease or disorder.

17. The use of claim 14, wherein the disease or disorder is a cardiovascular disease or disorder.

18. The use of claim 14, wherein the disease or disorder is a neurodegenerative disease or disorder.

19. The use of claim 14, wherein the disease or disorder is a cancer.

2063. The use~~method of any one of claims 14-32, wherein the antibody is a~~ bispecific antibody is to be administered to the subject as a pharmaceutical composition~~comprising:~~

- ~~(a) — a first heavy chain polypeptide comprising the sequence of SEQ ID NO: 55;~~
 - ~~— (b) — a first light chain polypeptide comprising the sequence of SEQ ID NO: 48;~~
 - ~~and~~
 - ~~— (c) — a second heavy chain polypeptide comprising the sequence of SEQ ID NO:~~
- 56.