Patent claims

1. An isolated heavy chain variable region polypeptide comprising an HVR-H1, HVR-H2 and HVR-H3 sequence, wherein:
(a) the HVR-H1 sequence is GYTFTX$_1$YP;
(b) the HVR-H2 sequence is INTNTGNP;
(c) the HVR-H3 sequence is ARX$_2$GX$_3$X$_4$X$_5$X$_6$X$_7$X$_8$X$_9$X$_{10}$X$_{11}$X$_{12}$X$_{13}$;
further wherein: X$_1$ is S or A; X$_2$ is V or T; X$_3$ is G or Y; X$_4$ is Y, S or F; X$_5$ is S, G or T; X$_6$ is V, S or G; X$_7$ is D, Y or P; X$_8$ is E, D or Y; X$_9$ is Y or W; X$_{10}$ is A, F or S; X$_{11}$ is F or D; X$_{12}$ is D or P; X$_{13}$ is V, I or absent.

2. The polypeptide of Claim 1 wherein X$_1$ is S or A; X$_2$ is V or T; X$_3$ is G or Y; X$_4$ is Y or S; X$_5$ is S or G; X$_6$ is V or S; X$_7$ is D or Y; X$_8$ is E; X$_9$ is Y; X$_{10}$ is A or F; X$_{11}$ is F; X$_{12}$ is D; X$_{13}$ is V or I.

3. The polypeptide of Claim 1 wherein wherein X$_1$ is S; X$_2$ is V or T; X$_3$ is G; X$_4$ is Y; X$_5$ is S or G; X$_6$ is V; X$_7$ is D or Y; X$_8$ is E; X$_9$ is Y; X$_{10}$ is A; X$_{11}$ is F; X$_{12}$ is D; X$_{13}$ is V or I.

4. The polypeptide of Claim 1 wherein X$_1$ is S; X$_2$ is V; X$_3$ is G; X$_4$ is Y; X$_5$ is S; X$_6$ is V; X$_7$ is D; X$_8$ is E; X$_9$ is Y; X$_{10}$ is A; X$_{11}$ is F; X$_{12}$ is D; X$_{13}$ is V.

5. The polypeptide of any one of Claims 1-4 further comprising variable region heavy chain framework sequences HC-FR1, HC-FR2, HC-FR3 and HC-FR4, juxtaposed between the HVRs, thus forming the sequence of the formula: (HC-FR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)-(HVR-H3)-(HC-FR4).

6. The polypeptide of Claim 5 wherein the heavy chain framework sequences are derived from human consensus framework sequences.

7. The polypeptide of Claim 5 wherein the heavy chain framework sequences are derived from human germline framework sequences.

8. The polypeptide of Claim 5 wherein one or more of the heavy chain framework sequences is the following:
HC-FR1 is QVQLVQSGSELKKPGASVKVSCKAS;
HC-FR2 is MNWVRQAPGQGLEWMGW;
HC-FR3 is TYAQGFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYYC;
HC-FR4 is WGQGTLVTVSS.

9. The polypeptide of any one of Claims 5-8 further comprising at least a C_H1 domain.

10. The polypeptide of Claim 9 further comprising a C_H2 and a C_H3 domain.

11. The isolated heavy chain polypeptide of any one of Claims 1-10 in combination with a variable region light chain comprising an HVR-L1, HVR-L2 and HVR-L3, wherein:
(a) the HVR-L1 sequence is QGISSY;
(b) the HVR-L2 sequence is AAS;
(c) the HVR-L3 sequence is $X_{14}QX_{15}X_{16}X_{17}X_{18}X_{19}X_{20}$;
further wherein X_{14} is Q, G or H; X_{15} is L, V or T; X_{16} is N, S, I or M; X_{17} is S, R or F; X_{18} is Y or R; X_{19} is P or L; X_{20} is T or A.

12. The polypeptide of Claim 11 wherein X_{14} is Q or G; X_{15} is L or V; X_{16} is N or S; X_{17} is S or R; X_{18} is Y; X_{19} is P; X_{20} is T.

13. The polypeptide of Claim 11 wherein X_{14} is Q; X_{15} is L; X_{16} is S; X_{17} is S; X_{18} is Y; X_{19} is P; X_{20} is T.

14. The polypeptide of any of Claims 11-13 further comprising variable region light chain framework sequences LC-FR1, LC-FR2, LC-FR3 and LC-FR4, juxtaposed between the HVRs, thus forming the sequence of the formula: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)-(HVR-L3)-(LC-FR4).

15. The polypeptide of Claim 14 wherein the light chain framework sequences are derived from human consensus framework sequences.

16. The polypeptide of Claim 14 wherein the light chain framework sequences are derived from human germline framework sequences.

17. The polypeptide of Claim 14 wherein the light chain framework sequences are kappa light chain sequences.

18. The polypeptide of Claim 14 wherein one or more of the light chain framework sequences is the following:
LC-FR1 is DIQLTQSPSFLSASVGDRVTITCRAS;
LC-FR2 is LAWYQQKPGKAPKLLIY;
LC-FR3 is TLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC;
LC-FR4 is FGGGTKVEIK.

19. The polypeptide of any one of Claims 14-18 further comprising a C_L domain.

20. An isolated anti-TIGIT antibody or antigen binding fragment thereof comprising a heavy chain and a light chain variable region sequence, wherein:
(a) the heavy chain comprises an HVR-H1, HVR-H2 and HVR-H3, wherein further: (i) the HVR-H1 sequence is GYTFTX_1YP; (ii) the HVR-H2 sequence is INTNTGNP; (iii) the HVR-H3 sequence is ARX_2G$X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}$;
(b) the light chain comprises an HVR-L1, HVR-L2 and HVR-L3, wherein further: (iv) the HVR-L1 sequence is QGISSY; (v) the HVR-L2 sequence is AAS; (vi) the HVR-L3 sequence is X_{14}Q$X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}$;
wherein further X_1 is S or A; X_2 is V or T; X_3 is G or Y; X_4 is Y, S or F; X_5 is S, G or T; X_6 is V, S or G; X_7 is D, Y or P; X_8 is E, D or Y; X_9 is Y or W; X_{10} is A, F or S; X_{11} is F or D; X_{12} is D or P; X_{13} is V, I or absent; X_{14} is Q, G or H; X_{15} is L, V or T; X_{16} is N, S, I or M; X_{17} is S, R or F; X_{18} is Y or R; X_{19} is P or L; X_{20} is T or A.

21. The antibody or antibody fragment of Claim 20 wherein X_1 is S or A; X_2 is V or T; X_3 is G or Y; X_4 is Y or S; X_5 is S or G; X_6 is V or S; X_7 is D or Y; X_8 is E; X_9 is Y; X_{10} is A or F; X_{11} is F; X_{12} is D; X_{13} is V or I; X_{14} is Q or G; X_{15} is L or V; X_{16} is N or S; X_{17} is S or R; X_{18} is Y; X_{19} is P; X_{20} is T.

22. The antibody or antibody fragment of Claim 20 wherein X_1 is S; X_2 is V or T; X_3 is G; X_4 is Y; X_5 is S or G; X_6 is V; X_7 is D or Y; X_8 is E; X_9 is Y; X_{10} is A; X_{11} is F; X_{12} is D; X_{13} is V or I; X_{14} is Q; X_{15} is L; X_{16} is S; X_{17} is S; X_{18} is Y; X_{19} is P; X_{20} is T.

23. The antibody or antibody fragment of Claim 20 wherein X_1 is S; X_2 is V; X_3 is G; X_4 is Y; X_5 is S; X_6 is V; X_7 is D; X_8 is E; X_9 is Y; X_{10} is A; X_{11} is F; X_{12} is D; X_{13} is V; X_{14} is Q; X_{15} is L; X_{16} is S; X_{17} is S; X_{18} is Y; X_{19} is P; X_{20} is T.

24. The antibody or antibody fragment of Claim 20, wherein
(a) the HVR-H1 sequence is GYTFTSYP,
(b) the HVR-H2 sequence is INTNTGNP,
(c) the HVR-H3 sequence is ARVGGYSVDEYAFDV;
and wherein
(d) the HVR-L1 sequence is QGISSY,
(e) the HVR-L2 sequence is AAS,
(f) the HVR-L3 sequence is QQLSSYPT.

25. The antibody or antibody fragment of any of Claims 20 – 24 further comprising:
(a) variable region heavy chain framework sequences HC-FR1, HC-FR2, HC-FR3 and HC-FR4, juxtaposed between the HVRs, thus forming the sequence of the formula: (HC-FR1)-(HVR-H1)-(HC-FR2)-(HVR-H2)-(HC-FR3)- (HVR-H3)-(HC-FR4), and
(b) variable region light chain framework sequences LC-FR1, LC-FR2, LC-FR3 and LC-FR4, juxtaposed between the HVRs, thus forming the sequence of the formula: (LC-FR1)-(HVR-L1)-(LC-FR2)-(HVR-L2)-(LC-FR3)- (HVR-L3)-(LC-FR4).

26. The antibody or antibody fragment of Claim 25 wherein the framework sequences are derived from human consensus framework sequences.

27. The antibody or antibody fragment of Claim 25 wherein the framework sequences are derived from human germline framework sequences.

28. The antibody or antibody fragment of Claim 25 wherein one or more of the framework sequences is the following:
HC-FR1 is QVQLVQSGSELKKPGASVKVSCKAS;
HC-FR2 is MNWVRQAPGQGLEWMGW;
HC-FR3 is TYAQGFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYYC;
HC-FR4 is WGQGTLVTVSS.

29. The antibody or antibody fragment of Claim 25 wherein one or more of the framework sequences is the following:
LC-FR1 sequence is DIQLTQSPSFLSASVGDRVTITCRAS;
LC-FR2 sequence is LAWYQQKPGKAPKLLIY;
LC-FR3 sequence is TLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC;
LC-FR4 sequence is FGGGTKVEIK.

30. The antibody or antibody fragment of Claim 25 wherein:
(a) the variable heavy chain framework sequences are the following:
(i) HC-FR1 is QVQLVQSGSELKKPGASVKVSCKAS;
(ii) HC-FR2 is MNWVRQAPGQGLEWMGW;
(iii) HC-FR3 is TYAQGFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYYC;
(iv) HC-FR4 is WGQGTLVTVSS; and
(b) the variable light chain framework sequences are the following:
(i) LC-FR1 sequence is DIQLTQSPSFLSASVGDRVTITCRAS;
(ii) LC-FR2 sequence is LAWYQQKPGKAPKLLIY;
(iii) LC-FR3 sequence is TLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC;
(iv) LC-FR4 sequence is FGGGTKVEIK.

31. An isolated anti-TIGIT antibody or antigen binding fragment thereof, having the HC-FR and LC-FR sequences of claim 30, selected from the following:

i) an antibody, wherein the HVR-H1, HVR-H2, HVR-H3 sequences are selected from one of the ID's shown in Table 2, and wherein

(a) the HVR-L1 sequence is QGISSY,

(b) the HVR-L2 sequence is AAS,

(c) the HVR-L3 sequence is QQLNSYPT;

ii) an antibody wherein the HVR-L1, HVR-L2, HVR-L3 sequences are selected from one of the ID's shown in Table 3, and wherein

(a) the HVR-H1 sequence is GYTFTSYP,

(b) the HVR-H2 sequence is INTNTGNP,

(c) the HVR-H3 sequence is ARVGGYSVDEYAFDV; or

iii) an antibody chosen from Table 4.

32. The antibody or antibody fragment of any one of Claims 25-31 further comprising at least a C_H1 domain.

33. The antibody or antibody fragment of Claim 32 further comprising a C_H2 and a C_H3 domain.

34. The antibody or antibody fragment of any one of Claims 25-33 further comprising a C_L domain.

35. The antibody of Claim 34, wherein the constant region is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4.

36. The antibody of Claim 35 wherein the constant region is IgG1.

37. The antibody or antibody fragment of any one of the preceding Claims which is a fully human antibody.

38. An isolated anti-TIGIT antibody or antigen binding fragment thereof comprising a heavy chain variable region sequence and a light chain variable region sequence, wherein:

(a) the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence:
QVQLVQSGSELKKPGASVKVSCKASGYTFTSYPMNWVRQAPGQGLEWMGWINTNTG
NPTYAQGFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARVGGYSVDEYAFDVWGQ
GTLVTVSS, and

(b) the light chain sequence has at least 85% sequence identity to the light chain sequence:
DIQLTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYAASTLQSGVP
SRFSGSGSGTEFTLTISSLQPEDFATYYCQQLSSYPTFGGGTKVEIK.

39. The antibody or antigen binding fragment of Claim 38, wherein the sequence identity is at least 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or is 100%.

40. The antibody or antigen binding fragment of Claim 39, wherein the sequence identity is 100%.

41. An isolated anti-TIGIT antibody wherein the heavy chain is:
QVQLVQSGSELKKPGASVKVSCKASGYTFTSYPMNWVRQAPGQGLEWMGWINTNTG
NPTYAQGFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARVGGYSVDEYAFDVWGQ
GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG, and

(b) the light chain is:

DIQLTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYAASTLQSGVP
SRFSGSGSGTEFTLTISSLQPEDFATYYCQQLSSYPTFGGGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS
TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC.

42. The antibody of any one of Claims 20-41 wherein the antibody is capable of binding to human and cynomolgus monkey TIGIT.

43. The antibody of any one of Claims 20-20 wherein the antibody is capable of blocking the interaction between human, or cynomolgus monkey TIGIT and the respective human, or cynomolgus monkey PVR.

44. The antibody of any of Claims 20-43 wherein the antibody binds to human TIGIT with a K_D of $10x10^{-9}$ M or less.

45. An isolated anti-TIGIT antibody or antigen binding fragment thereof which binds to a functional epitope comprising residues Q53, T55, Y113 and P114 of human TIGIT.

46. The isolated anti-TIGIT antibody or antigen binding fragment of claim 45 wherein the functional epitope further comprises residues Q56, N70, and H111 of human TIGIT.

47. An isolated anti-TIGIT antibody or antigen binding fragment thereof which binds to a conformational epitope comprising residues T51, A52, Q53, T55, Q56, N70, D72, H111, T112, Y113, P114, and G116 of human TIGIT.

48. An isolated anti-TIGIT antibody or antigen binding fragment thereof wherein the antibody cross-competes for binding to TIGIT with an antibody or antigen binding fragment of any of Claims 20-42.

49. A pharmaceutical composition comprising the anti-TIGIT antibody or antigen binding fragment of any of Claims 20-48 and at least one pharmaceutically acceptable carrier.

50. An isolated nucleic acid encoding a polypeptide of any one of Claims 1-41.

51. An isolated nucleic acid encoding the light chain or a heavy chain sequence of an anti-TIGIT antibody or antigen binding fragment of any one of Claims 20-41.

52. An isolated nucleic acid encoding the heavy chain according to Claim 41, which nucleic acid has the following sequence:

ATGGAAACAGACACCCTGCTGCTGTGGGTGCTGCTGCTGTGGGTGCCCGGCTCCA
CAGGCCAGGTGCAGCTGGTGCAGTCCGGCTCCGAGCTGAAGAAACCCGGCGCCT
CCGTGAAGGTGTCCTGCAAGGCCTCCGGCTACACCTTCACCTCCTACCCCATGAA
CTGGGTGAGGCAGGCTCCTGGCCAGGGACTGGAGTGGATGGGCTGGATCAACAC
CAACACCGGCAACCCTACCTACGCCCAGGGCTTCACCGGCAGGTTCGTGTTCTCC
CTGGACACCAGCGTGTCCACCGCCTACCTGCAGATCTCCTCCCTGAAGGCCGAGG
ACACCGCCGTGTACTACTGCGCCAGGGTGGGAGGCTACTCCGTGGACGAGTACG
CCTTCGACGTGTGGGGCCAGGGCACCCTGGTGACCGTGTCCTCCGCTAGCACCAA
GGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACA
GCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCG
TGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGT
CCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGG
CACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGAC
AAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGC
ACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGAC
ACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCC
ACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAA
TGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAG
CGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAG
GTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAG
GGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCACGGGAGGAGATGA
CCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACAT
CGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCC

TCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCT
GCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCCCCGGGT.

53. An isolated nucleic acid encoding the light chain according to Claim 41, which nucleic acid has the following sequence:
ATGAGGGCCCTGCTGGCTAGACTGCTGCTGTGCGTGCTGGTCGTGTCCGACAGCA
AGGGCGACATCCAGCTGACCCAGTCCCCCTCCTTCCTGTCCGCTTCCGTGGGCGA
CAGGGTGACCATCACTTGTCGTGCCTCCCAGGGCATCTCCTCCTACCTGGCCTGG
TACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGCCGCTTCCACAC
TGCAGTCCGGCGTGCCCTCCAGGTTTTCCGGATCCGGCTCCGGCACCGAGTTCAC
CCTGACCATCTCCTCCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAG
CTGTCCTCCTACCCCACCTTCGGCGGCGGCACAAAGGTGGAGATCAAGCGTACGG
TGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACA
GTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAG
CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAG
CAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAG
CTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT.

54. A vector comprising the nucleic acid of any of claims 50-53.

55. A host cell comprising the vector of Claim 54.

56. The host cell of Claim 55 which is eukaryotic.

57. The host cell of Claim 56 which is mammalian.

58. The host cell of Claim 57 which is a Chinese Hamster Ovary (CHO) cell, preferably CHO-K1SV.

59. A process for making an anti-TIGIT antibody or antigen binding fragment thereof comprising culturing the host cell of any one of Claims 55-58 under conditions suitable for the expression of the vector encoding the anti-TIGIT antibody or antigen binding fragment, and recovering the antibody or fragment.