

CLAIMS

1. An antigen binding protein specifically binding to a PRAME antigenic peptide that comprises or consists of the amino acid sequence SLLQHLIGL of SEQ ID NO: 50 and is in a complex with a major histocompatibility complex (MHC) protein, the antigen binding protein comprising
 - (a) a first polypeptide comprising a variable domain V_A comprising complementarity determining regions (CDRs) CDRa1, CDRa2 and CDRa3, wherein

the CDRa1 comprises or consists of the amino acid sequence selected from the group consisting of VKEFQD (SEQ ID NO: 16), NKEFQD (SEQ ID NO: 17), TKEFQD (SEQ ID NO: 21), VREFQD (SEQ ID NO: 22), VSEFQD (SEQ ID NO: 24), and VAEFQD (SEQ ID NO: 25), and

the CDRa3 comprises or consists of the amino acid sequence selected from ALYNNLDMR (SEQ ID NO: 33), ALYNNYDMR (SEQ ID NO: 34), ALYNNADMR (SEQ ID NO: 219), ALYNNDDMR (SEQ ID NO: 221), ALYNNEDMR (SEQ ID NO: 223), ALYNNFDMR (SEQ ID NO: 225), ALYNNHDMR (SEQ ID NO: 227), ALYNNIDMR (SEQ ID NO: 229), ALYNNKDMR (SEQ ID NO: 231), ALYNNQDMR (SEQ ID NO: 233), ALYNNRDMR (SEQ ID NO: 235), ALYNNVDMR (SEQ ID NO: 237), and

the CDRa2 comprises or consists of the amino acid sequence selected from the group consisting of FGPYGVE (SEQ ID NO: 29), FGPYGRE (SEQ ID NO: 30), FGPYGTE (SEQ ID NO: 31), and FGPYGKE (SEQ ID NO: 32), and
 - (b) a second polypeptide comprising a variable domain V_B comprising CDRb1, CDRb2 and CDRb3, wherein

the CDRb1 comprises or consists of the amino acid sequence SGHNS (SEQ ID NO: 10), and

the CDRb3 comprises or consists of the amino acid sequence selected from the group consisting of ASSPGATDTQY (SEQ ID NO: 47), ASSPGATDKQY (SEQ ID NO: 48), ASSPGATDLQY (SEQ ID NO: 239), ASSPGATDRQY (SEQ ID NO: 241), ASSPGATDHQY (SEQ ID NO: 243), ASSPGATDEQY (SEQ ID NO: 245), ASSPGATDAQY (SEQ ID NO: 247), ASSPGATDQQY (SEQ ID NO: 249), ASSPGATDNQY (SEQ ID NO: 251), ASSPGATDFQY (SEQ ID NO: 253), ASSPGATDYQY (SEQ ID NO: 255), ASSPGATDIQY (SEQ ID NO: 257), ASSPGATDVQY (SEQ ID NO: 259), ASSAGSTDAQY (SEQ ID NO: 292), ASSRGSTDAQY (SEQ ID NO: 293), and

the CDRb2 comprises or consists of the amino acid sequence selected from the group consisting of FQNTAV (SEQ ID NO: 36), YQNTAV (SEQ ID NO: 37),

FQNTAT (SEQ ID NO: 39), FQNTAL (SEQ ID NO: 41), LQNTAV (SEQ ID NO: 43) and MQNTAV (SEQ ID NO: 44).

2. The antigen binding protein of claim 1, comprising a CDRa1 comprising SEQ ID NO: 16, a CDRa2 comprising SEQ ID NO: 32, a CDRa3 comprising SEQ ID NO: 33 or SEQ ID NO: 34, a CDRb1 comprising SEQ ID NO: 10, a CDRb2 comprising SEQ ID NO: 36, and a CDRb3 comprising SEQ ID NO: 48 or SEQ ID NO: 292.
3. The antigen binding protein of claim 1 or 2, wherein said antigen binding protein specifically binds to a functional epitope comprising or consisting of at least 3, 4 or 5 amino acid positions selected from the group consisting of positions 3, 5, 6, 7 and 8, in particular 3, 5 and 7, of SEQ ID NO: 50, preferably to a functional epitope consisting of amino acid positions 3, 5 and 7, or 3, 5, 6 and 7, or 3, 5, 7 and 8, or 3, 5, 6, 7 and 8 of SEQ ID NO: 50, but preferably not amino acid positions 1 and 4 of SEQ ID NO: 50, or specifically binds to a functional epitope comprising or consisting of at least 6 or 7 amino acid positions selected from the group consisting of positions 1, 3, 4, 5, 6, 7 and 8 of SEQ ID NO: 50.
4. The antigen binding protein of any one of claims 1 to 3, wherein said antigen binding protein binds to at least 1, at least 2, at least 3, at least 4, at least 5, at least 10, at least 20 or all peptides selected from the group consisting of TMED9-001 (SEQ ID NO: 51), CAT-001 (SEQ ID NO: 52), DDX60L-001 (SEQ ID NO: 53), LRRC70-001 (SEQ ID NO: 54), PTPLB-001 (SEQ ID NO: 55), HDAC5-001 (SEQ ID NO: 56), VPS13B-002 (SEQ ID NO: 57), ZNF318-001 (SEQ ID NO: 58), CCDC51-001 (SEQ ID NO: 59), IFT17-003 (SEQ ID NO: 60), DIAPH1-004 (SEQ ID NO: 62), FADS2-001 (SEQ ID NO: 63), FRYL-003 (SEQ ID NO: 64), GIMAP8-001 (SEQ ID NO: 65), HSF1-001 (SEQ ID NO: 66), KNT-001 (SEQ ID NO: 67), MAU-001 (SEQ ID NO: 68), MCM4-001 (SEQ ID NO: 69), MPPE1-001 (SEQ ID NO: 71), MYO1B-002 (SEQ ID NO: 72), PRR12-001 (SEQ ID NO: 73), PTRF-003 (SEQ ID NO: 74), RASGRP1-001 (SEQ ID NO: 75), SMARCD1-001 (SEQ ID NO: 76), TGM2-001 (SEQ ID NO: 77), VAV1-001 (SEQ ID NO: 78), VIM-009 (SEQ ID NO: 317), FARSA-001 (SEQ ID NO: 306), ALOX15B-003 (SEQ ID NO: 304), FAM114A2-002 (SEQ ID NO: 305), GPR56-002 (SEQ ID NO: 307), IGHD-002 (SEQ ID NO: 308), NOMAP-3-0972 (SEQ ID NO: 309), NOMAP-3-1265 (SEQ ID NO: 310), NOMAP-3-1408 (SEQ ID NO: 311), NOMAP-3-1587 (SEQ ID NO: 312), NOMAP-3-1768 (SEQ ID NO: 313), NOMAP-5-0765 (SEQ ID NO: 314), PDCD10-004 (SEQ ID NO: 315), TSN-001 (SEQ ID NO: 316), ARMC9-002 (SEQ ID NO: 187), CLI-001 (SEQ ID NO: 188), COPG1-001 (SEQ ID NO: 190), COPS7A-001 (SEQ ID NO: 192), EIF-009 (SEQ ID NO: 193),

194), EXT2-006 (SEQ ID NO: 196), LMNA-001 (SEQ ID NO: 198), PKM-005 (SEQ ID NO: 200), PSMB3-002 (SEQ ID NO: 202), RPL-007 (SEQ ID NO: 204), SPATS2L-003 (SEQ ID NO: 206), SYNE1-002 (SEQ ID NO: 208), TGM2-002 (SEQ ID NO: 210) and TPR-004 (SEQ ID NO: 212), in a complex with a MHC protein, with a KD that is increased by a factor of ≥ 100 compared to the KD for binding to a peptide comprising the amino acid sequence of SEQ ID NO: 50 in a complex with a MHC protein.

5. The antigen binding protein of any one of claims 1 to 4, wherein the antigen binding protein is multispecific, e.g. tetra-, tri- or bispecific, preferably bispecific, in particular said antigen binding protein is a bispecific TCR, a bispecific antibody or a bispecific TCR-antibody molecule.
6. The antigen binding protein of any one of claims 1 to 5, wherein
 - the first and the second polypeptide are comprised in a single polypeptide chain or two polypeptide chains, preferably wherein V_A is comprised in a first polypeptide chain and V_B is comprised in a second polypeptide chain; and/or
 - the variable domain V_A is a V_α or V_γ domain and the variable domain V_B is a V_β or V_δ domain.
7. The antigen binding protein of any one of claims 1 to 6, wherein V_A further comprises one or more framework regions, preferably all framework regions, selected from the group consisting of FR1-a, FR2-a, FR3-a and FR4-a, wherein
 - FR1-a comprises or consists of the amino acid sequence of SEQ ID NO: 345 or SEQ ID NO: 346, or an amino acid sequence at least 95% identical to SEQ ID NO: 345 comprising K or N, more preferably K, at position 20 and/or L or M, more preferably L, at position 2;
 - FR2-a comprises or consists of the amino acid sequence of SEQ ID NO: 347 or SEQ ID NO: 348, or an amino acid sequence at least 95% identical to SEQ ID NO: 347 comprising L, I or M, more preferably L or I, at position 39, A or D, more preferably A, at position 47, K or W, preferably K, at position 44, F or A, preferably F, at position 52 and/or Y or V, preferably Y, at position 55;
 - FR3-a comprises or consists of the amino acid sequence of SEQ ID NO: 349 or an amino acid sequence at least 95% identical to SEQ ID NO: 349 comprising T or K, more preferably T, at position 92 and/or D or G, preferably D, at position 93;
 - FR4-a comprises or consists of the amino acid sequence of SEQ ID NO: 350 or an amino acid sequence at least 95% identical to SEQ ID NO: 350; and

V_B further comprises one or more framework regions, preferably all framework regions, selected from the group consisting of FR1-b, FR2-b, FR3-b and FR4-b, wherein

- FR1-b comprises or consists of the amino acid sequence of SEQ ID NO: 351 or SEQ ID NO: 352 or an amino acid sequence at least 95% identical to SEQ ID NO: 351 comprising H or N, more preferably H, at position 10, E, L or K, preferably E, at position 11 and/or R or H, at position 22;
- FR2-b comprises or consists of the amino acid sequence of SEQ ID NO: 353 or an amino acid sequence at least 95% identical to SEQ ID NO: 353 comprising R or K, more preferably R, at position 43, E or Q, preferably E, at position 44, M or P, more preferably P, at position 46, and/or R or Q, more preferably Q, at position 48;
- FR3-b comprises or consists of the amino acid sequence of SEQ ID NO: 354 or SEQ ID NO: 355 or an amino acid sequence at least 95% identical to SEQ ID NO: 354 comprising D, A, E, R, K Q, N or S, more preferred D, A, E, Q, N or S, more preferably D or A, even more preferably D, at position 84; and
- FR4-b comprises or consists of the amino acid sequence of SEQ ID NO: 356 or an amino acid sequence at least 95% identical to SEQ ID NO: 356.

8. The antigen binding protein of any one of claims 1 to 7, wherein

- V_A comprises or consists of the amino acid sequence of SEQ ID NO: 132 or an amino acid sequence at least 95% identical to SEQ ID NO: 132 comprising a CDRa1 of SEQ ID NO: 16, a CDRa2 of SEQ ID NO: 32 and a CDRa3 of SEQ ID NO: 33, SEQ ID NO: 34, or SEQ ID NO: 9, and further K or N, preferably K, at position 20, L, M, or I, preferably L or I, at position 39, K or W, preferably K, at position 44, F or A, preferably F, at position 52, Y or V, preferably Y, at position 55, T or K, preferably T, at position 92 and/or D or G, preferably D, at position 93, in particular V_A comprises or consists of the amino acid sequence of SEQ ID NO: 132, SEQ ID NO: 129, SEQ ID NO: 137 or SEQ ID NO: 142; and
- V_B comprises or consists of the amino acid sequence of SEQ ID NO: 134 or an amino acid sequence at least 95% identical to SEQ ID NO: 134 comprising a CDRb1 of SEQ ID NO: 10, a CDRb2 of SEQ ID NO: 36, and a CDRb3 of SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 47, SEQ ID NO: 281, SEQ ID NO: 292, SEQ ID NO: 294, SEQ ID NO: 297, SEQ ID NO: 298, SEQ ID NO: 301 or SEQ ID NO: 283, and further E, L or K, preferably E, at position 11, R or H at position 22, E or Q, preferably E, at position 44, P or M, preferably P, at position 46, Q or R, preferably Q, at position 48 and/or D, A, E, Q, N, or S, preferably D or A, at position 84, in particular V_B comprises or consists of the amino acid sequence of SEQ ID NO: 134, SEQ ID NO: 130, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140,

SEQ ID NO: 141, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147 or SEQ ID NO: 148.

9. The antigen binding protein of any one of claims 1 to 8, further comprising an antibody light chain variable domain (V_L) and an antibody heavy chain variable domain (V_H), wherein preferably wherein V_L and V_H bind to an antigen selected from the group consisting of CD2, CD3, in particular CD3 γ , CD3 δ , and/or CD3 ϵ , CD4, CD5, CD7, CD8, CD10, CD11b, CD11c, CD14, CD16, CD18, CD22, CD25, CD28, CD32a, CD32b, CD33, CD41, CD41b, CD42a, CD42b, CD44, CD45RA, CD49, CD55, CD56, CD61, CD64, CD68, CD90, CD94, CD95, CD117, CD123, CD125, CD134, CD137, CD152, CD163, CD193, CD203c, CD235a, CD278, CD279, CD287, Nkp46, NKG2D, GITR, $F_{c\epsilon}RI$, TCR α/β and TCR γ/δ , HLA-DR and 4-1 BB, or combinations thereof and/or bind to an effector cell, in particular a T cell or natural killer cell.

10. The antigen binding protein of claim 9, wherein the antigen binding protein comprises a first and a second polypeptide chain, and wherein the first polypeptide chain is represented by a formula [Ia]:

$$V_1-L_1-D_1-L_2-V_2-L_3-D_2 \quad [Ia],$$

and the second polypeptide chain is represented by a formula [IIa]

$$V_3-L_4-D_3-L_5-V_4-L_6-D_4 \quad [IIa],$$

wherein

- V_1 , V_2 , V_3 , and V_4 are variable domains, wherein one of V_1 to V_4 is V_A , one is V_B , one is V_L and one is V_H ;
- D_1 , D_2 , D_3 , and D_4 are dimerization domains and may be present or absent, wherein D_1 and D_3 , and D_2 and D_4 , specifically bind to each other and at least one pair of D_1 and D_3 , or D_2 and D_4 is present; and
- L_1 , L_2 , L_3 , L_4 , L_5 , and L_6 are linkers, wherein L_1 and L_4 are present and L_2 , L_3 , L_5 , and L_6 may be present or absent.

11. The antigen binding protein of claim 10, wherein the antigen binding protein comprises a first and a second polypeptide chain, and wherein the first polypeptide chain is represented by a formula [Ib]:

$$V_L-L_1-V_B-F_{c1} \quad [Ib],$$

and the second polypeptide chain is represented by a formula [IIb]

$$V_A-L_4-V_H-F_{c2} \quad [IIb],$$

wherein

- V_A consists of the amino acid sequence of SEQ ID NO: 132 and V_B consists of the amino acid sequence of SEQ ID NO: 135;
 - L_1 and L_4 are linkers of 5-25 amino acids, wherein preferably L_1 and L_4 consist of the amino acid sequence of SEQ ID NO: 214;
 - V_L and V_H are antibody variable domains together forming an antigen binding site binding to CD3, or a TCR α/β CD3 complex;
 - F_{c1} and F_{c2} are a pair of F_c domains, wherein preferably F_{c1} consist of the amino acid sequence of SEQ ID NO: 149 (knob) and F_{c2} consist of the amino acid sequence of SEQ ID NO: 150 (hole).
12. The antigen binding protein of any one of claims 1 to 11, a first and a second polypeptide chain at least 95% identical to amino acid sequences selected from 100 and 101, 103 and 102, 105 and 104, 106 and 107, 106 and 101, 111 and 110, 111 and 102, 103 and 110, 100 and 107, 100 and 119, 100 and 121, 122 and 121, 106 and 121, 126 and 121, 128 and 121, 100 and 131, 100 and 133, 122 and 133, 106 and 133, 126 and 133, 128 and 133, 100 and 143, 122 and 143, 106 and 143, 126 and 143, 128 and 143, 103 and 152, 155 and 152, 157 and 152, 159 and 152, 103 and 160, 155 and 162, 157 and 162, 167 and 160, 169 and 168, 171 and 168, 173 and 168, 167 and 168, 177 and 176, 179 and 176, 181 and 176, 183 and 176, 159 and 184, 105 and 186, 189 and 186, 191 and 186, 193 and 186, 195 and 160, 197 and 160, 199 and 160, 201 and 160, 203 and 160, 205 and 160, 207 and 160, 209 and 160, 211 and 160, 213 and 160, 215 and 160, 217 and 216, 217 and 218, 217 and 220, 217 and 222, 217 and 224, 217 and 228, 217 and 230, 217 and 232, 217 and 234, 217 and 236, 217 and 238, 217 and 240, 217 and 242, 217 and 244, 217 and 246, 217 and 248, 217 and 250, 217 and 252, 217 and 254, 217 and 256, 217 and 258, 217 and 260, 217 and 262, 217 and 264, 217 and 266, 155 and 268, 189 and 270, 189 and 272, 189 and 274, 189 and 276, 189 and 278, 189 and 282, 285 and 284, 291 and 284, 295 and 186, 295 and 296, 299 and 162, 285 and 300, 303 and 162, 303 and 284, 156 and 162, 158 and 284, 158 and 300, 303 and 161, 303 and 163, 291 and 164, 291 and 156, 166 and 300, 291 and 170, 291 and 172, 291 and 174, 166 and 170, 166 and 172, 166 and 174, 291 and 182, 291 and 185, 175 and 186, 178 and 186, and 180 and 186.
13. The antigen binding protein of any one of claims 1 to 12, comprising a first and a second polypeptide chain selected from 100 and 101, 103 and 102, 105 and 104, 106 and 107, 106 and 101, 111 and 110, 111 and 102, 103 and 110, 100 and 107, 100 and 119, 100 and 121, 122 and 121, 106 and 121, 126 and 121, 128 and 121, 100 and 131, 100 and 133, 122 and 133, 106 and 133, 126 and 133, 128 and 133, 100 and 143, 122 and 143,

106 and 143, 126 and 143, 128 and 143, 103 and 152, 155 and 152, 157 and 152, 159 and 152, 103 and 160, 155 and 162, 157 and 162, 167 and 160, 169 and 168, 171 and 168, 173 and 168, 167 and 168, 177 and 176, 179 and 176, 181 and 176, 183 and 176, 159 and 184, 105 and 186, 189 and 186, 191 and 186, 193 and 186, 195 and 160, 197 and 160, 199 and 160, 201 and 160, 203 and 160, 205 and 160, 207 and 160, 209 and 160, 211 and 160, 213 and 160, 215 and 160, 217 and 216, 217 and 218, 217 and 220, 217 and 222, 217 and 224, 217 and 228, 217 and 230, 217 and 232, 217 and 234, 217 and 236, 217 and 238, 217 and 240, 217 and 242, 217 and 244, 217 and 246, 217 and 248, 217 and 250, 217 and 252, 217 and 254, 217 and 256, 217 and 258, 217 and 260, 217 and 262, 217 and 264, 217 and 266, 155 and 268, 189 and 270, 189 and 272, 189 and 274, 189 and 276, 189 and 278, 189 and 282, 285 and 284, 291 and 284, 295 and 186, 295 and 296, 299 and 162, 285 and 300, 303 and 162, 303 and 284, 156 and 162, 158 and 284, 158 and 300, 303 and 161, 303 and 163, 291 and 164, 291 and 156, 166 and 300, 291 and 170, 291 and 172, 291 and 174, 166 and 170, 166 and 172, 166 and 174, 291 and 182, 291 and 185, 175 and 186, 178 and 186, and 180 and 186

- .

14. The antigen binding protein of any one of claims 1 to 13, comprising a first polypeptide chain according to SEQ ID NO: 158, and a second polypeptide chain according to SEQ ID NO: 300.
15. An isolated nucleic acid comprising a sequence encoding the antigen binding protein of any one of claims 1 to 14.
16. A vector comprising the nucleic acid of claim 15.
17. A host cell comprising the antigen binding protein of any one of claims 1 to 14, or the nucleic acid of claim 15, or the vector of claim 16, preferably wherein the host cell is a lymphocyte, preferably a T lymphocyte or T lymphocyte progenitor cell, or a cell for recombinant expression, such as a Chinese Hamster Ovary (CHO) cell or a yeast cell.
18. A pharmaceutical composition comprising the antigen binding protein of any one of claims 1 to 14, the nucleic acid of claim 15, the vector of claim 16, or the host cell of claim 17 and a pharmaceutically acceptable carrier.
19. The pharmaceutical composition of claim 18, wherein the antigen binding protein is dissolved or dispersed in a pharmaceutically acceptable carrier or aqueous medium.

20. A method of producing the antigen binding protein according to any one of claims 1 to 14, comprising
 - a. providing a host cell,
 - b. providing a genetic construct comprising a coding sequence encoding the antigen binding protein of any of claims 1 to 14,
 - c. introducing said genetic construct into said host cell, and
 - d. expressing said genetic construct by said host cell,
 - e. optionally further comprising the isolation and purification of the antigen binding protein from the host cell.
21. An antigen binding protein produced by the method of claim 20, wherein the host cell is a mammalian cell, preferably a mammalian cell line selected from Vero cells, CHO cells, 3T3 cells, COS cells, and HEK cells.
22. Use of the antigen binding protein of any one of claims 1 to 14, the nucleic acid of claim 15, the vector of claim 16, the host cell of claim 17, or the pharmaceutical composition of claim 18 or 19 for the manufacture of a medicament for the treatment of a cancer presenting a PRAME antigenic peptide comprising the amino acid sequence of SEQ ID NO: 50, wherein said cancer is selected from the group of cancers consisting of acute myeloid leukemia, breast cancer, cholangiocellular carcinoma, gallbladder cancer, glioblastoma, hepatocellular carcinoma, head and neck squamous cell carcinoma, melanoma, amelanotic melanoma, non-Hodgkin lymphoma, non-small cell lung cancer adenocarcinoma, non-small cell lung cancer, squamous cell non-small cell lung cancer, ovarian cancer, esophageal cancer, renal cell carcinoma, small cell lung cancer, urinary bladder carcinoma, uterine and endometrial cancer, osteosarcoma, chronic lymphocytic leukemia, colorectal carcinoma, and synovial sarcoma.