

SUMMARY

[0008] This disclosure 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 disclosure refers to an antigen binding protein specific for TL1A wherein:

- a. the antigen binding protein has one or two light chain variable domains and one or two heavy chain variable domains;
- b. the light chain variable domain comprises a LCDR1, LCDR2, and LCDR3;
- c. the 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).

[0008b] In another aspect, the present disclosure refers to one or more isolated nucleic acids encoding the antigen binding protein of the disclosure. In yet another aspect, the present disclosure refers to one or more expression vectors comprising the nucleic acid or acids of the

disclosure. In a still further aspect, the present disclosure refers to a host cell comprising the one or more expression vectors of the disclosure. In a further aspect, the present disclosure refers to a method for the preparation of an antigen binding protein, comprising a) culturing the host cell of the disclosure under conditions that allow expression of the antigen binding protein; and b) recovering the antigen binding protein from the culture. In a further aspect, the present disclosure refers to a pharmaceutical composition comprising the antigen binding protein of the disclosure and a pharmaceutically acceptable diluent, excipient or carrier. In yet another aspect, the present disclosure refers to the use of the antigen binding protein of the disclosure in the preparation of a medicament for treating a condition associated with TL1A in a patient in need thereof, wherein the condition is inflammatory bowel disease, Crohn's disease, or ulcerative colitis. In still another aspect, the present disclosure refers to the antigen binding protein of the disclosure for use in therapy.

[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.

[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- α 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- α . 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- α . 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- α . 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- α 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- α binding arm. However, the two binding arms can be switched such that HC1 and LC1 correspond to the anti-TNF- α 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- α bispecific antigen binding proteins. As shown, the structure

CLAIMS

What is claimed is:

1. An antigen binding protein specific for TL1A wherein:
 - a. the antigen binding protein has one or two light chain variable domains and one or two heavy chain variable domains;
 - b. the light chain variable domain comprises a LCDR1, LCDR2, and LCDR3;
 - c. the 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).
2. The antigen binding protein of claim 1, wherein the HCDR3 comprises a sequence selected from Table A (SEQ ID NOS: 168, 174, 180, 186, 192, 489, 781, 787, 796, 802, 807, 813, 823, 829, 834, 840, 845, 851, 855, and 861).
3. The antigen binding protein of claim 1, wherein the HCDR3 has a sequence selected from antibodies and 9C8 and 3B3 (SEQ ID NO: 180 and 192).
4. The antigen binding protein of claim 2, wherein:
 - a. the HCDR1 has a sequence selected from Table A (SEQ ID NOS: 164, 170, 182, 188, 777, 783, 792, 798, 804, 809, 815, 819, 265, 836, 847, and 857) and

- b. the HCDR2 has a sequence selected from Table A (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, and 864).
- 5. The antigen binding protein of claim 3 wherein:
 - a. the HCDR1 has a sequence selected from antibodies 9C8 and 3B3 (SEQ ID NO: 170 and 188) and
 - b. the HCDR2 has a sequence selected from antibodies 9C8 and 3B3 (SEQ ID NO: 178 and 190).
- 6. The antigen binding protein of claim 1 wherein the LCDR3 has a sequence selected from Tables A, B, and C (SEQ ID NOS: 102, 108, 263, 120, 126, 687, 693, 701, 707, 717, 727, 733, 739, 745, 751, 757, 763, 767, 771, 775, 637, 638, 631, 653, 663, 637, 233, 940, 978, 989, 990, 991, 992, 993, 1005, 1006, 1007, 1008, 1009, 1034, 1035, 1036, 1055, 1056, 1057, 1065, 1086, 1093, 1094, 1099, 1100, 1101, 1107, 228, 231, 234, 237, 243, 240, 674, 936, 938, 701, 707, , 949, , 942, and 944).
- 7. The antigen binding protein of claim 4 wherein the LCDR3 has a sequence selected from Table A (SEQ ID NOS: 102, 108, 263, 120, 126, 687, 693, 701, 707, 717, 727, 733, 739, 745, 751, 757, 763, 767, 771, and 775).
- 8. The antigen binding protein of claim 5 wherein the LCDR3 has a sequence selected from antibodies 9C8 and 3B3 (SEQ ID NOS: 263 and 126).
- 9. The antigen binding protein of claim 6 wherein:
 - a. the LCDR1 has a sequence selected from Tables A, B, and C (SEQ ID NOS: 98, 104, 110, 116, 122, 128, 467, 469, 683, 689, 235, 697, 146, 709, 713, 719, 723, 229, 226, 741, 747, 753, 773, 635, 642, 646, 651, 658, 661, 668, 759, 743, 765, 977, 986, 987, 1001, 1016, 1021, 1025, 1031, 1032, 1033, 1044, 1053, 1064, 1072, 1078, 1079, 1080, 1106, 226, 229, 232, 235, 241, 238, , 1113, , 146, and 947) and
 - b. the LCDR2 has a sequence selected from Tables A, B, and C (SEQ ID NOS: 100, 106, 112, 118, 124, 235, 699, 705, 721, 725, 731, 737, 749, 755, 761, 769, 636, 643, 647, 652, 662, 789, 988, 1001, 1002, 1004, 1026, 1054, 1073, 1081, 1082, 1083, 1084, 1085, 1092, 1098, 242, 935, 148, 948, and 943).
- 10. The antigen binding protein of claim 7 wherein:

- a. the LCDR1 has a sequence selected from Table A (SEQ ID NOS: 98, 104, 110, 116, 122, 128, 467, 469, 683, 689, 235, 697, 146, 709, 713, 719, 723, 229, 226, 741, 747, 753, and 773) and
 - b. the LCDR2 has a sequence selected from Table A (SEQ ID NOS: 100, 106, 112, 118, 124, 685, 699, 705, 721, 725, 731, 737, 749, 755, 761, and 769).
11. The antigen binding protein of claim 8 wherein:
 - a. the LCDR1 has a sequence selected from antibodies 9C8 and 3B3 (SEQ ID NOS: 110 and 122) and
 - b. the LCDR2 has a sequence selected from antibodies 9C8 and 3B3 (SEQ ID NOS: 112 and 124).
12. The antigen binding protein of claim 1 wherein the heavy chain variable domain comprises a sequence at least about 90% identical to a heavy chain variable domain sequence selected from Table D (SEQ ID NOS: 8, 12, 16, 20, 24, 28, 32, 495, 497, 868, 872, 876, 880, 884, 888, 892, 896, 900, 904, 908, 912, 916, 920, 926, 930, and 934).
13. The antigen binding protein of claim 1 wherein the heavy chain variable domain comprises a heavy chain variable domain sequence selected from Table D (SEQ ID NOS: 8, 12, 16, 20, 24, 28, 32, 495, 497, 868, 872, 876, 880, 884, 888, 892, 896, 900, 904, 908, 912, 916, 920, 926, 930, and 934).
14. The antigen binding protein of claim 1, wherein the light chain variable domain comprises a sequence at least about 90% identical to a light chain variable domain sequence selected from Table D (SEQ ID NOS: 6, 10, 14, 18, 22, 26, 30, 491, 493, 866, 870, 874, 878, 882, 886, 890, 894, 898, 902, 906, 910, 914, 918, 922, 924, 928, and 932,).
15. The antigen binding protein of claim 1, wherein the light chain variable domain comprises a light chain variable domain sequence selected from Table D (SEQ ID NOS: 6, 10, 14, 18, 22, 26, 30, 491, 493, 866, 870, 874, 878, 882, 886, 890, 894, 898, 902, 906, 910, 914, 918, 922, 924, 928, and 932).
16. The antigen binding protein of claim 12, wherein the light chain variable domain comprises a sequence at least about 90% identical to a light chain variable domain sequence selected from Table D (SEQ ID NOS: 6, 10, 14, 18, 22, 26, 30, 491, 493, 866,

- 870, 874, 878, 882, 886, 890, 894, 898, 902, 906, 910, 914, 918, 922, 924, 928, and 932,).
17. The antigen binding protein of claim 13, wherein the light chain variable domain comprises a light chain variable domain sequence selected from Table D (SEQ ID NOS: 6, 10, 14, 18, 22, 26, 30, 491, 493, 866, 870, 874, 878, 882, 886, 890, 894, 898, 902, 906, 910, 914, 918, 922, 924, 928, and 932).
 18. The antigen binding protein of claim 1 wherein:
 - a. the light chain variable domain sequence comprises a light chain variable domain sequence selected from antibodies 9C8 and 3B3 (SEQ ID NOS: 14 and 22) and
 - b. the heavy chain variable domain comprises a heavy chain variable domain sequence selected from antibodies 9C8 and 3B3 (SEQ ID NOS: 16 and 24).
 19. The antigen binding protein of claim 1 wherein the protein comprises a heavy chain having a heavy chain sequence selected from Table E (SEQ ID NOS: 52, 56, 60, 64, 68, 72, 76, 457, 461, 1118, 1122, 1126, 1130, 1134, 1138, 1142, 1146, 1150, 1154, 1158, 1162, 1166, 1170, 1174, 1178, 1182, 1186 and 1190).
 20. The antigen binding protein of claim 1 wherein the protein comprises a light chain having a light chain sequence selected from Table E (SEQ ID NOS: 66, 54, 58, 62, 66, 70, 74, 455, 459, 1116, 1120, 1124, 1128, 1132, 1136, 1140, 1144, 1148, 1152, 1156, 1160, 1164, 1168, 1172, 1176, 1180, 1184 and 1188).
 21. The antigen binding protein of claim 1 comprising the light and heavy chain sequences of an antibody selected from Table E, SEQ ID NOS:
 - a. 50 and 52,
 - b. 54 and 56,
 - c. 58 and 60,
 - d. 62 and 64,
 - e. 66 and 68,
 - f. 70 and 72,
 - g. 74 and 76,
 - h. 455 and 457,
 - i. 459 and 461,
 - j. 1116 and 1118,

- k. 1120 and 1122,
 - l. 1124 and 1126,
 - m. 1128 and 1130,
 - n. 1132 and 1134,
 - o. 1136 and 1138,
 - p. 1140 and 1142,
 - q. 1144 and 1146,
 - r. 1148 and 1150,
 - s. 1152 and 1154,
 - t. 1156 and 1158,
 - u. 1160 and 1162,
 - v. 1164 and 1166,
 - w. 1168 and 1170,
 - x. 1172 and 1174,
 - y. 1176 and 1178,
 - z. 1180 and 1182,
 - aa. 1184 and 1186, and
 - bb. 1188 and 1190.
- 22. One or more isolated nucleic acids encoding the antigen binding protein of any one of claims 1 to 21.
 - 23. One or more expression vectors comprising the nucleic acid or acids of claim 22.
 - 24. A host cell comprising the one or more expression vectors of claim 23.
 - 25. A method for the preparation of an antigen binding protein, comprising:
 - a. culturing the host cell of claim 24 under conditions that allow expression of the antigen binding protein; and
 - b. recovering the antigen binding protein from the culture.
 - 26. A pharmaceutical composition comprising the antigen binding protein of any one of claims 1 to 21 and a pharmaceutically acceptable diluent, excipient or carrier.
 - 27. Use of the antigen binding protein of any one of claims 1 to 21 in the preparation of a medicament for treating a condition associated with TL1A in a patient in need thereof,

wherein the condition is inflammatory bowel disease, Crohn's disease, or ulcerative colitis.

28. The antigen binding protein of any one of claims 1 to 21 for use in therapy.