

Obexelimab (also known as XmAb5871) is an Fc-engineered antibody that binds both CD19 and FcγRIIb, and inhibits B cell function by engaging the inhibitory FcγRIIb receptor signaling (Szili, et al., MAbs. 6(4): 991–999, 2014). However, high affinity binding of obexelimab to FcγRIIb could lead to non-specific binding to other cell types. In human patients, obexelimab was reported to have a short half-life, with $T_{1/2}$ of 3.5 ± 1.0 days; and reduce peripheral human B cell counts, with a mean reduction of about 30-40% of the baseline level (Jaraczewska-Baumann, et al., European League Against Rheumatism (EULAR) 2015 Annual Meeting Poster: *A Phase 1b/2a Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of XmAb®5871 in Patients with Rheumatoid Arthritis*, June 12, 2015, available at <https://investors.xencor.com/static-files/0017dcf1-deb2-46eb-93ff-90ba164ec50c>).

Therefore, there remains a need for alternative anti-human CD19 antibodies that specifically bind and inhibit human B cells, without depleting them, for treating B cell associated disorders.

SUMMARY

In one aspect of the present disclosure, there is provided an antibody that binds human CD19, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, wherein

the HCDR1 comprises SEQ ID NO: 29,

the HCDR2 comprises SEQ ID NO: 30,

the HCDR3 comprises SEQ ID NO: 31,

the LCDR1 comprises SEQ ID NO: 32,

the LCDR2 comprises SEQ ID NO: 33, and

the LCDR3 comprises SEQ ID NO: 34.

In another aspect of the present disclosure, there is provided an antibody that binds human CD19, wherein the antibody comprises a VH and a VL, wherein the VH comprises HCDR1, HCDR2, and HCDR3, and the VL comprises LCDR1, LCDR2, and LCDR3, wherein

the HCDR1 comprises SEQ ID NO: 29,

the HCDR2 comprises SEQ ID NO: 30,

the HCDR3 comprises SEQ ID NO: 31,
the LCDR1 comprises SEQ ID NO: 43,
the LCDR2 comprises SEQ ID NO: 44, and
the LCDR3 comprises SEQ ID NO: 45.

In a further aspect of the present disclosure, there is provided an antibody that binds human CD19, wherein the antibody comprises a VH and a VL, wherein the VH comprises HCDR1, HCDR2, and HCDR3, and the VL comprises LCDR1, LCDR2, and LCDR3, wherein
the HCDR1 comprises SEQ ID NO: 15,
the HCDR2 comprises SEQ ID NO: 16,
the HCDR3 comprises SEQ ID NO: 17,
the LCDR1 comprises SEQ ID NO: 18,
the LCDR2 comprises SEQ ID NO: 19, and
the LCDR3 comprises SEQ ID NO: 20.

In another aspect of the present disclosure, there is provided a nucleic acid comprising a sequence encoding SEQ ID NO: 35, 52, 39, 46, 21, 54, or 25.

In a further aspect of the present disclosure, there is provided a vector comprising the nucleic acid disclosed herein.

In another aspect of the present disclosure, there is provided a composition comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 35 or 52, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 39 or 46.

In a further aspect of the present disclosure, there is provided a composition comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 21 or 54, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 25.

In another aspect of the present disclosure, there is provided a cell comprising the vector disclosed herein.

In a further aspect of the present disclosure, there is provided a cell comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 35 or 52, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 39 or 46.

In another aspect of the present disclosure, there is provided a cell comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 21 or 54, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 25.

In a further aspect of the present disclosure, there is provided a process of producing an antibody comprising culturing the cell disclosed herein under conditions such that the antibody is expressed and recovering the expressed antibody from the culture medium.

In another aspect of the present disclosure, there is provided an antibody produced by the process disclosed herein.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the antibody disclosed herein, and a pharmaceutically acceptable excipient, diluent or carrier.

In another aspect of the present disclosure, there is provided an antibody disclosed herein for use in therapy.

In a further aspect of the present disclosure, there is provided an antibody disclosed herein, or the pharmaceutical composition disclosed herein, for use in the treatment of a B cell associated disorder.

In another aspect of the present disclosure, there is provided a use of the antibody disclosed herein, in the manufacture of a medicament for the treatment of a B cell associated disorder.

DETAILED DESCRIPTION

Provided herein are antibodies that bind human CD19 and inhibit B cell responses (e.g., proliferation, activation, and differentiation) without depleting the B cells (i.e., “non-depleting anti-human CD19 antibodies”). Such non-depleting anti-human CD19 antibodies can be used to treat B cell associated disorders, e.g., autoimmune diseases, without destroying those important immune cells, and thus avoid problematic concurrent immunocompromise, long-term immune suppression, and other complications resulting from B cell depletion. The anti-human CD19 antibodies provided herein have one or more of the following properties: 1) bind human CD19 (and sometimes cynomolgus monkey CD19) with desirable binding affinities and/or association and dissociation rates, 2) bind human B cells specifically and inhibit primary human B cell proliferation, activation and/or differentiation, 3) do not deplete human B cells, 4) being internalized into human B cells, 5) low immunogenicity risk, 6) low hydrophobicity, and/or 7) good stability, solubility, viscosity, and pharmacokinetic characteristics for development and use in the treatment of autoimmune disorders. As described below, in a side-by-side comparison, one such anti-human CD19 antibody CB3f is shown to bind human B cells with high specificity in a whole blood assay, whereas obexelimab shows non-specific binding to human neutrophils in addition to B cell binding. Since neutrophil is the most abundant type of white blood cells in

CLAIMS:

1. An antibody that binds human CD19, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, wherein
 - the HCDR1 comprises SEQ ID NO: 29,
 - the HCDR2 comprises SEQ ID NO: 30,
 - the HCDR3 comprises SEQ ID NO: 31,
 - the LCDR1 comprises SEQ ID NO: 32,
 - the LCDR2 comprises SEQ ID NO: 33, and
 - the LCDR3 comprises SEQ ID NO: 34.
2. The antibody of claim 1, wherein the VH comprises SEQ ID NO: 37 and the VL comprises SEQ ID NO: 41.
3. The antibody of claim 1 or 2, wherein the antibody comprises a heavy chain (HC) comprising SEQ ID NO: 35 and a light chain (LC) comprising SEQ ID NO: 39.
4. The antibody of claim 1 or 2, wherein the antibody comprises a HC comprising SEQ ID NO: 52 and a LC comprising SEQ ID NO: 39.
5. An antibody that binds human CD19, wherein the antibody comprises a VH and a VL, wherein the VH comprises HCDR1, HCDR2, and HCDR3, and the VL comprises LCDR1, LCDR2, and LCDR3, wherein
 - the HCDR1 comprises SEQ ID NO: 29,
 - the HCDR2 comprises SEQ ID NO: 30,
 - the HCDR3 comprises SEQ ID NO: 31,
 - the LCDR1 comprises SEQ ID NO: 43,
 - the LCDR2 comprises SEQ ID NO: 44, and

the LCDR3 comprises SEQ ID NO: 45.

6. The antibody of claim 5, wherein the VH comprises SEQ ID NO: 37 and the VL comprises SEQ ID NO: 48.

7. The antibody of claim 5 or 6, wherein the antibody comprises a HC comprising SEQ ID NO: 35 and a LC comprising SEQ ID NO: 46.

8. The antibody of claim 5 or 6, wherein the antibody comprises a HC comprising SEQ ID NO: 52 and a LC comprising SEQ ID NO: 46.

9. An antibody that binds human CD19, wherein the antibody comprises a VH and a VL, wherein the VH comprises HCDR1, HCDR2, and HCDR3, and the VL comprises LCDR1, LCDR2, and LCDR3, wherein

the HCDR1 comprises SEQ ID NO: 15,

the HCDR2 comprises SEQ ID NO: 16,

the HCDR3 comprises SEQ ID NO: 17,

the LCDR1 comprises SEQ ID NO: 18,

the LCDR2 comprises SEQ ID NO: 19, and

the LCDR3 comprises SEQ ID NO: 20.

10. The antibody of claim 9, wherein the VH comprises SEQ ID NO: 23 and the VL comprises SEQ ID NO: 27.

11. The antibody of claim 9 or 10, wherein the antibody comprises a HC comprising SEQ ID NO: 21 and a LC comprising SEQ ID NO: 25.

12. The antibody of claim 9 or 10, wherein the antibody comprises a HC comprising SEQ ID NO: 54 and a LC comprising SEQ ID NO: 25.

13. The antibody of any one of claims 1-12, wherein the antibody is a non-depleting antibody.
14. A nucleic acid comprising a sequence encoding SEQ ID NO: 35, 52, 39, 46, 21, 54, or 25.
15. A vector comprising the nucleic acid of claim 14.
16. The vector of claim 15, wherein the vector comprises a first nucleic acid sequence encoding SEQ ID NO: 35 or 52, and a second nucleic acid sequence encoding SEQ ID NO: 39 or 46.
17. The vector of claim 15, wherein the vector comprises a first nucleic acid sequence encoding SEQ ID NO: 21 or 54, and a second nucleic acid sequence encoding SEQ ID NO: 25.
18. A composition comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 35 or 52, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 39 or 46.
19. A composition comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 21 or 54, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 25.
20. A cell comprising the vector of claim 16 or 17.
21. A cell comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 35 or 52, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 39 or 46.
22. A cell comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 21 or 54, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 25.
23. The cell of any one of claims 20-22, wherein the cell is a mammalian cell.

24. A process of producing an antibody comprising culturing the cell of any one of claims 20-23 under conditions such that the antibody is expressed and recovering the expressed antibody from the culture medium.

25. An antibody produced by the process of claim 24.

26. A pharmaceutical composition comprising the antibody of any one of claims 1-13 or 25, and a pharmaceutically acceptable excipient, diluent or carrier.

~~27. A method of treating a B cell associated disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the antibody of any one of claims 1-13 or 25, or the pharmaceutical composition of claim 26.~~

~~28. The method of claim 27, wherein the B cell associated disorder is an autoimmune disease.~~

~~29. The method of claim 27, wherein the B cell associated disorder is selected from systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, Sjogren's syndrome, idiopathic thrombocytopenia purpura, Type 1 diabetes, pemphigus vulgaris, neuromyelitis optica, ANCA vasculitis, or myasthenia gravis.~~

~~30~~27. The antibody of any one of claims 1-13 or 25 for use in therapy.

~~31~~28. The antibody of any one of claims 1-13 or 25, or the pharmaceutical composition of claim 26, for use in the treatment of a B cell associated disorder.

~~32~~29. The antibody or pharmaceutical composition for use of claim ~~31~~28, wherein the B cell associated disorder is an autoimmune disease.

3330. The antibody or pharmaceutical composition for use of claim ~~3128~~, wherein the B cell associated disorder is selected from systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, Sjogren's syndrome, idiopathic thrombocytopenia purpura, Type 1 diabetes, pemphigus vulgaris, neuromyelitis optica, ANCA vasculitis, or myasthenia gravis.

3431. Use of the antibody of any one of claims 1-13 or 25, in the manufacture of a medicament for the treatment of a B cell associated disorder.

3532. The use of claim 3431, wherein the B cell associated disorder is an autoimmune disease.

3633. The use of claim 3431, wherein the B cell associated disorder is selected from systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, Sjogren's syndrome, idiopathic thrombocytopenia purpura, Type 1 diabetes, pemphigus vulgaris, neuromyelitis optica, ANCA vasculitis, or myasthenia gravis.