for example, in Iri-Sofla *et al*., 2011, *Experimental Cell Research* 317:2630-2641 and Jamnani *et al*., 2014, *Biochim Biophys Acta*, 1840:378-386.

SUMMARY

[0009] Examples of the disclosure include antibodies that bind to CD19, comprising a heavy chain variable region comprising: (a) a CDR1 sequence having two or fewer substitutions in SEQ ID NO: 1; and/or (b) a CDR2 sequence having two or fewer substitutions in SEQ ID NO: 2; and/or (c) a CDR3 sequence having two or fewer substitutions in any one of SEQ ID NOs: 3-4.

[0010] In some examples, the CDR1, CDR2, and CDR3 sequences are present in a human VH framework. In some examples, an antibody further comprises a heavy chain constant region sequence in the absence of a CH1 sequence.

[0011] In some examples, an antibody comprises: (a) a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1 and 38; and/or (b) a CDR2 sequence selected from the group consisting of SEQ ID NOs: 2 and 39; and/or (c) a CDR3 sequence selected from the group consisting of SEQ ID NOs: 3-4. In some examples, an antibody comprises: (a) a CDR1 sequence comprising SEQ ID NO: 1 or SEQ ID NO: 38; and (b) a CDR2 sequence comprising SEQ ID NO: 2 or SEQ ID NO: 39; and (c) a CDR3 sequence comprising SEQ ID NO: 3 or SEQ ID NO: 4. In some examples, an antibody comprises: (a) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 3; or (b) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 4; or (c) a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 3; or (d) a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 4; or (e) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 3; or (f) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 4.

[0012] In some examples, an antibody comprises a heavy chain variable region having at least 95% sequence identity to any one of the sequences of SEQ ID NOs: 5, 6, 40, and 41. In some examples, an antibody comprises a heavy chain variable region sequence selected from the group consisting of SEQ ID NOs: 5, 6, 40, and 41. In some examples, an antibody comprises a heavy chain variable region sequence of SEQ ID NO: 5. In some examples, an antibody comprises a heavy chain variable region sequence of SEQ ID NO: 6. In some examples, an antibody comprises a heavy chain variable region sequence of SEQ ID NO: 40. In some examples, an antibody comprises a heavy chain variable region sequence of SEQ ID NO: 41.

[0013] Examples of the disclosure include antibodies that binds to CD19, comprising a heavy chain variable region comprising CDR1, CDR2 and CDR3 sequences in a human VH framework, wherein the CDR sequences are sequences having two or fewer substitutions in a CDR sequence selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 38 and 39. In some examples, an antibody comprises

a heavy chain variable region comprising CDR1, CDR2 and CDR3 sequences in a human VH framework, wherein the CDR sequences are selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 38 and 39.

[0014] Examples of the disclosure include antibodies that binds to CD19, comprising a heavy chain variable region comprising: (a) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 3, in a human VH framework; or (b) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 4, in a human VH framework; or (c) a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 3, in a human VH framework; or (d) a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 4, in a human VH framework; or (e) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 3, in a human VH framework; or (f) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 4, in a human VH framework.

[0015] In some examples, an antibody is multi-specific. In some examples, an antibody is bispecific. In some examples, an antibody binds to two different CD19 proteins. In some examples, an antibody binds to two different epitopes on the same CD19 protein. In some examples, an antibody binds to an effector cell. In some examples, an antibody binds to a T-cell antigen. In some examples, an antibody binds to CD3. In some examples, an antibody is in a CAR-T format.

[0016] Examples of the disclosure include CAR-T cells comprising a CAR comprising an extracellular antigen-binding domain that binds to CD19, comprising a heavy chain variable region comprising: (a) a CDR1 sequence comprising SEQ ID NO: 1 or SEQ ID NO: 38; and (b) a CDR2 sequence comprising SEQ ID NO: 2 or SEQ ID NO: 39; and (c) a CDR3 sequence comprising SEQ ID NO: 3 or SEQ ID NO: 4.

[0017] In some examples, the heavy chain variable region comprises (a) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 3, in a human VH framework; or (b) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 4, in a human VH framework; or (c) a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 3, in a human VH framework; or (d) a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 4, in a human VH framework; or (e) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 3, in a human VH framework; or (f) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 4, in a human VH framework.

[0018] In some examples, the extracellular antigen-binding domain that binds to CD19 comprises a heavy chain variable region having at least 95% sequence identity to any one of the sequences of SEQ

ID NOs: 5, 6, 40 and 41. In some examples, the extracellular antigen-binding domain that binds to CD19 comprises a heavy chain variable region sequence selected from the group consisting of SEQ ID NOs: 5-6. In some examples, the extracellular antigen-binding domain that binds to CD19 comprises a heavy chain variable region sequence of SEQ ID NO: 5, 6, 40 and 41. In some examples, the extracellular antigen-binding domain that binds to CD19 comprises a heavy chain variable region sequence of SEQ ID NO: 6. In some examples, the extracellular antigen-binding domain that binds to CD19 comprises a heavy chain variable region sequence of SEQ ID NO: 40. In some examples, the extracellular antigen-binding domain that binds to CD19 comprises a heavy chain variable region sequence of SEQ ID NO: 41.

[0019] Examples of the disclosure include pharmaceutical compositions comprising an antibody or a CAR-T cell as described herein.

[0020] Examples of the disclosure include methods for the treatment of a B-cell disorder characterized by expression of CD19, comprising administering to a subject with said disorder an antibody, a CAR-T cell, or a pharmaceutical composition as described herein.

[0021] In some examples, the disorder is diffuse large B-cell lymphoma (DLBCL). In some examples, the disorder is acute lymphoblastic leukemia (ALL). In some examples, the disorder is non-Hodgkin's lymphoma (NHL). In some examples, the disorder is systemic lupus erythematosus (SLE). In some examples, the disorder is rheumatoid arthritis (RA). In some examples, the disorder is multiple sclerosis (MS).

[0022] Examples of the disclosure include polynucleotides encoding an antibody or a CAR of a CAR-T cell as described herein, vectors comprising such polynucleotides, and cells comprising such vectors.

[0023] Examples of the disclosure include methods of producing an antibody as described herein, the methods comprising growing a cell as described herein under conditions permissive for expression of the antibody, and isolating the antibody from the cell and/or a cell culture medium in which the cell is grown.

[0024] Examples of the disclosure include methods of making an antibody as described herein, the methods comprising immunizing a UniRat animal with CD19 and identifying CD19-binding heavy chain sequences.

[0025] Examples of the disclosure include methods of treatment, comprising administering to an individual in need an effective dose of an antibody, a CAR-T cell, or a pharmaceutical composition as described herein.

[0026] Examples of the disclosure include use of an antibody or a CAR-T cell as described herein in the preparation of a medicament for the treatment of a disease or disorder in an individual in need.

[0027] Examples of the disclosure include kits for treating a disease or disorder in an individual in need, comprising an antibody, a CAR-T cell, or a pharmaceutical composition as described herein, and instructions for use. In some examples, a kit further comprises at least one additional reagent. In some embodiments, the at least one additional reagent comprises a chemotherapeutic drug.

[0027a] In one aspect, the present disclosure relates to an antibody that binds to CD19, comprising a heavy chain variable region comprising: (a) a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 3; or (b) a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 4; or (c) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 3; or (d) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 4.

[0027b] In another aspect, the present disclosure relates to CAR-T cell comprising a CAR comprising an extracellular antigen-binding domain that binds to CD19, comprising a heavy chain variable region comprising (a) a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 3; or (b) a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 4; or (c) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 3; or (d) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 4.

[0027c] In another aspect, the present disclosure relates to a pharmaceutical composition comprising the CAR-T cell as disclosed herein.

[0027d] In another aspect, the present disclosure relates to the CAR-T cell as disclosed herein for use in therapy.

[0027e] In another aspect, the present disclosure relates to use of the CAR T-cell as disclosed herein in the manufacture of a medicament for treating a B-cell disorder characterized by expression of CD19.

[0027f] In another aspect, the present disclosure relates to a kit for treating a disease or disorder in an individual in need, comprising the CAR-T cell as disclosed herein.

.

CLAIMS

1. An antibody that binds to CD19, comprising a heavy chain variable region comprising:

(a) a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 3; or

(b) a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 4; or

(c) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 3; or

(d) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 4.

2. A CAR-T cell comprising a CAR comprising an extracellular antigen-binding domain that binds to CD19, comprising a heavy chain variable region comprising:

(a) a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 3; or

(b) a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 4; or

(c) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 3; or

(d) a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 4.

3. The CAR-T cell of claim 2, wherein the CDR1, CDR2 and CDR3 sequences are present in a human VH framework.

4. The CAR-T cell of claim 2, wherein the heavy chain variable region comprises a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 3.

5. The CAR-T cell of claim 2, wherein the heavy chain variable region comprises a CDR1 sequence of SEQ ID NO: 38, a CDR2 sequence of SEQ ID NO: 2, and a CDR3 sequence of SEQ ID NO: 4.

6. The CAR-T cell of claim 2, wherein the heavy chain variable region comprises a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 3.

7. The CAR-T cell of claim 2, wherein the heavy chain variable region comprises a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 39, and a CDR3 sequence of SEQ ID NO: 4.

8. The CAR-T cell of claim 2, wherein the extracellular antigen-binding domain that binds to CD19 comprises a heavy chain variable region having at least 95% sequence identity to any one of the sequences of SEQ ID NOs:40 and 41.

9. The CAR-T cell of claim 8, wherein the extracellular antigen-binding domain that binds to CD19 comprises a heavy chain variable region sequence selected from the group consisting of SEQ ID NOs: 40 and 41.

10. The CAR-T cell of claim 9, wherein the extracellular antigen-binding domain that binds to CD19 comprises a heavy chain variable region sequence of SEQ ID NO: 40.

11. The CAR-T cell of claim 9, wherein the extracellular antigen-binding domain that binds to CD19 comprises a heavy chain variable region sequence of SEQ ID NO: 41.

12. A pharmaceutical composition comprising the CAR-T cell of claim 2.

13. The CAR-T cell of claim 2 for use in therapy.

14. Use of the CAR T-cell of claim 2 in the manufacture of a medicament for treating a B-cell disorder characterized by expression of CD19.

15. The use of claim 14, wherein the disorder is diffuse large B-cell lymphoma (DLBCL).

16. The use of claim 14, wherein the disorder is acute lymphoblastic leukemia (ALL).

17. The use of claim 14, wherein the disorder is non-Hodgkin’s lymphoma (NHL).

18. The use of claim 14, wherein the disorder is systemic lupus erythematosus (SLE).

19. The use of claim 14, wherein the disorder is rheumatoid arthritis (RA).

20. The use of claim 14, wherein the disorder is multiple sclerosis (MS).

21. A kit for treating a disease or disorder in an individual in need, comprising the CAR-T cell of claim 2.

22. The kit of claim 21, further comprising at least one additional reagent.

23. The kit of claim 22, wherein the at least one additional reagent comprises a chemotherapeutic drug.