

CLAIMS

WHAT IS CLAIMED:

- ~~1.—A method of treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, the method comprising administering to the subject a therapeutically effective amount of an inhibitor of Tumor necrosis factor-like cytokine 1A (TL1A) activity or expression, wherein at least three polymorphisms that are predictive of a positive therapeutic response in the subject to a treatment with the inhibitor of TL1A activity or expression with a positive predictive value or a specificity of at least about 51%, are detected in a sample obtained from the subject, and wherein the inhibitor of TL1A activity or expression is an antibody or antigen binding fragment thereof that competes for binding to human TL1A with a reference antibody comprising a heavy chain variable region comprising: (a) an HCDR1 comprising an amino acid sequence set forth by SEQ ID NO: 1; (b) an HCDR2 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 2-5; and (c) an HCDR3 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 6-9; and the light chain variable region comprises: (d) an LCDR1 comprising an amino acid sequence set forth by SEQ ID NO: 10; (e) an LCDR2 comprising an amino acid sequence set forth by SEQ ID NO: 11; and (f) an LCDR3 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 12-15.~~
- ~~2.—The method of claim 1, wherein the at least three polymorphisms comprises rs16901748, rs56124762, rs6478109, rs1892231, rs2070558, rs2070561, rs11897732, rs6740739, rs17796285, rs7935393, rs12934476, rs12457255, rs2070557, rs4246905, rs10974900, rs12434976, rs2815844, rs889702, rs2409750, rs1541020, rs4942248, rs12934476, rs12457255, rs2297437, rs41309367, rs10733509, rs10750376, rs10932456, rs1326860, rs1528663, rs951279, rs9806914, rs7935393, rs1690492, rs420726, rs7759385, rs10974900, rs1326860, rs2548147, rs2815844, rs889702, rs9806914, rs7278257, or rs11221332, or a proxy polymorphism in linkage disequilibrium therewith as determined with an R^2 of at least 0.85, or a combination thereof.~~
- ~~3.—A method of treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, the method comprising administering to the subject a therapeutically effective amount of an inhibitor of Tumor necrosis factor-like cytokine 1A (TL1A) activity or expression,~~

~~wherein at least three polymorphisms comprise rs16901748, rs56124762, rs6478109, rs1892231, rs2070558, rs2070561, rs11897732, rs6740739, rs17796285, rs7935393, rs12934476, rs12457255, rs2070557, rs4246905, rs10974900, rs12434976, rs2815844, rs889702, rs2409750, rs1541020, rs4942248, rs12934476, rs12457255, rs2297437, rs41309367, rs10733509, rs10750376, rs10932456, rs1326860, rs1528663, rs951279, rs9806914, rs7935393, rs1690492, rs420726, rs7759385, rs10974900, rs1326860, rs2548147, rs2815844, rs889702, rs9806914, rs7278257, or rs11221332, or a proxy polymorphism in linkage disequilibrium therewith as determined with an R^2 of at least 0.85, or a combination thereof, are detected in a sample obtained from the subject, and~~

~~wherein the inhibitor of TL1A activity or expression is an antibody or antigen binding fragment thereof that competes for binding to human TL1A with a reference antibody comprising a heavy chain variable region comprising: (a) an HCDR1 comprising an amino acid sequence set forth by SEQ ID NO: 1; (b) an HCDR2 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 2-5; and (c) an HCDR3 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 6-9; and the light chain variable region comprises: (d) an LCDR1 comprising an amino acid sequence set forth by SEQ ID NO: 10; (e) an LCDR2 comprising an amino acid sequence set forth by SEQ ID NO: 11; and (f) an LCDR3 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 12-15.~~

- ~~4. A method of treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, the method comprising administering to the subject a therapeutically effective amount of an inhibitor of Tumor necrosis factor-like cytokine 1A (TL1A) activity or expression,~~

~~wherein at least three polymorphisms that are predictive of a positive therapeutic response in the subject to a treatment with the inhibitor of TL1A activity or expression with a positive predictive value or a specificity of at least about 51%, are detected in a sample obtained from the subject, and~~

~~wherein the inhibitor of TL1A activity or express is an antibody or antigen binding fragment thereof that binds to TL1A, comprising a heavy chain variable region comprising: (a) an HCDR1 comprising an amino acid sequence set forth by SEQ ID NO: 1; (b) an HCDR2 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 2-5; and (c) an HCDR3 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 6-9; and the light chain variable region comprises: (d) an~~

~~LCDR1 comprising an amino acid sequence set forth by SEQ ID NO: 10; (e) an LCDR2 comprising an amino acid sequence set forth by SEQ ID NO: 11; and (f) an LCDR3 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 12-15.~~

~~5. The method of claim 4, wherein the at least three polymorphisms comprises rs16901748, rs56124762, rs6478109, rs1892231, rs2070558, rs2070561, rs11897732, rs6740739, rs17796285, rs7935393, rs12934476, rs12457255, rs2070557, rs4246905, rs10974900, rs12434976, rs2815844, rs889702, rs2409750, rs1541020, rs4942248, rs12934476, rs12457255, rs2297437, rs41309367, rs10733509, rs10750376, rs10932456, rs1326860, rs1528663, rs951279, rs9806914, rs7935393, rs1690492, rs420726, rs7759385, rs10974900, rs1326860, rs2548147, rs2815844, rs889702, rs9806914, rs7278257, or rs11221332, or a proxy polymorphism in linkage disequilibrium therewith as determined with an R^2 of at least 0.85, or a combination thereof.~~

~~6. A method of treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, the method comprising administering to the subject a therapeutically effective amount of an inhibitor of Tumor necrosis factor like cytokine 1A (TL1A) activity or expression, wherein at least three polymorphisms comprise rs16901748, rs56124762, rs6478109, rs1892231, rs2070558, rs2070561, rs11897732, rs6740739, rs17796285, rs7935393, rs12934476, rs12457255, rs2070557, rs4246905, rs10974900, rs12434976, rs2815844, rs889702, rs2409750, rs1541020, rs4942248, rs12934476, rs12457255, rs2297437, rs41309367, rs10733509, rs10750376, rs10932456, rs1326860, rs1528663, rs951279, rs9806914, rs7935393, rs1690492, rs420726, rs7759385, rs10974900, rs1326860, rs2548147, rs2815844, rs889702, rs9806914, rs7278257, or rs11221332, or a proxy polymorphism in linkage disequilibrium therewith as determined with an R^2 of at least 0.85, or a combination thereof, are detected in a sample obtained from the subject, and wherein the inhibitor of TL1A activity or express is an antibody or antigen binding fragment thereof that binds to TL1A, comprising a heavy chain variable region comprising: (a) an HCDR1 comprising an amino acid sequence set forth by SEQ ID NO: 1; (b) an HCDR2 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 2-5; and (c) an HCDR3 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 6-9; and the light chain variable region comprises: (d) an~~

~~LCDR1 comprising an amino acid sequence set forth by SEQ ID NO: 10; (e) an LCDR2 comprising an amino acid sequence set forth by SEQ ID NO: 11; and (f) an LCDR3 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 12-15.~~

~~71. A method of Use of an inhibitor of tumor necrosis factor-like cytokine 1A (TL1A) activity or expression ("TL1A inhibitor") in the manufacture of a medicament for treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, the method comprising administering to the subject a therapeutically effective amount of an inhibitor of Tumor necrosis factor-like cytokine 1A (TL1A) activity or expression,~~

wherein at least three polymorphisms that are predictive of a positive therapeutic response in ~~the a~~ subject to ~~a~~ treatment with the ~~inhibitor of~~ TL1A ~~inhibitor activity or expression~~ with a positive predictive value or a specificity of at least about 51%, are detected in a sample obtained from the subject of the treatment, and

wherein the TL1A inhibitor ~~of TL1A activity or express~~ is an antibody or antigen binding fragment thereof that binds to ~~tumor necrosis factor-like protein 1A (TL1A)~~, comprising a heavy chain variable domain comprising an amino acid sequence at least about 9997% identical to ~~any one of~~ SEQ ID NOS: 104101-135, or 340-302, and a light chain variable domain comprising an amino acid sequence at least about 9997% identical to ~~any one of~~ SEQ ID NOS: 201-206 or 303.

wherein optionally the heavy chain variable domain comprises an amino acid sequence at least about 98%, 99%, or 100% identical to SEQ ID NO: 104 and wherein optionally the light chain variable domain comprises an amino acid sequence at least about 98%, 99%, or 100% identical to SEQ ID NO: 201.

~~82. The method use of claim 71, wherein the at least three polymorphisms comprises~~ rs16901748, rs56124762, rs6478109, rs1892231, rs2070558, rs2070561, rs11897732, rs6740739, rs17796285, rs7935393, rs12934476, rs12457255, rs2070557, rs4246905, rs10974900, rs12434976, rs2815844, rs889702, rs2409750, rs1541020, rs4942248, rs12934476, rs12457255, rs2297437, rs41309367, rs10733509, rs10750376, rs10932456, rs1326860, rs1528663, rs951279, rs9806914, rs7935393, rs1690492, rs420726, rs7759385, rs10974900, rs1326860, rs2548147, rs2815844, rs889702, rs9806914, rs7278257, or rs11221332, or a proxy polymorphism in linkage

disequilibrium therewith as determined with an R^2 of at least 0.85, or a combination thereof.

- ~~9. The method of any one of claims 1-8, wherein the heavy chain variable domain comprises an amino acid sequence at least about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NOS: 101-135, or 310-302.~~
- ~~10. The method of any one of claims 1-8, wherein the light chain variable domain comprises an amino acid sequence at least about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NOS: 201-206 or 303.~~
- ~~11. A method of treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, the method comprising administering to the subject a therapeutically effective amount of an inhibitor of Tumor necrosis factor-like cytokine 1A (TL1A) activity or expression, wherein at least three polymorphisms comprise rs16901748, rs56124762, rs6478109, rs1892231, rs2070558, rs2070561, rs11897732, rs6740739, rs17796285, rs7935393, rs12934476, rs12457255, rs2070557, rs4246905, rs10974900, rs12434976, rs2815844, rs889702, rs2409750, rs1541020, rs4942248, rs12934476, rs12457255, rs2297437, rs41309367, rs10733509, rs10750376, rs10932456, rs1326860, rs1528663, rs951279, rs9806914, rs7935393, rs1690492, rs420726, rs7759385, rs10974900, rs1326860, rs2548147, rs2815844, rs889702, rs9806914, rs7278257, or rs11221332, or a proxy polymorphism in linkage disequilibrium therewith as determined with an R^2 of at least 0.85, or a combination thereof, are detected in a sample obtained from the subject, and wherein the inhibitor of TL1A activity or express is an antibody or antigen binding fragment thereof that binds to tumor necrosis factor-like protein 1A (TL1A), comprising a heavy chain variable domain comprising an amino acid sequence at least about 90% identical to any one of SEQ ID NOS: 101-135, or 310-302, and a light chain variable domain comprising an amino acid sequence at least about 90% identical to any one of SEQ ID NOS: 201-206 or 303.~~
123. Use of A method of an inhibitor of tumor necrosis factor-like cytokine 1A (TL1A) activity or expression ("TL1A inhibitor") in the manufacture of a medicament for treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, the method comprising administering to the subject a therapeutically effective amount of an inhibitor of Tumor necrosis factor-like cytokine 1A (TL1A) activity or expression;

wherein at least three polymorphisms that are predictive of a positive therapeutic response in ~~the a~~ subject to ~~a~~ treatment with the ~~inhibitor of~~ TL1A ~~inhibitor activity or expression~~ with a positive predictive value or a specificity of at least about 51%, are detected in a sample obtained from the subject of the treatment, and

wherein the TL1A inhibitor ~~of TL1A activity or express~~ is an antibody or antigen binding fragment thereof that binds to TL1A that comprises: (a) a heavy chain variable framework region comprising a human IGHV1-46*02 framework or a modified human IGHV1-46*02 framework; and (b) 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 ~~about~~ 14 amino acid modifications from the human IGHV1-46*02 framework and the human IGKV3-20 framework.

134. The ~~method-use~~ of claim 123, wherein the at least three polymorphisms comprise rs16901748, rs56124762, rs6478109, rs1892231, rs2070558, rs2070561, rs11897732, rs6740739, rs17796285, rs7935393, rs12934476, rs12457255, rs2070557, rs4246905, rs10974900, rs12434976, rs2815844, rs889702, rs2409750, rs1541020, rs4942248, rs12934476, rs12457255, rs2297437, rs41309367, rs10733509, rs10750376, rs10932456, rs1326860, rs1528663, rs951279, rs9806914, rs7935393, rs1690492, rs420726, rs7759385, rs10974900, rs1326860, rs2548147, rs2815844, rs889702, rs9806914, rs7278257, or rs11221332, or a proxy polymorphism in linkage disequilibrium therewith as determined with an R^2 of at least 0.85, or a combination thereof.

~~14. A method of treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, the method comprising administering to the subject a therapeutically effective amount of an inhibitor of Tumor necrosis factor-like cytokine 1A (TL1A) activity or expression, wherein at least three polymorphisms comprise rs16901748, rs56124762, rs6478109, rs1892231, rs2070558, rs2070561, rs11897732, rs6740739, rs17796285, rs7935393, rs12934476, rs12457255, rs2070557, rs4246905, rs10974900, rs12434976, rs2815844, rs889702, rs2409750, rs1541020, rs4942248, rs12934476, rs12457255, rs2297437, rs41309367, rs10733509, rs10750376, rs10932456, rs1326860, rs1528663, rs951279, rs9806914, rs7935393, rs1690492, rs420726, rs7759385,~~

~~rs10974900, rs1326860, rs2548147, rs2815844, rs889702, rs9806914, rs7278257, or rs11221332, or a proxy polymorphism in linkage disequilibrium therewith as determined with an R^2 of at least 0.85, or a combination thereof, are detected in a sample obtained from the subject, and wherein the inhibitor of TL1A activity or express is an antibody or antigen binding fragment thereof that binds to TL1A that comprises: (a) a heavy chain variable framework region comprising a human IGHV1-46*02 framework or a modified human IGHV1-46*02 framework; and (b) 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 about 14 amino acid modifications from the human IGHV1-46*02 framework and the human IGKV3-20 framework.~~

155. The use method of any one of claims ~~12-143~~ 4, wherein ~~an amino acid modification of~~ the less than 14 amino acid modifications comprises: (a) ~~the-an~~ amino acid modification ~~is-at~~ position 47 in the heavy chain variable region, ~~and- wherein~~ 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-an~~ amino acid modification ~~is-at~~ position 45 in the heavy chain variable region, ~~and- wherein~~ 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-an~~ amino acid modification ~~is-at~~ position 55 in the heavy chain variable region, ~~and- wherein~~ 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-an~~ amino acid modification ~~is-at~~ position 78 in the heavy chain variable region, ~~and- wherein~~ the amino acid at position 78 is A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, or Y; (e) ~~the-an~~ amino acid modification ~~is-at~~ position 80 in the heavy chain variable region, ~~and- wherein~~ the amino acid at position 80 is A, R, N, D, C, Q, E, G, H, I, L, K, F, P, S, T, W, Y, or V; (f) ~~the-an~~ amino acid modification ~~is-at~~ position 82 in the heavy chain variable region, ~~and- wherein~~ the amino acid at position 82 is A, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y, or V; (g) ~~the-an~~ amino acid modification ~~is-at~~ position 89 in the heavy chain variable region, ~~and- wherein~~ the amino acid at position 89 is A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, or Y; or (h) ~~the-an~~ amino acid modification ~~is-at~~ position 91 in the heavy chain variable region, ~~and- wherein~~ the amino acid at position 91 is A, R, N, D, C, Q, E, G, H, I, L, K, F, P, S, T, W, Y, or V; or a combination of two or more amino acid modifications selected from (a) to (h); ~~wherein~~

~~16. The method of claim 15, wherein an optionally the~~ amino acid modification of the less than 14 amino acid modifications comprises: A47R, R45K, ~~M55I, V78A,~~ M80I, ~~R82T, V89A, and~~ M91L in the heavy chain variable region, per Aho ~~or Kabat~~ numbering.

~~17. The method of claim 15, wherein an amino acid modification of the less than 14 amino acid modifications 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 or Kabat numbering.~~

~~186.~~ The use method of any one of claims ~~12-143~~ 5, wherein ~~an amino acid modification of~~ the less than 14 amino acid modifications comprises: (a) ~~the an~~ amino acid modification ~~is~~ at position 54 ~~of in~~ the light chain variable region, ~~and wherein~~ the amino acid at position 54 is A, R, N, D, C, Q, E, G, H, I, K, M, F, P, S, T, W, Y, or V; and/or (b) ~~the an~~ amino acid modification ~~is~~ at position 55 ~~of in~~ the light chain variable region, ~~and wherein~~ the amino acid at position 55 is A, R, N, D, C, Q, E, G, H, I, K, M, F, P, S, T, W, Y, or V, wherein optionally the

~~19. The method of claim 18, wherein an~~ amino acid modification of the less than 14 amino acid modifications comprises L54P ~~and/or L55W~~ in the light chain variable region, per Aho ~~or Kabat~~ numbering.

~~207.~~ Use of an inhibitor of tumor necrosis factor-like cytokine 1A (TL1A) activity or expression (TL1A inhibitor) in the manufacture of a medicament for A method of treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, ~~the method comprising administering to the subject a therapeutically effective amount of an inhibitor of Tumor necrosis factor like cytokine 1A (TL1A) activity or expression,~~

wherein at least three polymorphisms that are predictive of a positive therapeutic response in ~~the a~~ subject to ~~a~~ treatment with the ~~inhibitor of~~ TL1A inhibitor activity or expression with a positive predictive value or a specificity of at least about 51%, are detected in a sample obtained from the subject of the treatment, and wherein the TL1A inhibitor ~~of TL1A activity or express~~ is an antibody or antigen binding fragment thereof that binds to TL1A and comprises:

a heavy chain variable region comprising SEQ ID NO: 301

X1VQLVQSGAEVKKPGASVKVSCKAS[HCDR1]WVX2QX3PGQGLEW

X4G[HC DR2]RX5TX6TX7DTSTSTX8YX9ELSSLRSEDTAVYYCAR[HC DR3]WGQGTTVTVSS, and

a light chain variable region comprising SEQ ID NO: 303

EIVLTQSPGTLSLSPGERATLSC[LCD R1]WYQQKPGQAPRX10X11IY[LCD R2]GIPDRFSGSGSGTDFTLISRLEPEDFAVYYC[LCD R3]FGGGTKLEIK, wherein each of X1-X11 is independently selected from A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y, or V.

~~21. A method of treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, the method comprising administering to the subject a therapeutically effective amount of an inhibitor of Tumor necrosis factor like cytokine 1A (TL1A) activity or expression, wherein at least three polymorphisms that are predictive of a positive therapeutic response in the subject to a treatment with the inhibitor of TL1A activity or expression with a positive predictive value or a specificity of at least about 51%, are detected in a sample obtained from the subject, and wherein the inhibitor of TL1A activity or expression is an antibody or antigen-binding fragment thereof that binds to TL1A and comprises:~~

~~a heavy chain variable region comprising SEQ ID NO: 302~~

~~X1VQLVQSGAEVKKPGASVKVSCKAS[HC DR1]WVX2QX3PGQGLEW X4G[HC DR2]RX5TX6TX7DTSTSTX8YX9ELSSLRSEDTAVYYC[HC DR3]WGQGTTVTVSS, and~~

~~a light chain variable region comprising SEQ ID NO: 303~~

~~EIVLTQSPGTLSLSPGERATLSC[LCD R1]WYQQKPGQAPRX10X11IY[LCD R2]GIPDRFSGSGSGTDFTLISRLEPEDFAVYYC[LCD R3]FGGGTKLEIK, wherein each of X1-X11 is independently selected from A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y, or V.~~

~~228.~~ The use method of ~~any one of claims 20-21~~claim 7, wherein the at least three polymorphisms comprises rs16901748, rs56124762, rs6478109, rs1892231, rs2070558, rs2070561, rs11897732, rs6740739, rs17796285, rs7935393, rs12934476, rs12457255, rs2070557, rs4246905, rs10974900, rs12434976, rs2815844, rs889702, rs2409750, rs1541020, rs4942248, rs12934476, rs12457255, rs2297437, rs41309367, rs10733509, rs10750376, rs10932456, rs1326860, rs1528663, rs951279, rs9806914, rs7935393, rs1690492, rs420726, rs7759385, rs10974900, rs1326860, rs2548147, rs2815844, rs889702, rs9806914, rs7278257, or rs11221332, or a proxy

polymorphism in linkage disequilibrium therewith as determined with an R^2 of at least 0.85, or a combination thereof.

- ~~23. A method of treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, the method comprising administering to the subject a therapeutically effective amount of an inhibitor of Tumor necrosis factor like cytokine 1A (TL1A) activity or expression, wherein at least three polymorphisms comprise rs16901748, rs56124762, rs6478109, rs1892231, rs2070558, rs2070561, rs11897732, rs6740739, rs17796285, rs7935393, rs12934476, rs12457255, rs2070557, rs4246905, rs10974900, rs12434976, rs2815844, rs889702, rs2409750, rs1541020, rs4942248, rs12934476, rs12457255, rs2297437, rs41309367, rs10733509, rs10750376, rs10932456, rs1326860, rs1528663, rs951279, rs9806914, rs7935393, rs1690492, rs420726, rs7759385, rs10974900, rs1326860, rs2548147, rs2815844, rs889702, rs9806914, rs7278257, or rs11221332, or a proxy polymorphism in linkage disequilibrium therewith as determined with an R^2 of at least 0.85, or a combination thereof, are detected in a sample obtained from the subject, and wherein the inhibitor of TL1A activity or express is an antibody or antigen binding fragment thereof that binds to TL1A and comprises:~~
- ~~a heavy chain variable region comprising SEQ ID NO: 301~~
~~X1VQLVQSGAEVKKPGASVKVCKAS[HC DR1]WVX2QX3PGQGLEW~~
~~X4G[HC DR2]RX5TX6TX7DTSTSTX8YX9ELSSLRSEDTAVYYCAR[HC~~
~~DR3]WGQGTTVTVSS, and~~
 - ~~a light chain variable region comprising SEQ ID NO: 303~~
~~EIVLTQSPGTLSPGERATLSC[LC DR1]WYQQKPGQAPRX10X11HY[LC~~
~~DR2]GIPDRFSGSGSGTDFTLISRLEPEDFAVYYC[LC DR3]FGGGTKL~~
~~EIK, wherein each of X1-X11 is independently selected from A, R, N, D, C,~~
~~Q, E, G, H, I, L, K, M, F, P, S, T, W, Y, or V.~~

- ~~24. A method of treating an inflammatory, a fibrotic, or a fibrostenotic disease or condition in a subject, the method comprising administering to the subject a therapeutically effective amount of an inhibitor of Tumor necrosis factor like cytokine 1A (TL1A) activity or expression, wherein at least three polymorphisms comprise rs16901748, rs56124762, rs6478109, rs1892231, rs2070558, rs2070561, rs11897732, rs6740739, rs17796285, rs7935393, rs12934476, rs12457255, rs2070557, rs4246905, rs10974900, rs12434976,~~

~~rs2815844, rs889702, rs2409750, rs1541020, rs4942248, rs12934476, rs12457255, rs2297437, rs41309367, rs10733509, rs10750376, rs10932456, rs1326860, rs1528663, rs951279, rs9806914, rs7935393, rs1690492, rs420726, rs7759385, rs10974900, rs1326860, rs2548147, rs2815844, rs889702, rs9806914, rs7278257, or rs11221332, or a proxy polymorphism in linkage disequilibrium therewith as determined with an R^2 of at least 0.85, or a combination thereof, are detected in a sample obtained from the subject, and wherein the inhibitor of TL1A activity or express is an antibody or antigen binding fragment thereof that binds to TL1A and comprises:~~

~~a heavy chain variable region comprising SEQ ID NO: 302~~

~~X1VQLVQSGAEVKKPGASVKVSCKAS[HCDR1]WVX2QX3PGQGLEW
X4G[HCDR2]RX5TX6TX7DTSTSTX8YX9ELSSLRSEDTAVYYC[HCDR3]
JWGQGTTVTVSS, and~~

~~a light chain variable region comprising SEQ ID NO: 303~~

~~EIVLTQSPGTLSSLSPGERATLSC[LCDR1]WYQQKPGQAPRX10X11HY[L
CDR2]GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC[LCDR3]FGGGTKL
EIK, wherein each of X1-X11 is independently selected from A, R, N, D, C,
Q, E, G, H, I, L, K, M, F, P, S, T, W, Y, or V~~

~~25. THE METHOD OF ANY ONE OF CLAIMS 20-24, WHEREIN:~~

~~(A) X1 IS Q OR E;~~

~~(B) X2 IS R OR K~~

~~(C) X3 IS A OR R;~~

~~(D) X4 IS M OR I;~~

~~(E) X5 IS V OR A;~~

~~(F) X6 IS M OR I;~~

~~(G) X7 IS R OR T;~~

~~(H) X8 IS V OR A;~~

~~(I) X9 IS M OR L~~

~~(J) X10 IS L OR P;~~

~~(K) X11 IS L OR W; OR~~

~~(L) X1-X11 ARE ANY COMBINATION OF (A) TO (K).~~

~~269.~~ The use method of any one of claims ~~20-24~~ 1-8, wherein ~~the~~:

(i) the antibody or antigen binding fragment comprises a heavy chain CDR1 as set forth by SEQ ID NO: 1, a heavy chain CDR2 as set forth by ~~any one of~~ SEQ ID

NOS: 2-5, a heavy chain CDR3 as set forth by ~~any one of~~ SEQ ID NOS: 6-9, a light chain CDR1 as set forth by SEQ ID NO: 10, a light chain CDR2 as set forth by SEQ ID NO: 11, and a light chain CDR3 as set forth by ~~any one of~~ SEQ ID NOS: 12-15; and/or

~~27. The method of any one of claims 20-24, wherein~~

(ii) the antibody or antigen binding fragment comprises a heavy chain framework (FR) 1 as set forth by SEQ ID NO: 304, a heavy chain FR2 as set forth by SEQ ID NO: 305 ~~or SEQ ID NO: 313~~, a heavy chain FR3 as set forth by any one of SEQ ID NOS: 306, or 307, ~~314, or 315~~, a heavy chain FR4 as set forth by SEQ ID NO: 308, a light chain FR1 as set forth by SEQ ID NO: 309, a light chain FR2 as set forth by SEQ ID NO: 310, a light chain FR3 as set forth by SEQ ID NO: 311, or a light chain FR4 as set forth by SEQ ID NO: 312, or a combination thereof.

~~2810.~~ The use method of any one of claims ~~1-271~~ 9, wherein:

(i) the antibody or antigen binding fragment comprises a human IgG1 fragment crystallizable (Fc) region comprising amino acid modifications selected from (a) 297A, 297Q, 297G, or 297D, (b) 279F, 279K, or 279L, (c) 228P, (d) 235A, 235E, 235G, 235Q, 235R, or 235S, (e) 237A, 237E, 237K, 237N, or 237R, (f) 234A, 234V, or 234F, (g) 233P, (h) 328A, (i) 327Q or 327T, (j) 329A, 329G, 329Y, or 329R, (k) 331S, (l) 236F or 236R, (m) 238A, 238E, 238G, 238H, 238I, 238V, 238W, or 238Y, (n) 248A, (o) 254D, 254E, 254G, 254H, 254I, 254N, 254P, 254Q, 254T, or 254V, (p) 255N, (q) 256H, 256K, 256R, or 256V, (r) 264S, (s) 265H, 265K, 265S, 265Y, or 265A, (t) 267G, 267H, 267I, or 267K, (u) 268K, (v) 269N or 269Q, (w) 270A, 270G, 270M, or 270N, (x) 271T, (y) 272N, (z) 292E, 292F, 292G, or 292I, (aa) 293S, (bb) 301W, (cc) 304E, (dd) 311E, 311G, or 311S, (ee) 316F, (ff) 328V, (gg) 330R, (hh) 339E or 339L, (ii) 343I or 343V, (jj) 373A, 373G, or 373S, (kk) 376E, 376W, or 376Y, (ll) 380D, (mm) 382D or 382P, (nn) 385P, (oo) 424H, 424M, or 424V, (pp) 434I, (qq) 438G, (rr) 439E, 439H, or 439Q, (ss) 440A, 440D, 440E, 440F, 440M, 440T, or 440V, (tt) E233P, (uu) L235E, (vv) L234A and L235A, (ww) L234A, L235A, and G237A, (xx) L234A, L235A, and P329G, (yy) L234F, L235E, and P331S, (zz) L234A, L235E, and G237A, (aaa) L234A, L235E, G237A, and P331S (bbb) L234A, L235A, G237A, P238S, H268A, A330S, and P331S (IgG1 σ , (ccc) L234A, L235A, and P329A, (ddd) G236R and L328R, (eee) G237A, (fff) F241A, (ggg) V264A, (hhh) D265A, (iii) D265A and N297A, (jjj) D265A and N297G, (kkk)

D270A, (III) A330L, (mmm) P331A or P331S, ~~or and~~ (nnn) any combination of two or more selected from (a) – (uu), per Kabat numbering;

~~29. The method of any one of claims 1-27, wherein the antibody or antigen binding fragment comprises a human IgG4 Fc region.~~

~~30. The method of any one of claims 1-27, wherein (ii) the antibody or antigen binding fragment comprises an Fc region comprising a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NOS: 320-362;~~

~~31. The method of any one of claims 1-27, wherein (iii) the antibody or antigen binding fragment comprises an fragment crystallizable (Fc) region comprising reduced antibody-dependent cell-mediated cytotoxicity (ADCC) function as compared to human IgG1 and/or reduced complement-dependent cytotoxicity (CDC) function as compared to human IgG1, wherein optionally the ADCC function is at least about 50% reduced as compared to human IgG1 and/or the CDC function is at least about 50% reduced as compared to human IgG1;~~

~~32. The method of any one of claims 1-27, wherein (iv) the antibody or antigen binding fragment comprises a human IgG1 Fc region comprising the sequence set forth by the Fc comprises the human IgG1 comprises SEQ ID NO: 320;~~

~~33. The method of any one of claims 1-27, wherein the ADCC function of the Fc region comprising reduced ADCC is at least about 50% reduced as compared to human IgG1.~~

~~34. wherein the CDC function of the Fc region comprising reduced CDC is at least about 50% reduced as compared to human IgG1.~~

~~35. The method of any one of claims 1-27, wherein the Fc comprises (i) a human IgG4 Fc region or (ii) a human IgG4 Fc region comprising (a) S228P, (b) S228P and L235E, or (c) S228P, F234A, and L235A, per Kabat numbering.~~

~~36. The method of any one of claims 1-27, wherein the Fc comprises a human IgG2 Fc region; IgG2-IgG4 cross-subclass Fc region; IgG2-IgG3 cross-subclass Fc region; IgG2 comprising H268Q, V309L, A330S, P331S (IgG2m4); or IgG2 comprising V234A, G237A, P238S, H268A, V309L, A330S, P331S (IgG2σ).~~

~~37. The method of any one of claims 1-27, wherein (v) the antibody or antigen binding fragment comprises a human IgG1 Fc region comprising the Fc comprises a human IgG1 with a substitution selected from 329A, 329G, 329Y, 331S, 236F, 236R, 238A, 238E, 238G, 238H, 238I, 238V, 238W, 238Y, 248A, 254D, 254E,~~

254G, 254H, 254I, 254N, 254P, 254Q, 254T, 254V, 264S, 265H, 265K, 265S, 265Y, 265A, 267G, 267H, 267I, 267K, 434I, 438G, 439E, 439H, 439Q, 440A, 440D, 440E, 440F, 440M, 440T, and 440V, per Kabat numbering;

~~38. The method of any one of claims 1-27, wherein the Fc comprises a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NOS: 320-362.~~

~~39. The method of any one of claims 1-27, wherein (vi) the antibody or antigen binding fragment comprises an Fc comprising any one of SEQ ID NOS: 401-413 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOS: 401-413; or~~

~~40. The method of any one of claims 1-27, wherein (vii) the antibody or antigen binding fragment comprises a heavy chain comprising any one of SEQ ID NOS: 501-513 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOS: 501-513.~~

~~41.1. The use method of any one of claims 1-27-10, wherein:~~

~~(i) the antibody or antigen binding fragment comprises a light chain comprising any one of SEQ ID NO: 514 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NO: 514; and/or~~

~~(ii) the antibody or antigen binding fragment comprises a heavy chain comprising SEQ ID NO: 505 or a sequence at least about 96%, 97%, 98%, or 99% identical to any one of SEQ ID NO: 505.~~

~~42. The method of any one of claims 1-41, wherein the at least three polymorphisms are predictive of the positive therapeutic response with the positive predictive value and a specificity of at least about 51%.~~

~~43.12. The use method of any one of claims 1-41-11, wherein:~~

~~(i) the positive predictive value is greater than or equal to about 60%, 65%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%; and/or~~

~~44. The method of any one of claims 1-41, wherein the positive predictive value is between about 60%-100%, 65%-95%, 70%-90%, 75%-85%, and 70%-80%.~~

~~45. The method of any one of claims 1-41, wherein~~

(ii) the specificity is greater than or equal to about 60%, 65%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%.

~~46. The method of any one of claims 1-41, wherein the specificity is between about 60%-100%, 65%-95%, 70%-90%, 75%-85%, and 70%-80%.~~

47.13. The use method of any one of claims ~~1-41~~ 1-12, wherein the at least three polymorphisms comprise:

(i) rs6478109, rs56124762, and rs1892231;

~~48. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (ii) rs6478109, rs56124762, and rs16901748;~~

~~49. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (iii) rs6478109, rs1892231, and rs16901748;~~

~~50. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (iv) rs56124762, rs1892231, and rs16901748;~~

~~51. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (v) rs6478109, rs2070558, and rs1892231;~~

~~52. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (vi) rs6478109, rs2070558, and rs16901748;~~

~~53. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (vii) rs6478109, rs1892231, and rs16901748;~~

~~54. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (viii) rs2070558, rs1892231, and rs16901748;~~

~~55. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (ix) rs6478109, rs2070561, and rs1892231;~~

~~56. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (x) rs6478109, rs2070561, and rs16901748;~~

~~57. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xi) rs6478109, rs1892231, and rs16901748;~~

~~58. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xii) rs2070561, rs1892231, and rs16901748;~~

~~59. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xiii) rs6478109, rs7935393, and rs1892231;~~

~~60. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xiv) rs6478109, rs7935393, and rs9806914;~~

61. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xv) rs6478109, rs7935393, and rs7278257;.
62. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xvi) rs6478109, rs7935393, and rs2070557;.
63. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xvii) rs6478109, rs1892231, and rs9806914;.
64. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xviii) rs6478109, rs1892231, and rs7278257;.
65. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xix) rs6478109, rs1892231, and rs2070557;.
66. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xx) rs6478109, rs9806914, and rs7278257;.
67. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xxi) rs6478109, rs9806914, and rs2070557;.
68. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xxii) rs6478109, rs7278257, and rs2070557;.
69. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xxiii) rs7935393, rs1892231, and rs9806914;.
70. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xxiv) rs7935393, rs1892231, and rs7278257;.
71. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xxv) rs7935393, rs1892231, and rs2070557;.
72. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xxvi) rs7935393, rs9806914, and rs7278257;.
73. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (iv) rs7935393, rs9806914, and rs2070557;.
74. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xxvii) rs7935393, rs7278257, and rs2070557;.
75. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xxviii) rs1892231, rs9806914, and rs7278257;.
76. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xxix) rs1892231, rs9806914, and rs2070557;.
77. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xxx) rs1892231, rs7278257, and rs2070557;.

~~78. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xxxi) rs9806914, rs7278257, and rs2070557;~~

~~79. The method of any one of claims 1-41, wherein the at least three polymorphisms comprise: _____ (xxxii) rs6478109, rs56124762, and rs1892231;~~

~~_____ (xxxiii) rs6478109, rs56124762, rs1892231, rs16901748, rs12934476, rs7935393, rs9806914, rs2297437;~~

~~_____ (xxxiv) rs6478109, rs56124762, rs1892231, rs16901748, rs12934476, rs9806914, rs1326860, rs2815844;~~

~~_____ (xxxv) rs6478109, rs56124762, rs1892231, rs16901748, rs12934476, rs2297437, rs1326860, rs12457255;~~

~~_____ (xxxvi) rs6478109, rs56124762, rs1892231, rs16901748, rs12934476, rs1326860, rs12457255, rs2815844;~~

~~_____ (xxxvii) rs6478109, rs56124762, rs1892231, rs16901748, rs12934476, rs12457255, rs2815844, rs10974900;~~

~~_____ (xxxviii) rs6478109, rs56124762, rs1892231, rs16901748, rs7935393, rs1326860, rs12457255, rs2815844;~~

~~_____ (xxxix) rs6478109, rs56124762, rs1892231, rs16901748, rs9806914, rs1326860, rs12457255, rs10974900;~~

~~_____ (xl) rs6478109, rs56124762, rs1892231, rs16901748, rs2297437, rs1326860, rs12457255, rs2409750;~~

~~_____ (xli) rs6478109, rs56124762, rs1892231, rs16901748, rs2297437, rs12457255, rs2815844, rs2409750;~~

~~_____ (xlii) rs6478109, rs56124762, rs1892231, rs16901748, rs1326860, rs12457255, rs2815844, rs10974900;~~

~~_____ (xliii) rs6478109, rs56124762, rs1892231, rs16901748, rs12457255, rs2815844, rs10974900, rs1541020;~~

~~_____ (xliv) rs6478109, rs56124762, rs1892231, rs16901748, rs2815844, rs10974900, rs2409750, rs7759385;~~

~~_____ (xlv) rs6478109, rs56124762, rs1892231, rs16901748, rs10974900, rs1541020, rs4942248, rs7759385;~~

~~_____ (xlvi) rs6478109, rs56124762, rs1892231, rs16901748, rs2409750, rs1541020, rs4942248, rs7759385;~~

~~_____ (xlvii) rs6478109, rs56124762, rs1892231, rs16901748, rs12934476, rs7935393, rs2297437, rs1326860;~~

(xlviii) rs6478109, rs56124762, rs1892231, rs16901748, rs12934476, rs9806914, rs2297437, rs12457255;

(xlix) rs6478109, rs56124762, rs1892231, rs16901748, rs12934476, rs2297437, rs12457255, rs2409750; or

(l) rs6478109, rs56124762, rs1892231, rs16901748, rs12934476, rs2297437, rs4942248, rs7759385.

~~8014.~~ The use method of any one of claims ~~1-791-13~~, wherein the at least three polymorphisms further comprises ~~a fourth~~ an additional polymorphism comprising rs16901748, rs1892231, rs56124762, rs6478109, rs2070558, rs2070561, rs11897732, rs6740739, rs17796285, rs7935393, rs12934476, rs12457255, rs2070557, rs4246905, rs10974900, rs12434976, rs2815844, rs889702, rs2409750, rs1541020, rs4942248, rs12934476, rs12457255, rs2297437, rs41309367, rs10733509, rs10750376, rs10932456, rs1326860, rs1528663, rs951279, rs9806914, rs7935393, rs1690492, rs420726, rs7759385, rs10974900, rs1326860, rs2548147, rs2815844, rs889702, rs9806914, rs7278257, or rs11221332, or a proxy polymorphism in linkage disequilibrium therewith as determined with an R^2 of at least 0.85, or a combination thereof.

~~81. The method of any one of claims 1-80, wherein the at least three polymorphisms are detected in the sample by subjecting the sample to an assay configured to detect a presence of at least three nucleotides corresponding to nucleic acid position 501 within at least three of SEQ ID NOS: 2001-20041, or 20057-20059.~~

~~8215.~~ The use method of any one of claims ~~1-811-14~~, wherein the inflammatory, fibrotic, or fibrostenotic disease or condition comprises inflammatory bowel disease, Crohn's disease, obstructive Crohn's disease, ulcerative colitis, intestinal fibrosis, intestinal fibrostenosis, rheumatoid arthritis, pulmonary fibrosis, scleroderma, or primary sclerosing cholangitis, wherein optionally the Crohn's disease is ileal, ileocolonic, or colonic Crohn's disease and wherein optionally the subject of the treatment has a non-response or loss-of-response to a standard therapy comprising glucocorticosteroids, anti-TNF therapy, anti- $\alpha 4\beta 7$ therapy, anti-IL12p40 therapy, or a combination thereof.

~~83. The method of claim 82, wherein the Crohn's disease is ileal, ileocolonic, or colonic Crohn's disease.~~

~~84. The method of claim 82, wherein the pulmonary fibrosis comprises idiopathic pulmonary fibrosis.~~

- ~~85. The method of any one of claims 1-83, wherein the subject has, or is at risk for developing, a non-response or loss of response to a standard therapy comprising glucocorticosteroids, anti-TNF therapy, anti- α 4- β 7 therapy, anti-IL12p40 therapy, or a combination thereof.~~
- ~~86. The method of any one of claims 1-85, further comprising determining whether the subject with an inflammatory, a fibrotic, or a fibrostenotic disease or condition is suitable for treatment with an inhibitor of TL1A activity or expression based, at least in part, on the at least three polymorphisms detected in the sample.~~
- ~~87. The method of any one of claims 1-86, further comprising obtaining, or having obtained, the sample from the subject.~~
- ~~88. The method of any one of claims 1-87, wherein the at least three polymorphisms are detected in utilizing assay comprising a quantitative polymerase chain reaction (qPCR), nucleic acid sequencing reaction, or a genotyping array.~~
- ~~89. The method of any one of claims 1-88, wherein the at least three polymorphisms comprise:~~
- ~~(i) three polymorphisms selected from Table 1;~~
 - ~~(ii) four polymorphisms selected from Table 1;~~
 - ~~(iii) five polymorphisms selected from Table 1;~~
 - ~~(iv) six polymorphisms selected from Table 1;~~
 - ~~(v) seven polymorphisms selected from Table 1;~~
 - ~~(vi) eight polymorphisms from one or more 8-SNP models provided in Table 25~~
 - ~~(vii) nine polymorphisms selected from Table 1; or~~
 - ~~(viii) ten polymorphisms selected from Table 1.~~