

SUMMARY OF THE INVENTION

[0013a] In one aspect, provided herein is use of 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.

[0013b] In another aspect, provided herein is use of 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.

[0014] AspectExamples of the inventiondisclosure include methods of treating a disease or disorder characterized by expression of CD38, the methods 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. In some embodimentexamples, the disease or disorder is characterized by a hydrolase enzymatic activity of CD38, a cyclase enzymatic activity of CD38, or a combination thereof.

[0015] In some embodimentexamples, the disease or disorder is a telomere shortening disease. In some embodimentexamples, the telomere shortening disease is accelerated aging. In some embodimentexamples, the telomere shortening disease is aplastic anemia. In some embodimentexamples, the telomere shortening disease is dyskeratosis congenita. In some embodimentexamples, the telomere shortening disease is Franconi's anemia. In some embodimentexamples, the telomere shortening disease is idiopathic pulmonary fibrosis.

[0016] In some embodimentexamples, the disease or disorder is an inflammatory disease. In some embodimentexamples, the inflammatory disease is ulcerative colitis. In some embodimentexamples, the inflammatory disease is graft versus host disease (GvHD). In some embodimentexamples, the GvHD is acute GvHD. In some embodimentexamples, the GvHD is chronic GvHD. In some embodimentexamples, the GvHD is transplant-associated GvHD. In some embodimentexamples, the inflammatory disease is acute kidney injury.

[0017] In some embodimentexamples, the disease or disorder is fibrosis-associated disorder. In some embodimentexamples, the fibrosis-associated disorder is scleroderma.

[0018] In some embodimentexamples, the disease or disorder is a metabolic syndrome. In some embodimentexamples, the metabolic syndrome is type II diabetes mellitus (T2DM). In some embodimentexamples, the metabolic syndrome is obesity. In some embodimentexamples, the metabolic syndrome is systemic inflammation.

[0019] AspectExample of the inventiondisclosure include methods of treating a disease or disorder characterized by reduced sirtuin activity, the methods 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. In some embodimentexamples, a method further comprises administering nicotinamide mononucleotide (NMN) to the subject. In some embodimentexamples, the disease or disorder is a metabolic disease or disorder. In some embodimentexamples, the disease or disorder is a cardiovascular disease or disorder. In some embodimentexamples, the disease or disorder is a neurodegenerative disease or disorder. In some embodimentexamples, the disease or disorder is a cancer.

[0020] In some embodimentexamples, the antibody is administered to the subject as a pharmaceutical composition.

[0021] AspectExample of the inventiondisclosure include methods of increasing nicotinamide adenine dinucleotide (NAD⁺) concentration in a cell, the methods 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. In some embodimentexamples, a method further comprises contacting the cell with NMN.

[0022] AspectExamples of the inventiondisclosure include methods of increasing sirtuin activity in a cell, the methods 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. In some embodimentexamples, the methods further comprise contacting the cell with NMN.

[0023] In some embodimentexamples, 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. In some embodimentexamples, the CDR1, CDR2, and CDR3 sequences are present in a human framework.

[0024] In some embodimentexamples, 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.

[0025] In some embodimentexamples, 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.

[0026] In some embodimentexamples, 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.

[0027] In some embodimentexamples, 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.

[0028] In some embodimentexamples, the antibody comprises a variable region sequence having at least 95% sequence identity to any of the sequences of SEQ ID NOs: 18-28. In some embodimentexamples, the antibody comprises a variable region sequence selected from the group consisting of SEQ ID NOs: 18-28.

[0029] In some [embodimentexamples](#), 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.

[0030] In some [embodimentexamples](#), the antibody further comprises a heavy chain constant region sequence in the absence of a CH1 sequence. In some [embodimentexamples](#), the antibody is multi-specific. In some [embodimentexamples](#), the antibody is bispecific. In some [embodimentexamples](#), the antibody has binding affinity to an effector cell. In some [embodimentexamples](#), the antibody has binding affinity to a T-cell antigen. In some [embodimentexamples](#), the antibody has binding affinity to CD3. In some [embodimentexamples](#), the antibody is in a CAR-T format.

[0031] In some [embodimentexample](#), 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. In some [embodimentexamples](#), 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.

[0032] In some [embodimentexample](#), 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. In some [embodimentexamples](#), 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.

[0033] In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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.

[0034] In some [embodimentexamples](#), 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 some [embodimentexamples](#), the first polypeptide subunit further comprises a CH1 domain, at least a portion of a hinge region, a CH2 domain, and a CH3 domain. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), the human light chain framework is a human kappa light chain framework or a human lambda light chain framework. In some [embodimentexamples](#), the second polypeptide subunit further comprises a CL domain. In some [embodimentexamples](#), the 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. In some [embodimentexamples](#), the antibody comprises an asymmetric interface between the CH3 domain of the first polypeptide subunit and the CH3 domain of the third polypeptide subunit.

[0035] In some [embodimentexamples](#), 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.

[0036] In some [embodimentexamples](#), the antibody is a bispecific antibody 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.

[0037] These and further ~~aspects~~examples will be further explained in the rest of the disclosure, including the Examples.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] FIG. 1, panels A-E provide CDR sequences, variable region sequences, V-Gene and J-Gene information, percent CD38 hydrolase inhibition activity, and cell binding MFI data for anti-CD38 binding compounds in the F11 family.

[0039] FIG. 2, panels A-D, provide CDR sequences, variable region sequences, V-Gene and J-Gene information, percent CD38 hydrolase inhibition activity, and cell binding MFI data for anti-CD38 binding compounds in the F12 family.

[0040] FIG. 3, panels A-B, provide CDR sequences, variable region sequences, V-Gene and J-Gene information, percent CD38 hydrolase inhibition activity, and cell binding MFI data for anti-CD38 binding compounds in the F13 family.

[0041] FIG. 4 provides sequence information for additional amino acid sequences in the application.

[0042] FIG. 5 provides sequence information for additional amino acid sequences in the application.

[0043] FIG. 6 shows a graph depicting cell binding data as a function of concentration for the noted binding compounds.

[0044] FIG. 7 shows a graph depicting cell-based hydrolase activity as a function of concentration for the noted binding compounds.

[0045] FIG. 8 shows a graph depicting enzyme inhibition of the hydrolase activity of CD38 by bivalent UniAbsTM.

[0046] FIG. 9 shows a graph depicting enzyme inhibition of the hydrolase activity of CD38 by a mixture of either UniAbsTM CD38_F13A or CD38_F13B with Isatuximab.

[0047] FIG. 10 shows a graph depicting direct cytotoxicity of Daudi cells induced with binding compounds in accordance with embodiments of the invention.

[0048] FIG. 11 shows a schematic representation of two bivalent (Panels C and D) and two tetravalent (Panels A and B) UniAbTM formats in accordance with embodiments of the invention.

[0049] FIG. 12 shows a graph depicting enzyme inhibition of the hydrolase activity of human CD38 expressed on CHO cells by tetravalent UniAbsTM as described in FIG. 11.

[0050] FIG. 13 shows a graph depicting inhibition of mixtures of UniAbs with Isatuximab.

[0051] FIG. 14 shows a graph depicting inhibition of hydrolase activity of CD38 by mixtures of UniAbs.