

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 light chain variable domain and one two heavy chain variable domain;
- 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 TNF- α binding entity has one light chain variable domain and one heavy chain variable domain;
- e. the TNF- α binding entity light chain variable domain comprises an LCDR1, LCDR2, and LCDR3; and
- f. the TNF- α binding entity heavy chain variable domain comprises an HCDR1, HCDR2, and HCDR3; and
- g. the antigen binding protein comprises a combination of TL1A-binding and TNF- α binding LCDR1, LCDR2, LCDR3, HCDR1, HCDR2, and HCDR3 sequences selected from SEQ ID NOS:
 - i. 110, 106, 108, 170, 172, 174, 152, 154, 156, 218, 220, and 222 respectively;
 - ii. 128, 118, 120, 182, 196, 186, 152, 154, 156, 218, 220, and 222 respectively;
 - iii. 122, 124, 126, 188, 190, 192, 152, 154, 156, 218, 220, and 222 respectively;
 - iv. 122, 124, 126, 188, 190, 192, 140, 112, 144, 206, 208, and 210 respectively; and
 - v. 122, 124, 126, 188, 190, 192, 146, 148, 150, 212, 214, and 216 respectively.

[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 light chain variable domain and one heavy chain variable domain;
 - 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 TNF- α binding entity has one light chain variable domain and one heavy chain variable domain;
 - e. the TNF- α binding entity light chain variable domain comprises an LCDR1, LCDR2, and LCDR3; and
 - f. the TNF- α binding entity heavy chain variable domain comprises an HCDR1, HCDR2, and HCDR3; and
 - g. the antigen binding protein comprises a combination of TL1A-binding and TNF- α binding LCDR1, LCDR2, LCDR3, HCDR1, HCDR2, and HCDR3 sequences selected from SEQ ID NOS:
 - i. 110, 106, 108, 170, 172, 174, 152, 154, 156, 218, 220, and 222 respectively;
 - ii. 128, 118, 120, 182, 196, 186, 152, 154, 156, 218, 220, and 222 respectively;
 - iii. 122, 124, 126, 188, 190, 192, 152, 154, 156, 218, 220, and 222 respectively;
 - iv. 122, 124, 126, 188, 190, 192, 140, 112, 144, 206, 208, and 210 respectively; and

v. 122, 124, 126, 188, 190, 192, 146, 148, 150, 212, 214, and 216
respectively.

2. The antigen binding protein of claim 1 wherein the antigen binding protein comprises a combination of sequences of a TL1A binding entity light chain and heavy chain variable domains and TNF binding entity light chain and heavy chain variable domains selected from SEQ ID NOS:
 - a. 292, 294, 42, and 286;
 - b. 292, 294, 42, and 318;
 - c. 296, 298, 42, and 318;
 - d. 288, 290, 42, and 318;
 - e. 288, 290, 42, and 44;
 - f. 288, 290, 320, and 322; and
 - g. 288, 290, 312, and 314.

3. The antigen binding protein of claim 1 wherein the protein comprises a combination of sequences of TL1A binding entity heavy and light chains and TNF binding entity heavy and light chains selected from SEQ ID NOS:
 - a. 239, 138, 132, and 316;
 - b. 253, 323, 132, and 316;
 - c. 134, 130, 132, and 316;
 - d. 134, 130, 132, and 136;
 - e. 134, 130, 341, and 343;
 - f. 512, 555, 542, and 571; and
 - g. 134, 130, 337, and 339.