therapies available to IBD patients, especially those patients who may be non-responsive to existing IBD therapies. Accordingly, there is a need for novel therapeutics to treat IBD that specifically target IBD pathogenesis.

SUMMARY

[0005] The present disclosure provides tumor necrosis factor ligand 1A (TL1A) binding antibodies for the treatment of IBD, including severe forms of IBD characterized by intestinal fibrosis. In various aspects, antibodies described herein possess features useful for therapeutic application such as low immunogenicity, and/or features that facilitate antibody manufacture, such as high percentage of monomeric fraction as measured by size-exclusion chromatography, and/or high expression.

[0005a] In one aspect, provided herein is an antibody or antigen binding fragment thereof that binds to tumor necrosis factor-like ligand 1A (TL1A), comprising a heavy chain variable framework region comprising a human IGHV1-46*02 framework (SEQ ID NO: 316) or a modified human IGHV1-46*02 framework, and a light chain variable framework region comprising a human IGKV3-20 framework (SEQ ID NO: 317) or a modified human IGKV3-20 framework; wherein the heavy chain variable framework region and the light chain variable framework region collectively comprise one to eight amino acid modification(s) from the human IGHV1-46*02 framework and the human IGKV3-20 framework, wherein the amino acid modification(s) comprise: (a) a modification at amino acid position 45 in the heavy chain variable region; (b) a modification at amino acid position 47 in the heavy chain variable region; (c) a modification at amino acid position 55 in the heavy chain variable region; (d) a modification at amino acid position 78 in the heavy chain variable region; (e) a modification at amino acid position 80 in the heavy chain variable region; (f) a modification at amino acid position 82 in the heavy chain variable region; (g) a modification at amino acid position 89 in the heavy chain variable region; or (h) a modification at amino acid position 91 in the heavy chain variable region, per Aho_numbering; (i) or a combination of two or more modifications selected from (a) to (h).

[0005b] In one aspect, provided herein is an antibody or antigen binding fragment thereof that binds to tumor necrosis factor-like ligand 1A (TL1A), comprising a heavy chain variable framework region comprising a human IGHV1-46*02 framework (SEQ ID NO: 316) or a modified human IGHV1-46*02 framework, and a light chain variable framework region comprising a human IGKV3-20 framework (SEQ ID NO: 317) or a modified human IGKV3-20 framework; wherein the heavy chain variable framework region and the light chain

variable framework region collectively comprise one to eight amino acid modification(s) from the human IGHV1-46*02 framework and the human IGKV3-20 framework, wherein the amino acid modification(s) comprises: (a) a modification at amino acid position 54 in the light chain variable region; and/or (b) a modification at amino acid position 55 in the light chain variable region, per Aho numbering.

[0005c] In one aspect, provided herein is an antibody or antigen binding fragment thereof that binds to TL1A, wherein the antibody or antigen binding fragment thereof comprises: (a) a heavy chain variable region comprising an amino acid sequence at least 96% identical to SEQ ID NO: 104 and (b) a light chain variable region comprising an amino acid sequence at least 96% identical to SEQ ID NO: 201.

[0005d] In one aspect, provided herein is an antibody that binds to TL1A, wherein the antibody comprises: (a) a heavy chain comprising an amino acid sequence at least 96% identical to SEQ ID NO: 505 and (b) a light chain comprising an amino acid sequence at least 96% identical to SEQ ID NO: 514.

[0005e] In one aspect, provided herein is an isolated polynucleotide encoding the antibody or antigen binding fragment as described herein.

[0005f] In one aspect, provided herein is an isolated vector comprising the polynucleotide as described herein.

[0005g] In one aspect, provided herein is a host cell comprising the vector as described herein.

[0005h] In one aspect, provided herein is a method of making an antibody or antigen binding fragment thereof that binds to TL1A, wherein the method comprises: a) culturing the host cell as described herein under conditions suitable for expression of the polynucleotide encoding the antibody or antigen binding fragment thereof; and b) isolating the antibody or antigen binding fragment thereof.

[0005i] In one aspect, provided herein is a use of a therapeutically effective amount of the antibody or antigen binding fragment as described herein in the manufacture of a medicament for treating inflammatory bowel disease (IBD) in a subject in need thereof.

[0005j] In one aspect, provided herein is the antibody or antigen binding fragment as described herein for use in therapy.

[0006] In one aspect, provided herein, is an antibody or antigen binding fragment thereof that binds to TL1A, comprising a heavy chain variable framework region comprising a human IGHV1-46*02 framework or a modified human IGHV1-46*02 framework, and a light chain variable framework region comprising a human IGKV3-20 framework or a modified

human IGKV3-20 framework; wherein the heavy chain variable framework region and the light chain variable framework region collectively comprise less than 9 amino acid modifications from the human IGHV1-46*02 framework and the human IGKV3-20 framework. In some embodiments, the amino acid modification comprises: (a) a modification at amino acid position 47 in the heavy chain variable region; (b) a modification at amino acid position 45 in the heavy chain variable region; (c) a modification at amino acid position 55 in the heavy chain variable region; (d) a modification at amino acid position 78 in the heavy chain variable region; (e) a modification at amino acid position 80 in the heavy chain variable region; (f) a modification at amino acid position 82 in the heavy chain variable region; (g) a modification at amino acid position 89 in the heavy chain variable region; or (h) a modification at amino acid position 91 in the heavy chain variable region; per Kabat numbering; or a combination of two or more modifications selected from (a) to (h). In some embodiments, (a) the amino acid modification is at position 47 in the heavy chain variable region, and the amino acid at position 47 is R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y, or V; (b) the amino acid modification is at position 45 in the heavy chain variable region, and the amino acid at position 45 is A, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y, or V; (c) the amino acid modification is at position 55 in the heavy chain variable region, and the amino acid at position 55 is A, R, N, D, C, Q, E, G, H, I, L, K, F, P, S, T, W, Y, or V; (d) the amino acid modification is at position 78 in the heavy chain variable region, and the