

SUMMARY

[0008] This invention relates to the development of antigen binding proteins, particularly fully human antibodies that specifically bind TL1A. Preferred antigen binding proteins have strong binding affinity to both human and cynomolgus TL1A, and block TL1A mediated NF-kB activation and T cell activation. These antigen binding proteins have potential to be used as therapeutics for treatment of inflammatory bowel disease (IBD) and other autoimmune and inflammatory conditions.

[0008a] In one aspect, the present invention refers to an antigen binding protein comprising a TL1A binding entity and a second binding entity that is not a TL1A binding entity, wherein the binding entity that is not a TL1A binding entity is a TNF- α binding entity and further wherein:

- a. the TL1A binding entity has one or two light chain variable domains and one or two heavy chain variable domains;
- b. the TL1A binding entity light chain variable domain comprises a LCDR1, LCDR2, and LCDR3;
- c. the TL1A binding entity heavy chain variable domain comprises a HCDR1, HCDR2, and HCDR3; and
- d. the TL1A HCDR1 has a sequence selected from SEQ ID NOS: 170, 182, and 188;
- e. the TL1A HCDR2 has a sequence selected from SEQ ID NOS: 172, 178, 184, 190, 196, and 202;
- f. the TL1A HCDR3 sequence is selected from SEQ ID NOS: 174, 180, 186, and 192;

- g. the TL1A LCDR1 has a sequence selected from SEQ ID NOS: 110, 116, and 122;
- h. the TL1A LCDR2 has a sequence selected from SEQ ID NOS: 106, 112, 118, and 124;
- i. the TL1A LCDR3 has a sequence selected from SEQ ID NOS: 108, 120, and 126;
- j. the TNF- α binding entity has one or two light chain variable domains and one or two heavy chain variable domains;
- k. the TNF- α binding entity light chain variable domain comprises an LCDR1, LCDR2, and LCDR3; and
- l. the TNF- α binding entity heavy chain variable domain comprises an HCDR1, HCDR2, and HCDR3;
- m. the TNF- α binding entity HCDR1 comprises a sequence selected from Table G (SEQ ID NOS: 158, 218, 206, and 212);
- n. the TNF- α binding entity HCDR2 comprises a sequence selected from Table G (SEQ ID NOS: 160, 220, 208, and 214);
- o. the TNF- α binding entity HCDR3 comprises a sequence selected from Table G (SEQ ID NOS: 162, 222, 210, and 216);
- p. the TNF- α binding entity LCDR1 sequence selected from Table G (SEQ ID NOS: 92, 152, 140, and 146),
- q. the TNF- α binding entity LCDR2 sequence selected from Table G (SEQ ID NOS: 94, 154, 112, and 148), and
- r. the TNF- α binding entity LCDR3 sequence selected from Table G (SEQ ID NOS: 96, 156, 144, and 150).

[0009] The disclosure further relates to bispecific antigen binding proteins, particularly bispecific antibodies. Bispecific antigen binding proteins of the disclosure comprise a TL1A binding entity and a TNF- α binding entity. TL1A blocking proteins and TNF- α blocking proteins have different effects in studies measuring inhibition of induction of cytokines IFN γ , IL-5, IL-6, IL-8, and IL-10. TL1A but not TNF- α induces T cell activation in vivo. TL1A and TNF- α induce NF- κ B in different cell types in human peripheral blood monocytes (PBMCs). TL1A and TNF- α further induce different cytokines in human PBMCs. TL1A and TNF- α induce some of the same genes but in different cell types (16 overlapping genes induced by TL1A in whole blood and TNF- α in NCM460 cells; 13 overlapping genes induced by TL1A in whole blood and TNF- α in PBMCs). There is a strong genetic association of TL1A with inflammatory bowel disease (IBD) and anti-TNF agents are clinically validated for

treatment of IBD. Such bispecific antigen binding proteins thus are useful for treatment of IBD and other autoimmune and inflammatory conditions. For these and other reasons, there is a benefit to bispecific antigen binding proteins that specifically bind TL1A and TNF- α .

[0010] One format for such bispecific antigen binding proteins is heterodimeric immunoglobulins (hetero Ig). Such hetero Ig antigen binding proteins have one heavy chain-light chain pair directed to TL1A and another directed to TNF- α .

[0011] Another format for such bispecific antigen binding proteins is IgG-scFv molecules. In an IgG-scFv, each heavy chain of an antibody that specifically binds one target is linked to a single chain antibody (scFv) that specifically binds the other target. The scFv portion can be linked to the heavy chain of the IgG portion directly or through a peptide linker. In the IgG-scFv format, the IgG is directed to TL1A and the scFv portion to TNF- α or vice-versa. Bispecific antigen binding proteins in the IgG-scFv format have the advantage of being bivalent for both of their target antigens.

CLAIMS

What is claimed is:

1. An antigen binding protein comprising a TL1A binding entity and a second binding entity that is not a TL1A binding entity, wherein the binding entity that is not a TL1A binding entity is a TNF- α binding entity and further wherein:
 - a. the TL1A binding entity has one or two light chain variable domains and one or two heavy chain variable domains;
 - b. the TL1A binding entity light chain variable domain comprises a LCDR1, LCDR2, and LCDR3;
 - c. the TL1A binding entity heavy chain variable domain comprises a HCDR1, HCDR2, and HCDR3; and
 - d. the TL1A HCDR1 has a sequence selected from SEQ ID NOS:170, 182, and 188;
 - e. the TL1A HCDR2 has a sequence selected from SEQ ID NOS:172, 178, 184, 190, 196, and 202;
 - f. the TL1A HCDR3 sequence is selected from SEQ ID NOS: 174, 180, 186, and 192;
 - g. the TL1A LCDR1 has a sequence selected from SEQ ID NOS: 110, 116, and 122;
 - h. the TL1A LCDR2 has a sequence selected from SEQ ID NOS: 106, 112, 118, and 124;
 - i. the TL1A LCDR3 has a sequence selected from SEQ ID NOS: 108, 120, and 126;
 - j. the TNF- α binding entity has one or two light chain variable domains and one or two heavy chain variable domains;
 - k. the TNF- α binding entity light chain variable domain comprises an LCDR1, LCDR2, and LCDR3; and
 - l. the TNF- α binding entity heavy chain variable domain comprises an HCDR1, HCDR2, and HCDR3;
 - m. the TNF- α binding entity HCDR1 comprises a sequence selected from Table G (SEQ ID NOS: 158, 218, 206, and 212);
 - n. the TNF- α binding entity HCDR2 comprises a sequence selected from Table G (SEQ ID NOS: 160, 220, 208, and 214);

- o. the TNF- α binding entity HCDR3 comprises a sequence selected from Table G (SEQ ID NOS: 162, 222, 210, and 216);
 - p. the TNF- α binding entity LCDR1 sequence selected from Table G (SEQ ID NOS: 92, 152, 140, and 146),
 - q. the TNF- α binding entity LCDR2 sequence selected from Table G (SEQ ID NOS: 94, 154, 112, and 148), and
 - r. the TNF- α binding entity LCDR3 sequence selected from Table G (SEQ ID NOS: 96, 156, 144, and 150).
2. The antigen binding protein of claim 1, wherein the TL1A binding entity HCDR3 has a sequence selected from antibodies 9C8 and 3B3 (SEQ ID NO: 180 and 192).
 3. The antigen binding protein of claim 2 wherein;
 - a. the TL1A binding entity HCDR1 has a sequence selected from antibodies 9C8 and 3B3 (SEQ ID NO: 170 and 188) and
 - b. the TL1A binding entity HCDR2 has a sequence selected from antibodies 9C8 and 3B3 (SEQ ID NO: 178 and 190).
 4. The antigen binding protein of claim 2 wherein the TL1A binding entity LCDR3 has a sequence selected from antibodies 9C8 and 3B3 (SEQ ID NOS: 263 and 126).
 5. The antigen binding protein of claim 4 wherein;
 - a. the TL1A binding entity LCDR1 has a sequence selected from antibodies 9C8 and 3B3 (SEQ ID NOS: 110 and 122) and
 - b. the TL1A binding entity LCDR2 has a sequence selected from antibodies 9C8 and 3B3 (SEQ ID NOS: 112 and 124).
 6. The antigen binding protein of claim 1 wherein the TL1A binding entity heavy chain variable domain comprises a heavy chain variable domain sequence selected from SEQ ID NOS: 12, 16, 20, 24, 28, and 32.

7. The antigen binding protein of claim 1 wherein the TL1A binding entity heavy chain variable domain comprises a heavy chain variable domain sequence selected from antibodies 9C8 and 3B3 (SEQ ID NOS: 16 and 24).
8. The antigen binding protein of claim 1, wherein the TL1A binding entity light chain variable domain comprises a light chain variable domain sequence selected from SEQ ID NOS: 10, 14, 18, 22, 26, and 30.
9. The antigen binding protein of claim 6 wherein the TL1A binding entity light chain variable domain comprises a light chain variable domain sequence selected from Table D (SEQ ID NOS: 10, 14, 18, 22, 26, and 30).
10. The antigen binding protein of claim 7 wherein the TL1A binding entity light chain variable domain sequence comprises a light chain variable domain sequence selected from antibodies 9C8 and 3B3 (SEQ ID NOS: 14 and 22).
11. The antigen binding protein of claim 1 wherein the protein comprises a TL1A binding entity heavy chain having a heavy chain sequence selected from SEQ ID NOS: 56, 60, 64, 68, 72, and 76.
12. The antigen binding protein of claim 1 wherein the protein comprises a TL1A binding entity light chain having a light chain sequence selected from Table E (SEQ ID NOS: 54, 58, 62, 66, 70, and 74).
13. The antigen binding protein of claim 1 comprising the TL1A binding entity light and heavy chain sequences of an antibody selected from Table E, SEQ ID NOS:
 - a. 54 and 56,
 - b. 58 and 60,
 - c. 62 and 64,
 - d. 66 and 68,
 - e. 70 and 72, and

f. 74 and 76.

14. The antigen binding protein of any one of claims 1 to 13, wherein the TNF- α binding entity HCDR3 comprises a sequence selected from certolizumab (SEQ ID NO: 222).
15. The antigen binding protein of any one of claims 1 to 13, wherein the TNF- α binding entity heavy chain variable domain comprises a sequence at least about 90% identical to a heavy chain variable domain sequence selected from Table H (SEQ ID NOS: 4, 44, 318, 40, and 36).
16. The antigen binding protein of any one of claims 1 to 13, wherein the TNF- α binding entity heavy chain variable domain sequence is a heavy chain variable domain sequence selected from Table H (SEQ ID NOS: 4, 44, 318, 40, and 36).
17. The antigen binding protein of any one of claims 1 to 13, wherein the TNF- α binding entity light chain variable domain comprises a sequence at least about 90% identical to a light chain variable domain sequence selected from Table H (SEQ ID NOS: 2, 42, 38, and 34).
18. The antigen binding protein of any one of claims 1 to 13, wherein the TNF- α binding entity comprises light chain variable domain comprises a light chain variable domain sequence selected from Table H (SEQ ID NOS: 2, 42, 38, and 34).
19. The antigen binding protein of claim 15, wherein the TNF- α binding entity light chain variable domain comprises a sequence at least about 90% identical to a light chain variable domain sequence selected from Table H (SEQ ID NOS: 2, 42, 38, and 34).
20. The antigen binding protein of claim 16, wherein the TNF- α binding entity light chain variable domain sequence is a light chain variable domain sequence selected from Table H (SEQ ID NOS: 2, 42, 38, and 34).

21. The antigen binding protein of any one of claims 1 to 13, wherein the antigen binding protein comprises variable region sequences selected from a TNF- α antigen binding protein in Table I, SEQ ID NOS:
- a. 42, 286, 288, and 290;
 - b. 42, 44, 292, and 294;
 - c. 42, 44, 296, and 298;
 - d. 42, 44, 300 and 302;
 - e. 42, 44, 304, and 306;
 - f. 42, 44, 308, and 310;
 - g. 312, 314, 288, and 290;
 - h. 312, 314, 292, and 294;
 - i. 312, 314, 300 and 302;
 - j. 312, 314, 304, and 306;
 - k. 312, 314, 308, and 310;
 - l. 42, 318, 288, and 290;
 - m. 42, 318, 292, and 294;
 - n. 42, 318, 296, and 298;
 - o. 42, 318, 304, and 306;
 - p. 42, 318, 308, and 310;
 - q. 320, 322, 288, and 290;
 - r. 320, 322, 292, and 294;
 - s. 320, 322, 31, and 298;
 - t. 320, 322, 300, and 302;
 - u. 320, 322, 304, and 306; or
 - v. 320, 322, 308, and 310.