

NEUTRALIZING ANTI-TL1A MONOCLONAL ANTIBODIES

CROSS-REFERENCE

[0001] This application claims priority to US Provisional Application 62/413,188 filed October 26, 2016, the entirety of which is incorporated by reference herein.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 23, 2017, is named 52388-728_601_SL.txt and is 33,920 bytes in size.

BACKGROUND

[0003] Inflammatory bowel disease (IBD) refers to a collection of intestinal disorders causing inflammatory conditions in the gastrointestinal tract. The primary types of IBD are ulcerative colitis (UC) and Crohn's Disease (CD). These diseases are prevalent, with about 1.86 billion people diagnosed globally with UC, and about 1.3 million people diagnosed globally with CD. Unfortunately, there are a limited number of therapies available for IBD patients, and the development of new therapeutics has been hampered by sub-optimal results in clinical trials. Accordingly, there is a need for novel therapeutics to treat IBD.

SUMMARY

[0004] The present disclosure provides antibodies useful for the treatment of IBD. In one example, provided is an antibody or antigen-binding fragment that specifically binds to a TL1A polypeptide. In some examples, the antibody or antigen-binding fragment comprises: a heavy chain comprising complementarity determining regions (CDRs) of SEQ ID NOs: 6 - 8 and a light chain comprising complementarity determining regions (CDRs) of SEQ ID NOs: 14 - 16. In some examples, the antibody or antigen-binding fragment comprises: a heavy chain comprising complementarity determining regions (CDRs) of SEQ ID NOs: 22-24 and a light chain comprising complementarity determining regions (CDRs) of SEQ ID NOs: 30-32. In some examples, the antibody or antigen-binding fragment is: a monoclonal antibody, a chimeric antibody, a CDR- grafted antibody, a humanized antibody, a Fab, a Fab', a F(ab')₂, a Fv, a disulfide linked Fv, a scFv, a single domain antibody, a diabody, a multispecific antibody, a dual specific antibody, an anti-idiotypic antibody, a bispecific antibody, or a combination thereof. Further examples provide for pharmaceutical compositions comprising a therapeutically effective amount of the antibody or

antigen-binding fragment, and a pharmaceutically acceptable carrier. Further examples provide for a method of treating inflammatory bowel disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the antibody or an antigen-binding fragment. In some examples, the inflammatory bowel disease comprises Crohn's Disease, ulcerative colitis, medically refractive-ulcerative colitis, or a combination thereof. In some examples, prior to administering the antibody or antigen-binding fragment to the subject, the subject over-expresses TL1A. In some examples, the subject comprises a risk variant associated with the inflammatory bowel disease.

[0005] In another example, provided herein is a polypeptide comprising: one or more complementarity determining regions selected from the group consisting of SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 30, SEQ ID NO: 31, and SEQ ID NO: 32.

[0005a] In one aspect, provided herein is a humanized antibody or humanized antigen-binding fragment that binds human tumor necrosis factor-like protein 1A (TL1A), wherein the humanized antibody or humanized antigen-binding fragment competes for binding to the human TL1A with a reference antibody comprising heavy chain complementarity determining regions of SEQ ID NOS: 6-8 and light chain complementarity determining regions of SEQ ID NOS: 14-16, wherein the humanized antibody or humanized antigen-binding fragment binds to human TL1A with a binding affinity (KD) of 1E-10 M or less.

[0006] In another example, provided herein is an antibody or antigen binding fragment that binds to the same region of human TL1A as a reference antibody comprising the heavy chain complementarity determining regions (CDRs) of SEQ ID NOS: 6 - 8 and the light chain complementarity determining regions (CDRs) of SEQ ID NOS: 14 - 16. In some examples, the reference antibody comprises a heavy chain variable domain of SEQ ID NO: 5 and a light chain variable domain of SEQ ID NO: 13. In some examples, the antibody or antigen-binding fragment is: a monoclonal antibody, a chimeric antibody, a CDR- grafted antibody, a humanized antibody, a Fab, a Fab', a F(ab')₂, a Fv, a disulfide linked Fv, a scFv, a single domain antibody, a diabody, a multispecific antibody, a dual specific antibody, an anti-idiotypic antibody, a bispecific antibody, or a combination thereof. Further examples provide for a pharmaceutical composition comprising a therapeutically effective amount of the antibody or antigen-binding fragment, and a pharmaceutically acceptable carrier. Further examples provide for a method of treating inflammatory bowel disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the antibody or an antigen-binding fragment. In some examples, the inflammatory bowel disease comprises Crohn's Disease, ulcerative colitis, medically refractive-ulcerative colitis, or a combination thereof. In some examples, prior to administering the antibody or antigen-binding fragment to the subject, the subject over-expresses

TL1A. In some examples, the subject comprises a risk variant associated with the inflammatory bowel disease.

[0007] In another example, provided herein is an antibody or antigen binding fragment that binds to the same region of human TL1A as a reference antibody comprising the heavy chain complementarity determining regions (CDRs) of SEQ ID NOs: 22 - 24 and the light chain

complementarity determining regions (CDRs) of SEQ ID NOs: 30 - 32. In some examples, the reference antibody comprises a heavy chain variable domain of SEQ ID NO: 21 and a light chain variable domain of SEQ ID NO: 29. In some examples, the antibody or antigen-binding fragment is: a monoclonal antibody, a chimeric antibody, a CDR- grafted antibody, a humanized antibody, a Fab, a Fab', a F(ab')₂, a Fv, a disulfide linked Fv, a scFv, a single domain antibody, a diabody, a multispecific antibody, a dual specific antibody, an anti-idiotypic antibody, a bispecific antibody, or a combination thereof. Further examples provide for a pharmaceutical composition comprising a therapeutically effective amount of the antibody or antigen-binding fragment, and a pharmaceutically acceptable carrier. Further examples provide for a method of treating inflammatory bowel disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the antibody or an antigen-binding fragment. In some examples, the inflammatory bowel disease comprises Crohn's Disease, ulcerative colitis, medically refractive-ulcerative colitis, or a combination thereof. In some examples, prior to administering the antibody or antigen-binding fragment to the subject, the subject over-expresses TL1A. In some examples, the subject comprises a risk variant associated with the inflammatory bowel disease.

[0008] In another example, provided herein is a composition comprising a peptide having SEQ ID NO: 7. In some examples, the composition further comprises one or more peptides selected from SEQ ID NOs: 6, 8, and 14-16. Further examples provide for a method of treating a subject having an inflammatory bowel disease, the method comprising administering to the subject an effective amount of the composition.

[0009] In another example, provided herein is a composition comprising a peptide having SEQ ID NO: 23. In some examples, the composition further comprises one or more peptides selected from SEQ ID NOs: 22, 24 and 30-32. Further examples provide for a method of treating a subject having an inflammatory bowel disease, the method comprising administering to the subject an effective amount of the composition.

[0010] In another example, provided herein is a method of treating an inflammatory bowel disease in a subject in need thereof, the method comprising administering to the subject an effective amount of an anti-TL1A antibody, provided that the subject comprises one or more risk variants at the TNFSF15 locus, and provided that the anti-TL1A antibody comprises a heavy chain comprising complementarity determining regions (CDRs) of SEQ ID NOs: 6 - 8 and a light chain comprising complementarity determining regions (CDRs) of SEQ ID NOs: 14 - 16. In some examples, the anti-TL1A antibody is: a monoclonal antibody, a chimeric antibody, a CDR- grafted antibody, a humanized antibody, a Fab, a Fab', a F(ab')₂, a Fv, a disulfide linked Fv, a scFv, a single domain

antibody, a diabody, a multispecific antibody, a dual specific antibody, an anti-idiotypic antibody, a bispecific antibody, or a combination thereof. In some examples, the inflammatory bowel disease comprises Crohn's Disease, ulcerative colitis, medically refractive-ulcerative colitis, or a combination thereof.

[0011] In another example, provided herein is a method of treating an inflammatory bowel disease in a subject in need thereof, the method comprising administering to the subject an effective amount of an anti-TL1A antibody, provided that the subject comprises one or more risk variants at the TNFSF15 locus, and provided that the anti-TL1A antibody comprises a heavy chain comprising complementarity determining regions (CDRs) of SEQ ID NOs: 22-24 and a light chain comprising complementarity determining regions (CDRs) of SEQ ID NOs: 30-32. In some examples, the anti-TL1A antibody is: a monoclonal antibody, a chimeric antibody, a CDR- grafted antibody, a humanized antibody, a Fab, a Fab', a F(ab')₂, a Fv, a disulfide linked Fv, a scFv, a single domain antibody, a diabody, a multispecific antibody, a dual specific antibody, an anti-idiotypic antibody, a bispecific antibody, or a combination thereof. In some examples, the inflammatory bowel disease comprises Crohn's Disease, ulcerative colitis, medically refractive-ulcerative colitis, or a combination thereof.

[0012] In another example, provided herein is a method of treating an inflammatory bowel disease in a subject in need thereof, the method comprising administering to the subject an effective amount of an anti-TL1A antibody, provided that the subject over-express TL1A, and provided that the anti-TL1A antibody comprises a heavy chain comprising complementarity determining regions (CDRs) of SEQ ID NOs: 6 - 8 and a light chain comprising complementarity determining regions (CDRs) of SEQ ID NOs: 14 - 16. In some examples, the anti-TL1A antibody is: a monoclonal antibody, a chimeric antibody, a CDR- grafted antibody, a humanized antibody, a Fab, a Fab', a F(ab')₂, a Fv, a disulfide linked Fv, a scFv, a single domain antibody, a diabody, a multispecific antibody, a dual specific antibody, an anti-idiotypic antibody, a bispecific antibody, or a combination thereof. In some examples, the inflammatory bowel disease comprises Crohn's Disease, ulcerative colitis, medically refractive-ulcerative colitis, or a combination thereof.

[0013] In another example, provided herein is a method of treating an inflammatory bowel disease in a subject in need thereof, the method comprising administering to the subject an effective amount of an anti-TL1A antibody, provided that the subject over-express TL1A, and provided that the anti-TL1A antibody comprises a heavy chain comprising complementarity determining regions (CDRs) of SEQ ID NOs: 22-24 and a light chain comprising complementarity determining regions (CDRs) of SEQ ID NOs: 30-32. In some examples, the anti-TL1A antibody is: a monoclonal antibody, a chimeric antibody, a CDR- grafted antibody, a humanized antibody, a Fab, a Fab', a

F(ab')₂, a Fv, a disulfide linked Fv, a scFv, a single domain antibody, a diabody, a multispecific antibody, a dual specific antibody, an anti-idiotypic antibody, a bispecific antibody, or a combination thereof. In some examples, the inflammatory bowel disease comprises Crohn's Disease, ulcerative colitis, medically refractive-ulcerative colitis, or a combination thereof.

[0013b] In another aspect, provided herein is the antibody or an antigen-binding fragment as described herein for use in therapy.

[0013c] In another aspect, provided herein is the use of the antibody or an antigen-binding fragment as described herein in the manufacture of a medicament for treating an inflammatory bowel disease in a subject in need thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0014] Exemplary embodiments are illustrated in referenced figures. It is intended that the embodiments and figures disclosed herein are to be considered illustrative rather than restrictive.

[0015] FIG. 1 depicts agarose gel electrophoresis of total RNA from the hybridoma 684842-3 (5C3D11). DNA marker, Marker III, is shown in Lane M and Total RNA of 684842-3 is shown in Lane R.

[0016] FIG. 2 depicts agarose gel electrophoresis of PCR products of 684842-3. DNA marker, Marker III, is shown in Lane M, the variable heavy chain (VH) of 684842-3 is shown in Lane 1, and the variable light chain (VL) of 684842-3 is shown in Lane 2.

[0017] FIG. 3 depicts an agarose gel electrophoresis of total RNA from hybridoma 684842-6 (9E12E5). DNA marker, Marker III, is shown in Lane M and Total RNA of 684842-6 is shown in Lane R.

[0018] FIG. 4 depicts an agarose gel electrophoresis of PCR products of 684842-6. DNA marker, Marker III, is shown in Lane M, the VH of 684842-6 is shown in Lane 1, and the VL of 684842-6 is shown in Lane 2.

[0019] FIG. 5 demonstrates the inhibition of human TL1A induced IFN- γ production by 9E12E5 (panel A) and 5C3D11 (panel B).

[0020] FIG. 6 demonstrates the recognition capability of 5C3D11 (panel A) and 9E12E5 (panel B), to murine TL1A.

CLAIMS

WHAT IS CLAIMED IS:

1. A humanized antibody or humanized antigen-binding fragment that binds human tumor necrosis factor-like protein 1A (TL1A), wherein the humanized antibody or humanized antigen-binding fragment competes for binding to the human TL1A with a reference antibody comprising heavy chain complementarity determining regions of SEQ ID NOS: 6-8 and light chain complementarity determining regions of SEQ ID NOS: 14-16, wherein the humanized antibody or humanized antigen-binding fragment binds to human TL1A with a binding affinity (KD) of 1E-10 M or less.
2. The humanized antibody or humanized antigen-binding fragment of claim 1, wherein the humanized antibody or humanized antigen-binding fragment is: a monoclonal antibody, a chimeric antibody, a CDR- grafted antibody, a Fab, a Fab', a F(ab')₂, a Fv, a disulfide linked Fv, a scFv, a single domain antibody, a diabody, a multispecific antibody, a dual specific antibody, an anti-idiotypic antibody, a bispecific antibody, or a combination thereof.
3. The humanized antibody or humanized antigen-binding fragment of claim 1, wherein the reference antibody comprises a heavy chain variable region comprising SEQ ID NO: 5, and a light chain variable region comprising SEQ ID NO: 13.
4. The antibody or antigen-binding fragment of claim 1, wherein the reference antibody comprises a heavy chain variable region comprising SEQ ID NO: 35, and a light chain variable region comprising SEQ ID NO: 40.
5. The antibody or antigen-binding fragment of claim 1, wherein the reference antibody comprises a heavy chain variable region comprising SEQ ID NO: 36, and a light chain variable region comprising SEQ ID NO: 41.
6. The antibody or antigen-binding fragment of claim 1, wherein the reference antibody comprises a heavy chain variable region comprising SEQ ID NO: 37, and a light chain variable region comprising SEQ ID NO: 42.
7. The antibody or antigen-binding fragment of claim 1, wherein the reference antibody comprises a heavy chain variable region comprising SEQ ID NO: 38, and a light chain variable region comprising SEQ ID NO: 43.
8. The antibody or antigen-binding fragment of claim 1, wherein the reference antibody comprises a heavy chain variable region comprising SEQ ID NO: 39, and a light chain variable region comprising SEQ ID NO: 44.

9. The antibody or antigen-binding fragment of any one of claims 1-9, for use in therapy.
10. Use of the antibody or antigen-binding fragment of any one of claims 1-9, in the manufacture of a medicament for treating an inflammatory bowel disease in a subject in need thereof.
11. The use of claim 10, wherein the inflammatory bowel disease comprises Crohn's Disease, ulcerative colitis, medically refractory-ulcerative colitis, or a combination thereof.