human IFN-alpha to the murine cells, the toxicity of the antibody-IFN-alpha conjugate relative to free INF-alpha was not assessed.

[014] Antibodies and IFN-alpha may also be connected together in the form of a fusion protein. For example, WO 01/97844 describes a direct fusion of human IFN-alpha to the C-terminus of the heavy chain of an IgG specific for the tumor antigen CD20.

[015] In general, IFN may be targeted to cancer cells. While this approach may result in an increase in activity of the IFN against cancer cells, it does not completely address the issue of undesired activity of the IFN on healthy cells. Fusing IFN-alpha to the C-terminus of the heavy chain of an IgG may prolong the half-life of the IFN alpha leading to undesirable adverse events. Accordingly, there exists a need to decrease off-target activity of ligand-based drugs, while retaining the "on-target" therapeutic effect of such ligands.

SUMMARY

[016] The disclosure features new anti-CD38 antibodies and constructs comprising an anti-CD38 antibody and attenuated IFN-alpha. The antibodies, which comprise one or a plurality of mutations in their heavy and/or light chain variable regions retain the ability to specifically bind to CD38, including CD38 expressed on the surface of cells. The antibodies may be fused, for example, to an attenuated form of interferon alpha to form an anti-CD38 antibody-attenuated interferon fusion construct.

[017] In one aspect, there is provided an antibody that specifically binds to CD38, the antibody comprising: the heavy chain CDR1, CDR2, and CDR3 of SEQ ID NO: 665 and the light chain CDR1, CDR2, and CDR3 of SEQ ID NO: 666. In one aspect, the present invention refers to an anti-CD38 antibody-attenuated interferon alpha-2b fusion construct, comprising the antibody of the present disclosure; and an attenuated interferon alpha-2b comprising an alanine to aspartic acid or alanine to glycine substitution at position 145 relative to the amino acid sequence of SEQ ID NO: 648.. In some examples, an isolated antibody that binds specifically to CD38 comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 559 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 664. In some examples, an isolated antibody that binds specifically to CD38 comprising a heavy chain variable region comprising the amino acid sequence of

SEQ ID NO: 665 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 666. In some examples, an isolated antibody that binds specifically to CD38 comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 739 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 664. The heavy chain variable region amino acid sequence of SEQ ID NO: 559 excludes the amino acid sequence of SEQ ID NO: 13. The light chain variable region amino acid sequence of SEQ ID NO: 664 excludes the amino acid sequence of SEQ ID NO: 14. In some examples, an isolated antibody that binds specifically to CD38 comprises a heavy chain CDR1 comprising the amino acid sequence of , SEQ ID NO: 200, SEQ ID NO: 514 or SEQ ID NO: 697, a heavy chain CDR2 comprising the

[024] Kits comprising antibodies fused to attenuated interferon alpha-2b are provided. The kits comprise the anti-CD38-attenuated interferon alpha-2b fusion construct, and instructions for using the construct in a method for inhibiting the proliferation of a tumor cell expressing CD38 and a receptor for interferon alpha-2b on its surface, instructions for using the construct in a method for inducing apoptosis in a tumor cell expressing CD38 and a receptor for interferon alpha-2b on its surface, instructions for using the construct in a method for treating a tumor comprising cells expressing CD38 and a receptor for interferon alpha-2b on their surface in a subject in need thereof, and optionally, a pharmaceutically acceptable carrier. Kits comprising anti-CD38 antibodies are provided, and such kits comprise the anti-CD38 antibody and instructions for using the antibody in a method for detecting a CD38-positive tumor cell in a tissue sample isolated from a subject, the antibody may optionally be fused to an attenuated interferon alpha-2b protein.

[025] In one aspect, the present invention refers to a composition comprising the antibody of the present disclosure or the construct according to the present disclosure and a pharmaceutically acceptable carrier. In another aspect, there is provided a polynucleotide, comprising a nucleic acid sequence encoding the antibody according to the present disclosure or the construct according to the present disclosure. In another aspect, there is provided a vector comprising the polynucleotide of the present disclosure. In another aspect, there is provided a transformed mammalian cell comprising the vector of the present disclosure. In another aspect, there is provided the antibody according to the present disclosure or the construct according to the present disclosure for use as a medicament. In another aspect, the present invention refers to use of the antibody or the construct according to the present disclosure in the manufacture of a medicament for the treatment of B-cell lymphoma. In yet another aspect, the present invention refers to use of the antibody or the construct according to the present disclosure in the manufacture of a medicament for the treatment of multiple myeloma. In a further aspect, the present invention refers to use of the antibody or the construct according to the present disclosure in the manufacture of a medicament for the treatment of non-Hodgkin's lymphoma. In another aspect, the present invention refers to use of the antibody or the construct according to the present disclosure in the manufacture of a medicament for the treatment of chronic myelogenous leukemia. In yet another aspect, the present invention refers to use of the antibody or the construct

according to the present disclosure in the manufacture of a medicament for the treatment of chronic lymphocytic leukemia. In a further aspect, the present invention refers to use of the antibody or the construct according to the present disclosure in the treatment of or acute myelogenous leukemia. The anti-CD38 antibody-attenuated interferon alpha-2b fusion constructs may be used as a threrapy in the treatment of a tumor comprising cells expressing CD38 and a receptor for interferon alpha-2b on their surface. Generally, a treatment method comprises administering to a subject having the tumor an anti-CD38 antibody-attenuated interferon alpha-2b fusion construct in an amount effective to treat the tumor. The construct may comprise any construct described or exemplified herein. The subject is preferably a mammal, more preferably a non-human primate, and most preferably a human being. The tumor may comprise a B-cell lymphoma, multiple myeloma, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia or acute myelogenous leukemia.

[026] The anti-CD38 antibodies, optionally fused to an attenuated interferon alpha-2b protein, may be used in a method for detecting CD38 or a CD38-positive tumor cell in a tissue sample isolated from a subject. Generally, the method comprises contacting an antibody that binds specifically to CD38 with a tissue sample isolated from a subject and detecting a complex of the antibody and CD38 or a CD38-positive cell in the tissue sample. The tissue sample may be known to have or be suspected of having CD38-positive tumor cells. The tissue may comprise blood or bone marrow. The CD38-positive tumor cell may be a CD38-positive B-cell lymphoma cell, multiple myeloma cell, non-Hodgkin's lymphoma cell, chronic myelogenous leukemia cell, chronic lymphocytic leukemia cell, or acute myelogenous leukemia cell. The subject is preferably a mammal, more preferably a non-

We claim:

1. An antibody that specifically binds to CD38, the antibody comprising:

the heavy chain CDR1, CDR2, and CDR3 of SEQ ID NO: 665 and the light chain CDR1, CDR2, and CDR3 of SEQ ID NO: 666.

2. The antibody according to claim 1, wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 514, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 516, the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 518, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 608, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 591, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 612.

3. The antibody according to claim 1 or 2, comprising a heavy chain variable region comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 156 and a light chain variable region comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 185, wherein any amino acid changes in the heavy chain variable region or light chain variable region are outside of the CDRs.

4. The antibody according to any one of claims 1 to 3, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 156 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 185.

5. The antibody according to any one of claims 1 to 4, wherein the antibody comprises a human IgG1 heavy chain constant region.

6. The antibody according to any one of claims 1 to 4, wherein the antibody comprises a human IgG4 heavy chain constant region.

7. The antibody according to claim 6, wherein the human IgG4 heavy chain constant region comprises a proline at position 228 according to the EU numbering system.

8. The antibody according to claim 6 or 7, wherein the human IgG4 heavy chain constant region comprises a tyrosine at position 252, a threonine at position 254, and a glutamic acid at position 256 of the constant region according to the EU numbering system.

9. The antibody according to any one of claims 1, 2, or 5 to 8, wherein the antibody is a humanized antibody.

10. An anti-CD38 antibody-attenuated interferon alpha-2b fusion construct comprising:

the antibody of any one of claims 1 to 9; and

an attenuated interferon alpha-2b comprising an alanine to aspartic acid or alanine to glycine substitution at position 145 relative to the amino acid sequence of SEQ ID NO: 648.

11. The construct according to claim 10, wherein the attenuated interferon alpha-2b comprises an alanine to aspartic acid substitution at position 145 relative to the amino acid sequence of SEQ ID NO: 648.

12. The construct according to claim 10 or 11, wherein the attenuated interferon alpha-2b comprises the amino acid sequence SEQ ID NO: 647, SEQ ID NO: 649, SEQ ID NO: 650, or SEQ ID NO: 651.

13. A composition, comprising the antibody according to any one of claims 1 to 9 or the construct according to any one of claims 10 to 12 and a pharmaceutically acceptable carrier.

14. A polynucleotide, comprising a nucleic acid sequence encoding the antibody according to any one of claims 1 to 9 or the construct according to any one of claims 10 to 12.

15. The polynucleotide according to claim 14, wherein the nucleic acid sequence encoding the antibody heavy chain variable region comprises SEQ ID NO: 685 and the nucleic acid sequence encoding the antibody light chain variable region comprises SEQ ID NO: 691.

16. A vector comprising the polynucleotide of claim 14 or 15.

17. A transformed mammalian cell comprising the vector of claim 16.

18. The antibody according to any one of claims 1 to 9 or the construct according to any one of claims 10 to 12 for use as a medicament.

19. Use of the antibody according to any one of claims 1 to 9 or the construct according to any one of claims 10 to 12 in the manufacture of a medicament for the treatment of B-cell lymphoma.

20. Use of the antibody according to any one of claims 1 to 9 or the construct according to any one of claims 10 to 12 in the manufacture of a medicament for the treatment of multiple myeloma.

21. Use of the antibody according to any one of claims 1 to 9 or the construct according to any one of claims 10 to 12 in the manufacture of a medicament for the treatment of non-Hodgkin's lymphoma.

22. Use of the antibody according to any one of claims 1 to 9 or the construct according to any one of claims 10 to 12 in the manufacture of a medicament for the treatment of chronic myelogenous leukemia.

23. Use of the antibody according to any one of claims 1 to 9 or the construct according to any one of claims 10 to 12 in the manufacture of a medicament for the treatment of chronic lymphocytic leukemia.

24. Use of the antibody according to any one of claims 1 to 9 or the construct according to any one of claims 10 to 12 in the manufacture of a medicament for the treatment of acute myelogenous leukemia.