

## 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:

- 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 HCDR1 has a sequence selected from Tables A, B, and C (SEQ ID NOS: 164, 170, 182, 188, 777, 783, 792, 798, 804, 809, 815, 819, 265, 836, 847, 857, 639, 654, 655, 632, 664, 955, 979, 994, 1010, 1017, 1022, 1027, 1028, 1029, 1037, 1045, 1087, 253, 256, 259, 262, 268, 271, 265, and 950);
- e. the HCDR2 has a sequence selected from Tables A, B, and C (SEQ ID NOS: 166, 172, 178, 184, 190, 196, 202, 483, 485, 779, 785, 794, 800, 811, 817, 821, 827, 832, 838, 843, 849, 853, 859, 864, 640, 204, 678, 679, 644, 648, 649, 633, 656, 659, 660, 665, 666, 677, 114, 227, 230, 691, 715, 669, 711, 971, 972, 973, 974, 975, 980, 981, 982, 983, 984, 995, 996, 997, 998, 0999, 1011, 1023, 1030, 1038, 1039, 1040, 1041, 1042, 1046, 1047, 1048, 1058, 1059, 1060, 1061, 1062, 1066, 1067, 1068, 1069, 1070, 1074, 1088, 1089, 1090, 1095, 1096, 1097, 1102, 1103, 1104, 1108, 1109, 1110, 1111, 1112, 254, 260, 184, 269, 272, 266, 951, 953, 956, and 963); and
- f. the HCDR3 sequence is selected from Tables A, B, and C (SEQ ID NOS: 168, 174, 180, 186, 192, 489, 641, 645, 650, 657, 676, 657, 667, 671, 255, 258, 261, 264, 267, 270, 273, 672, and 675).

**[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- $\alpha$  binding entity. TL1A blocking proteins and TNF- $\alpha$  blocking proteins have different effects in studies measuring inhibition of induction of cytokines IFN $\gamma$ , IL-5, IL-6, IL-8, and IL-10. TL1A but not TNF- $\alpha$  induces T cell activation in vivo. TL1A and TNF- $\alpha$  induce NF- $\kappa$ B in different cell types in human peripheral blood monocytes (PBMCs). TL1A and TNF- $\alpha$  further induce different cytokines in human PBMCs. TL1A and TNF- $\alpha$  induce some of the same genes but in different cell types (16 overlapping genes induced by TL1A in whole blood and TNF- $\alpha$  in NCM460 cells; 13 overlapping genes induced by TL1A in whole blood and TNF- $\alpha$  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- $\alpha$ .

**[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- $\alpha$ .

**[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- $\alpha$  or vice-versa. Bispecific antigen binding proteins in the IgG-scFv format have the advantage of being bivalent for both of their target antigens.

**[0012]** A further format for such bispecific antigen binding proteins is IgG-Fab molecules. In this format, the antigen binding protein has a structure such that a Fab molecule that binds to one target is fused to each heavy chain of an IgG molecule that binds to another target. One chain of a Fab portion can be linked directly or through a peptide linker to the C-terminus of a heavy chain of the IgG portion. The resulting molecule has the advantage of being tetravalent and bispecific. All variations of the IgG-Fab format preferably comprise the CDR sequences of Tables 21.2A and 21.2B hereinafter. Preferred heavy and light chain sequences of IgG-Fab molecules appear in Table 21.1 hereinafter.

**[0013]** Other formats for bispecific antigen binding proteins are within the scope of this disclosure. One such format is IgG-Fab molecules. In this format, each heavy chain of an antibody that specifically binds to one target is linked to a Fab fragment that specifically binds to the other target. In the IgG-Fab format, the IgG is directed to TL1A and the Fab portion to TNF- $\alpha$  or vice-versa. Bispecific antigen binding proteins in the IgG-Fab format have the advantage of being bivalent for both of their target antigens. Other formats for bispecific antigen binding proteins within the scope of this disclosure are described infra.

**[0014]** The disclosure also relates to isolated nucleic acids encoding the TL1A-specific antigen binding proteins of the disclosure, as well as vectors comprising the nucleic acids, host cells comprising the vectors, and methods of making and using the TL1A-specific antigen binding proteins.

**[0015]** The disclosure also relates to isolated nucleic acids encoding the bispecific antigen binding proteins of the disclosure, as well as vectors comprising the nucleic acids, host cells comprising the vectors, and methods of making and using the bispecific antigen binding proteins.

**[0016]** In other examples, the present disclosure provides compositions comprising the TL1A-specific antigen binding proteins, the bispecific antigen binding proteins and kits comprising the anti-TL1A or bispecific antigen binding proteins, as well as articles of manufacture comprising the anti-TL1A or bispecific antigen binding proteins.

**[0017]** The TL1A-specific antigen binding proteins and the bispecific antigen binding proteins described herein can be used in the manufacture of pharmaceutical compositions or medicaments for the treatment of conditions associated with TL1A and/or, in the case of bispecific antigen binding proteins, conditions associated with TNF- $\alpha$ . Thus, the present disclosure also provides pharmaceutical compositions comprising a TL1A-specific antigen binding protein or a bispecific antigen binding protein and a pharmaceutically acceptable diluent, excipient or carrier.

**[0018]** The disclosure further relates to methods of treatment using the TL1A-specific antigen binding proteins. The TL1A-specific antigen binding proteins of the present disclosure are useful for the inhibition of the proinflammatory cytokine TL1A. The antibodies can be used to reduce, limit, neutralize, or block the proinflammatory effects of TL1A. Thus, in some examples, the disclosure relates to the treatment of IBD and other autoimmune or inflammatory conditions using the TL1A-specific antigen binding proteins.

**[0019]** The disclosure further relates to methods of treatment using bispecific antigen binding proteins. The bispecific antigen binding proteins of the present disclosure are useful for the inhibition of the proinflammatory cytokines, TL1A and TNF- $\alpha$ . The bispecific binding proteins can be used to reduce, limit, neutralize, or block the proinflammatory effects of TL1A. Likewise, the bispecific antigen binding proteins hereof can be used to reduce, limit, neutralize, or block the proinflammatory effects of TNF- $\alpha$ . Thus, in some examples, the disclosure relates to the treatment of IBD and other autoimmune or inflammatory conditions using TL1A-specific/TNF-specific antigen binding proteins.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

**[0020]** Figure 1 shows a schematic representation of four bispecific hetero Ig formats used to generate anti-TL1A/anti-TNF- $\alpha$  bispecific antigen binding proteins. As shown, a heavy chain directed to one antigen is disulfide-bonded to a heavy chain directed to a different antigen. A light chain for each antigen is disulfide-bonded to the heavy chain for the corresponding antigen. Figure 1 shows a preferred embodiment, in which the heavy and light chains comprise charge mutations to aid in correct association of the heavy and light chains. The Kabat-Eu numbering scheme is used to denote the positions of charge pair mutations within each of the chains and for all sequences throughout this specification. This IgG-like bispecific antigen binding protein format is a heterotetramer comprising two different light chains and two different heavy chains. HC1 and LC1 refer to the heavy chain and light chain, respectively, of one Fab binding arm and HC2 and LC2 refers to the heavy chain and light chain, respectively, of the second Fab binding arm. For example, in the schematic, HC1 and LC1 correspond to the anti-TL1A receptor binding arm and HC2 and LC2 correspond to the anti-TNF- $\alpha$  binding arm. However, the two binding arms can be switched such that HC1 and LC1 correspond to the anti-TNF- $\alpha$  binding arm and HC2 and LC2 correspond to the anti-TL1A receptor binding arm.

**[0021]** Figure 2 shows a schematic representation of the IgG-scFv format used to generate anti-TL1A/anti-TNF- $\alpha$  bispecific antigen binding proteins. As shown, the structure

44. The antigen binding protein of claim 35, wherein the bispecific antigen binding protein comprises two IgG1 heavy chains comprising substitutions R292C, V302C and N297G using EU numbering.
45. The antigen binding protein of claim 41, wherein the bispecific antigen binding protein comprises two IgG1 heavy chains comprising substitutions R292C, V302C and N297G using EU numbering.
46. The antigen binding protein of claim 40, wherein the bispecific antigen binding protein comprises two IgG1 heavy chains comprising substitutions R292C, V302C and N297G using EU numbering.
47. The antigen binding protein of claim 43, wherein the bispecific antigen binding protein comprises two IgG1 heavy chains comprising substitutions R292C, V302C and N297G using EU numbering.